






RESEARCH ARTICLE

Brain-wide versus genome-wide vulnerability biomarkers for severe mental illnesses

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Abstract

Severe mental illnesses (SMI), including major depressive (MDD), bipolar (BD), and schizophrenia spectrum (SSD) disorders have multifactorial risk factors and capturing their complex etiopathophysiology in an individual remains challenging. Regional vulnerability index (RVI) was used to measure individual's brain-wide similarity to the expected SMI patterns derived from meta-analytical studies. It is analogous to polygenic risk scores (PRS) that measure individual's similarity to genome-wide patterns in SMI. We hypothesized that RVI is an intermediary phenotype between genome and symptoms and is sensitive to both genetic and environmental risks for SMI. UK Biobank sample of $N = 17,053/19,265$ M/F (age = 64.8 ± 7.4 years) and an independent sample of SSD patients and controls ($N = 115/111$ M/F, age = 35.2 ± 13.4) were used to test this hypothesis. UKBB participants with MDD had significantly higher RVI-MDD (Cohen's $d = 0.20$, $p = 1 \times 10^{-23}$) and PRS-MDD ($d = 0.17$, $p = 1 \times 10^{-15}$) than nonpsychiatric controls. UKBB participants with BD and SSD showed significant elevation in the respective RVIs ($d = 0.65$ and 0.60 ; $p = 3 \times 10^{-5}$ and $.009$, respectively) and PRS ($d = 0.57$ and 1.34 ; $p = .002$ and $.002$, respectively). Elevated RVI-SSD were replicated in an independent sample ($d = 0.53$, $p = 5 \times 10^{-5}$). RVI-MDD and RVI-SSD but not RVI-BD were associated with childhood adversity ($p < .01$). In nonpsychiatric controls, elevation in RVI and PRS were associated with lower cognitive performance ($p < 10^{-5}$) in six out of seven domains and showed specificity with disorder-associated deficits. In summary, the RVI is a

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novel brain index for SMI and shows similar or better specificity for SMI than PRS, and together they may complement each other in the efforts to characterize the genomic to brain level risks for SMI.

KEYWORDS

big data, DTI, ENIGMA, meta-analysis, RVI, structural deficit patterns

1 | INTRODUCTION

Major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia spectrum disorder (SSD) are among the most common severe mental illnesses (SMI) that inflict a tremendous burden on patients, their families, and society. The genetic and brain imaging findings in SMI have historically suffered from heterogeneity and poor reproducibility, but more recent large-scale studies have derived replicable patterns of deficits (Ioannidis, 2014; Kochunov, Hong, et al., 2020; Kochunov, Thompson, & Hong, 2019). In genetics, findings from large meta-analyses have led to a shift from candidate gene research where findings often failed to replicate, toward well-powered genome-wide association studies (GWAS) that produced robust and reproducible patterns of risk alleles (Bosker et al., 2011; Farrell et al., 2015). Polygenic risk scores (PRS) were developed to utilize these genome-wide risk alleles for defining individual person's risk to a disorder, calculated as the linear combination of the risk alleles of an individual weighted by degree to which the alleles show case-control differences in large-scale meta-analytic studies for a specific illness of interest. PRS has been shown to be a more reproducible predictor of genetic risks and to have higher effect sizes than single risk allele for all three SMI (Choi et al., 2018; Colodro-Conde, Couvy-Duchesne, Whitfield, et al., 2018; Kochunov, Huang, et al., 2019; Liebers et al., 2016; Touloupoulou et al., 2018). Moreover, variance of PRS has also been associated with brain integrity and cognitive performance in both SMI patients and healthy controls (Choi et al., 2018; Colodro-Conde, Couvy-Duchesne, Whitfield, et al., 2018; Kochunov, Huang, et al., 2019; Liebers et al., 2016; Sabuncu et al., 2012; Touloupoulou et al., 2018).

In parallel, large-scale neuroimaging initiatives, including studies performed by the Enhancing Neuro Imaging Genetics through Meta Analyses (ENIGMA) consortium (Kelly et al., 2018; Schmaal et al., 2016; Schmaal et al., 2017; van Erp et al., 2016, 2018) identified highly reproducible structural deficit patterns across the brain, using large, ethnically, and geographically diverse cohorts (Alnaes et al., 2019; Kochunov et al., 2017; Kochunov, Fan, et al., 2020; Kochunov, Thompson, & Hong, 2019; Koshiyama et al., 2019; Okada et al., 2016). To extend these findings to individual level, we proposed a regional vulnerability index (RVI), to parallel the PRS, to quantify the agreement between an individual's structural pattern across brain regions and the expected regional structural pattern for a disorder as established by ENIGMA (Kochunov, Fan, et al., 2020; Kochunov, Hong, et al., 2020). In SSD, RVI was found to be more robust and reproducible than any single regional measurement and was predictive of cognitive performance in modest samples of schizophrenia patient

(Kochunov, Fan, et al., 2020; Kochunov, Hong, et al., 2020), although no PRS were available for comparison in those studies. Here, we proposed a direct comparison of the power and the implications of the brain-wide RVI approach versus the genome-wide PRS approach in identifying overlap versus separation of diagnostic and cognitive indices among the three major SMI.

We hypothesized that RVI and PRS can be complementary in understanding the genome-brain-illnesses axis as both indices circumvent the traditional individual region/locus approaches by utilizing the whole-brain/whole-genome disease pattern information. Specifically, RVI may serve as an intermediate phenotype in gene-brain-illnesses axis. RVI is measure of alignment between the phenotypic pattern in an individual and the expected pattern in a disorder based on large and inclusive meta-analyses. Therefore, RVI is likely to be sensitive to both genetic and environmental effects on the brain and thus may be more robust for identifying disease-related features than PRS alone. To test this, we compared RVI and PRS approaches in relation to (1) detecting case-control differences, (2) specificity across SMI, (3) association with developmental risk factors, and (4) cognitive function, including in unaffected controls. We used the UK Biobank (UKBB) cohort because it is the largest publicly available dataset with both genome-wide genetic data and high-quality brain MRI scans. To further test their relative specificity, we also examined how RVI versus PRS can separate SMI from classic neurological illnesses using Alzheimer disease (AD) as an example. Importantly, RVI and PRS differ in methodological details and biological interpretation (details see Section 2). The PRS is fundamentally a genetic risk factor, while the RVI measures the imaging phenotypic similarity to the illness-related brain pattern. Therefore, RVI is hypothesized to be aggregates of the consequences from both genetic and developmental risk factors on the brain. Accordingly, we tested the hypothesis that RVI would also be significantly influenced by both PRS and environmental risks for SMI, while PRS should not be related to environmental risks.

Finally, although SMI are diagnosed based on symptomatology, cognitive deficits are prominent in many SMI patients and are closely associated with their functional disability (Bowie et al., 2010). Genotypic similarity to SMI as captured by PRS can predict cognitive performance even in controls without psychiatric diagnoses (Liebers et al., 2016). Accordingly, we hypothesized that RVI and PRS derived from SMI can explain individual differences in cognitive performance in this large general population sample even without SMI diagnoses. The overall aim was to examine to what extent RVI can be used as a PRS analog for brain imaging data, and whether a combination of RVI and PRS may provide an even more powerful approach than PRS

alone to aid our understanding of the genetic and neurobiological underpinnings of SMI.

2 | METHODS

2.1 | Participants

2.1.1 | UKBB sample

Clinical, cognitive and neuroimaging data were available for $N = 36,318$ individuals (17,053/19,265 M/F). We used the UKBB parser software (https://github.com/USC-IGC/ukbb_parser) to identify $N = 3920$ (1380 M/2540 F, age = 62.1 ± 7.4) subjects with ICD codes corresponding to three SMI diagnoses (Table 1) who were free from other neurological or psychiatric conditions besides a self-reported *anxiety disorder*. Among participants with self-reported and ICD codes for psychiatric illness, we identified $N = 3853$ (1346 M/2507 F, age = 62.1 ± 7.4 years) with a lifetime diagnosis of MDD, $N = 56$ with BD (28 M/28 F, age = 62.6 ± 7.2), and $N = 11$ for SSD (6/5 M/F, age = 65.1 ± 7.1). For psychiatric versus neurological illness specificity testing, we identified $N = 13$ with AD (9/4 M/F, age = 71.0 ± 4.6) available in the UKBB dataset. A total of 24,538 individuals (11,164/13,374 M/F, age = 63.3 ± 7.5) in the overall sample were free of ICD codes of neurological or psychiatric illnesses including MDD, BD, SSD, anxiety, AD, head trauma, stroke, Parkinson disease, post-traumatic stress disorder, meningitis, multiple sclerosis, migraines, and other demyelinating diseases were treated as non-neuropsychiatric controls (Table 1). PRS analyses were limited to the sample of $N = 24,141$ (10,967/13,274 M/F) of Caucasian descent, because of the known biases in applying PRS estimates if combining groups of different ancestry (Landi et al., 2021; Mather & Thalamuthu, 2020). Data were collected between 2012 and 2019 in participants recruited in the United Kingdom (Manolio et al., 2012; Table 1). All participants provided written informed consent.

2.1.2 | SSD replication sample

Because SSD was only present in 11 UKBB participants, we further compared RVI-SSD and PRS-SSD in an independent local sample of $N = 63$ patients (age = 34.2 ± 11.1 ; 39 M/24 F) and $N = 163$ controls

(age = 35.5 ± 14.2 ; 76 M/87 F) of European ancestry collected at the Maryland Psychiatric Research Center, with both imaging and genetic data available. All participants had no current or past neurological conditions or major medical conditions. Patients were diagnosed with either DSM-IV schizophrenia or schizoaffective disorder. Controls had no Axis I psychiatric disorder. All participants with SSD were evaluated for their capacity to provide informed consent. All participants gave written informed consent as approved by the University of Maryland, Baltimore, Institutional Review Board.

2.2 | Imaging protocols and processing

In the UKBB sample, we examined regional cortical gray matter thickness, subcortical gray matter structural volume and tract-wise measures of fractional anisotropy (FA) values provided by the UKBB (see Appendix S1). These phenotypes were extracted from neuroimaging data collected with Siemens Skyra 3T scanner using a 32-channel head coil. It included T1-weighted 3D MP-RAGE scans (resolution = $1 \times 1 \times 1$ mm, FOV = $208 \times 256 \times 256$, duration = 5 min, sagittal, in-plane acceleration iPAT = 2, prescan-normalize). Diffusion data were collected with a resolution of $2 \times 2 \times 2$ mm and two diffusion shells of $b = 1000$ and 2000 s/mm² with 50 diffusion directions per shell and 5 $b = 0$ images (FOV = $104 \times 104 \times 72$, duration = 7 min).

The SSD replication sample was collected using a Siemens Trio 3T scanner equipped with a 32-channel head coil. T1-weighted data were collected at $0.8 \times 0.8 \times 0.8$ mm resolution (matrix = 320×320 , 224 sagittal slices, TR = 2300 ms, TE = 3.14 ms, TI = 900 ms, flip angle = 9° , iPAT = 2), using a dedicated motion corrected protocol (Kochunov et al., 2006). DTI data was collected using a gradient echo sequence with a spatial resolution of $1.7 \times 1.7 \times 3.0$ mm. The sequence parameters were: TE/TR = 87/8000 ms, FOV = 200 mm, axial slice orientation with 50 slices and no gaps, 64 isotropically distributed diffusion weighted directions, 2 diffusion weighting values ($b = 0$ and 700 s/mm²) and 5 $b = 0$ images.

2.3 | RVI calculations

The RVI uses effect sizes from independent case-controls imaging meta-analyses that established stable deficit patterns for that illness.

TABLE 1 Demographic information for the UKBB sample analyzed in this research

Group	Full sample		Caucasian only	
	N (male/female)	Average age \pm SD	N (male/female)	Average age \pm SD
SSD	11 (6/5)	65.1 ± 7.1	8 (4/4)	65.4 ± 5.9
BD	56 (28/28)	62.6 ± 7.2	45 (24/21)	63.1 ± 7.4
MDD	3853 (1346/2507)	62.1 ± 7.4	3316 (1201/2115)	62.3 ± 7.5
Total SMI	3920 (1380/2540)	62.1 ± 7.4	3369 (1229/2240)	62.2 ± 7.5
AD	13 (9/4)	71.0 ± 4.6	12 (9/3)	70.6 ± 4.5
Controls	24,538 (11,164/13,374)	63.3 ± 7.5	20,772 (9738/11,034)	63.4 ± 7.4

Here, we used imaging deficit patterns for MDD, BD, and SSD reported by ENIGMA. UKBB imaging data were processed using the UKBB workflow that is based on ENIGMA imaging processing pipelines. Briefly, the UKBB workflow provides brain imaging measurements that included 24 regional white matter tract FA values, 33 regional estimates of cortical gray matter thickness, volumes of the lateral ventricles, and 7 subcortical gray matter volumes per hemisphere that corresponded to those derived by ENIGMA workflows. Measures from the left and right structures were averaged. Details of the image preprocessing and analysis are provided by UKBB (biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf). The SSD replication sample data were processed using the ENIGMA-structural and DTI analysis pipelines (<http://enigma.ini.usc.edu/protocols/>), which includes quality control and assurance QC/QA steps (Jahanshad et al., 2013).

RVI scores were calculated using the brain-wide structures from cortical, subcortical, and white matter assessments based on the protocol documented in Kochunov, Zavaliangos-Petropuli, et al. (2020) using the “RVlpgk” in [R] software. Briefly, the effects of age, sex, the intracranial volume, and scanning site were regressed out from the imaging phenotypes and then transformed to z scores based on the average and SD of the controls. The Pearson's correlation coefficient was then calculated between a participant's z scores and corresponding effect sizes for patient–control group differences recorded by the ENIGMA consortium in MDD, BD, SSD, and effect size for AD reported by ADNI. The RVI values were then Fisher's z transformed to enhance normality. Both RVI and PRS can be thought of in terms of vector algebra. RVI is methodologically equivalent to the cosine of the angle in the multidimensional phenotype space between a vector of an individual subject and the vector of effect sizes for an illness.

2.4 | Genetic data

UKBB provided the whole genome association study (GWAS) data collected using Affymetrix UK BiLEVE Axiom array that included 850,000 genotyped variants. The protocol may be found in the UKBB Quality Control Documentation (https://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web-1.pdf). Briefly, low-quality single nucleotide polymorphisms (SNP) were filtered out according to Affymetrix recommendations. SNP variants were imputed with a merged UK10K and 1000 Genomes Phase 3 reference panel by a group headed by the Wellcome Trust Centre for Human Genetics using the IMPUTE3 program. All of these steps are detailed in the Imputation Documentation (https://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/imputation_documentation_May_2015-1.pdf).

The SSD replication data was genotyped using Illumina Omni2.5-8 BeadChip. The UKBB imputation steps were followed. Post-imputation quality control consisted of filtering SNPs based on minor allele frequency (MAF) (<0.01), Hardy–Weinberg Equilibrium ($<1 \times 10^{-6}$), R^2 ($<.03$), and call rate (<0.95).

2.5 | PRS analysis

In both samples, the PRS analyses were limited to Caucasian participants, based on genetic grouping provided by the UKBB (Table 1) because PRS calculation algorithms were developed from the large genetic association studies that were performed in people of Caucasian ancestry (see below; Curtis, 2018). The PRS for MDD, BD, SSD, and AD were calculated using PRSice software and the most recent GWAS summary statistics available to download from the Psychiatric Genomics Consortium (PGC) (<https://www.med.unc.edu/pgc/download-results/>). None of SMI GWAS summary statistics included the UKBB subjects. The SSD PRS summary statistics in Ripke et al. (Schizophrenia Working Group of the Psychiatric Genomics, 2014) were calculated from a sample of $N = 152,805$ (38,131 SSD/114,674 controls) including data from 52 PGC-SSD studies. For the BD PRS, the discovery GWAS meta-analysis summary statistics (Mullins et al., 2021) were calculated from cohorts in Europe, North America and Australia, including PGC-BD working groups, the Integrative Psychiatric Research group and deCODE genetics for a total sample of $N = 41,917$ BD and 371,549 controls of European ancestry. The summary statistics used in the MDD PRS were from the PGC study by Howard et al. (2019) and contained data from PGC-MDD USA and European sample sites, the deCODE genetics, Generation Scotland, Genetic Epidemiology Research on Adult Health and Aging, and iPSYCH datasets. When combined, this resulted in $N = 138,884$ (43,204 MDD/95,680 controls) participants of European descent. The AD summary statistics published by Jansen et al. (2019) and downloaded from the Center for Neurogenomics and Cognitive Research Complex Trait Genetics Lab GWAS summary statistics (https://ctg.cnr.nl/software/summary_statistics), were compiled from three PGC Alzheimer working groups in European twin datasets (DemGene, TwinGene, and Swedish Twin Studies of Aging), the International Genomics of Alzheimer Project, the Alzheimer Disease Sequencing Project, and the UKBB AD-by-proxy data, which identified parental AD status weighted by age, for a total of $N = 455,258$ (47,793 AD/AD-by proxy/383,378 controls) individuals of European descent. More information on the GWAS summary statistics can be found in the Methods S1. SNPs were clumped according to PRSice, and thresholds for significantly associated SNPs were set at $p = .05$. The PRS can be approximated using vector algebra as a dot product between a vector representing an individual genotype and the meta-analytical effects from case–control studies weighted by the expected minor allele frequency (MAF). The PRS scores are unnormalized and because MAF varies by ethnicity, the PRS analyses in multiethnic studies can be heavily biased by ethnic stratification. Therefore, the PRS analysis was restricted to Caucasian samples because the above-mentioned, meta-analytical GWAS effect sizes for calculating PRS were only available in Caucasians. In ad-hoc analyses we calculated PRS scores for other ethnicities and as expected, these scores showed significant ($p = 10^{-8-75}$) differences among ethnic lines. For the sake of comparing with RVI, the PRS results in a full sample showed significant reduction in the effect sizes compared with Caucasians, even after correcting for ethnic stratification by using first 10 principle components of the genetic data as a covariate, thus emphasizing this important caveat of the PRS approach.

2.6 | Environmental risks: Childhood development

Some SMI are known to have strong environmental contributions, and developmental risks during childhood are typically the most relevant (Anglin et al., 2021; Barzilay et al., 2019; Colodro-Conde, Couvy-Duchesne, Zhu, et al., 2018; Grattan et al., 2019; Kvarita et al., 2021). UKBB participants completed an adverse childhood experiences (ACEs) survey that was measured by five items adapted from the Childhood Trauma Screener (CTS; Glaesmer, 2016). The five ACEs items were summed, resulting in a total score ranging from 0 to 20.

2.7 | Cognitive assessment

UKBB participants completed the cognitive battery on a touchscreen computer (Sudlow et al., 2015). We used nine tests in the current study, covering cognitive domains of processing speed, cognitive flexibility, working memory, visuospatial learning/memory, perceptual reasoning, executive functioning/planning, and fluid intelligence (Table S1). As the UKBB cognitive tests were unsupervised, we followed the suggested quality control steps to enhance validity (Sudlow et al., 2015; Table S1).

2.8 | Statistics

All statistical analyses were performed using RStudio v3.6.3 [71]. All measurements were preprocessed by regressing age and sex prior to analyses. The effect sizes were computed using the *effectsize* package [72]. The group-wise comparisons in RVI and PRS were performed using Student's *t*-test using Bonferroni correction for multiple comparisons.

The effects of genetics (PRS) and developmental environment (adverse childhood events or ACEs) on RVI were evaluated using Model 1:

$$\text{RVI} \sim \beta_{\text{PRS}} \cdot \text{PRS} + \beta_{\text{ACEs}} \cdot \text{ACEs} + \beta_{\text{PRS} \times \text{ACEs}} \cdot \text{PRS} \cdot \text{ACEs} \quad (\text{Model 1})$$

The relative effects of RVI and/or PRS on cognition were tested using Model 2.

$$\text{Cognition} \sim \beta_{\text{RVI}} \cdot \text{RVI} + \beta_{\text{PRS}} \cdot \text{PRS} \quad (\text{Model 2})$$

Model 2 examined whether being merely similar to SMI in genetics and/or brain deficit patterns in non-neuropsychiatric controls, even when there was no SMI diagnosis, could still be associated with poorer cognitive performance. This approach also avoided the potential biases associated with possible secondary effects of disorders and psychotropic medications on cognitive performance in participants diagnosed with SMI. However, we also explored this effect in SMI patients. We used Bonferroni approach throughout the study to correct for multiple comparisons.

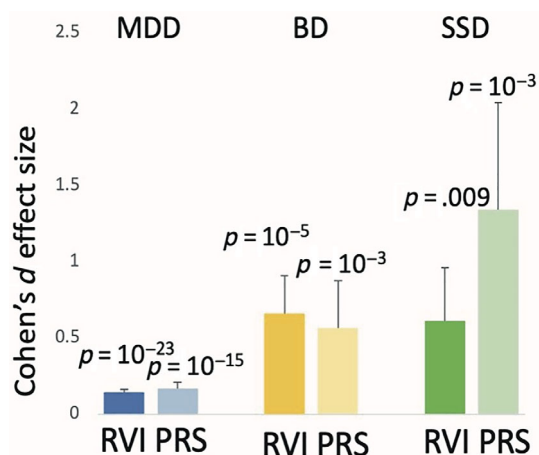


FIGURE 1 Absolute values for effect size comparisons of RVI and PRS among the three severe mental illnesses—comparing cases to non-neuropsychiatric controls. Raw values are shown in Figure 2. BD, bipolar disorder; MDD, major depressive disorder; PRS, polygenic risk score; RVI, regional vulnerability index; SSD, schizophrenia spectrum disorder. The *p* values are based on statistical comparisons to controls. Error bars denote SE. The *p* values are very different between diagnoses likely due to their different sample sizes; *p* values are comparable between RVI and PRS within diagnosis.

3 | RESULTS

3.1 | Effect sizes of SMI on RVI versus PRS

Compared with non-neuropsychiatric controls, participants with each of the three SMI, that is, MDD, BD, and SSD, had significantly elevated RVI for the respective disorder (Cohen's $d = 0.20, 0.65, \text{ and } 0.61; p = 10^{-23}, 3 \times 10^{-5}, \text{ and } .009$, respectively; Figure 1). Caucasian and non-Caucasian participants were not significantly different in the frequency of disorder versus control groups in any SMI ($t = 1.8, 0.95, \text{ and } 1.2$, all $p > .06$ for MDD, BD, and SSD). Likewise, there were no significant difference between Caucasian and non-Caucasian participants for RVI for each of the SMI ($t = 0.09, 0.19 \text{ and } 0.28$, all $p > .5$ for MDD, BD, and SSD, respectively). Therefore, RVI analyses were performed in the full sample.

The PRS (in Caucasians) for all three SMI were significantly elevated in participants with the respective illnesses compared with non-neuropsychiatric controls ($d = 0.17, 0.56 \text{ and } 1.34, p = 10^{-15}, .002, \text{ and } .002$, for MDD, BD, and SSD, respectively; Figure 1).

Comparing RVI and PRS, there were no significant differences in the magnitude of effect sizes between the measures for respective disorders (all $z < 1.5; p > 0.2$), suggesting that RVI as a brain vulnerability index has similar power to PRS as a genetic vulnerability index in separating patients from controls for each SMI (Figure 1).

3.2 | RVI versus PRS disease specificity among the SMI

RVI values for controls were not significantly different from zero for any of the three SMI RVIs (all $p > .7$; Figure 2a–c). The highest RVI-

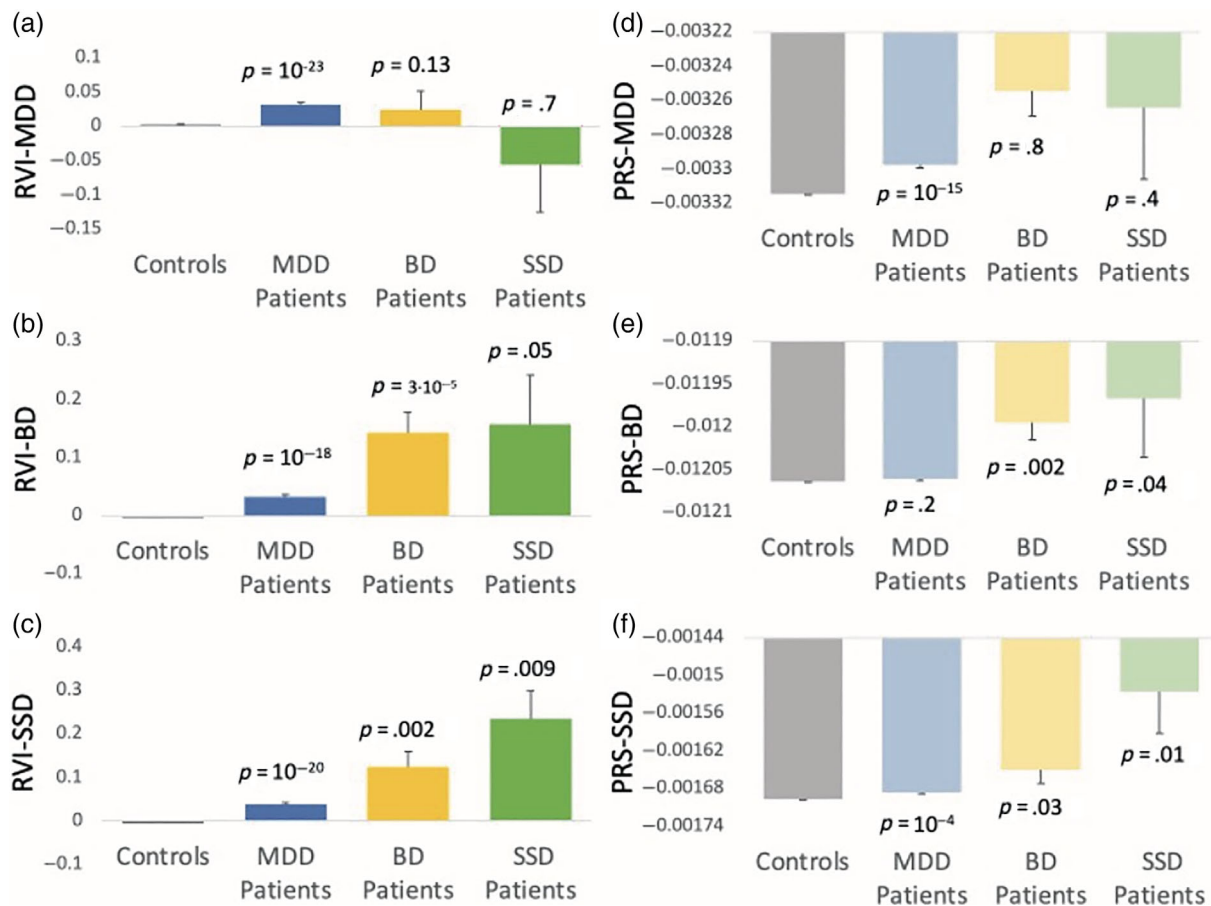


FIGURE 2 A cross-disease comparison of disease-specific regional vulnerability index (RVI) values and polygenic risk score (PRS) values among the three severe mental illness and control participants. (a–c) RVI comparisons across the four groups. (d–f) PRS comparisons across the four groups. The p values are significance levels for the statistical comparisons with controls. Error bars denote SE.

MDD was observed in participants with MDD (0.032 ± 0.001), followed by BD (0.025 ± 0.03) and SSD (-0.023 ± 0.05) (Figure 2a). The highest RVI-BD was observed among participants in SSD rather than BD, ranked from SSD (0.16 ± 0.03), BD (0.13 ± 0.09) to MDD (0.039 ± 0.003) (Figure 2b). The highest RVI-SSD was observed in SSD (0.15 ± 0.08) and this was higher than BD (0.13 ± 0.03) and MDD (0.028 ± 0.005) (Figure 2c). For patients with each illness, the RVI for that illness always showed significant differences from controls.

Controls showed the lowest PRS scores (more negative) in all SMIs (Figure 2d–f). The highest PRS-MDD score was observed in participants with BD followed by SSD, paradoxically with MDD being the least (Figure 2d). The highest PRS-BD score was found in SSD rather than BD, followed by BD and MDD (Figure 2e). However, the highest PRS-SSD was found in SSD followed by BD and MDD (Figure 2f). Overall, RVI and PRS appeared similar as they both can significantly separate SMI patients from controls, although their capacity for between-SMI separation was limited, with PRS performing worse.

3.3 | Comparisons of RVI versus PRS in separating a neurological condition from SMI

UKBB participants with AD showed significantly elevated RVI-AD compared with controls ($d = 1.37$; $p = 10^{-6}$) (Figure 3a). Participants with AD had numerically higher RVI-AD than RVI for each of the three SMI (Figure 3a,b). In comparison, PRS-AD scores did not reach significant difference compared with controls ($d = 0.33$, $p = .3$) (Figure 3a, c), overall suggesting that RVI was more robust than PRS when it comes to separating SMI from AD.

3.4 | RVI and PRS in SSD replication sample

Compared with non-neuropsychiatric controls, participants with SSD also had significantly elevated RVI-SSD ($p = 5 \times 10^{-5}$), which were not significantly different from those observed in UKBB sample (Cohen's $d = 0.53$ vs. UKBB 0.61; effect size d comparison: $Z = 0.6$, $p > .1$) (Figures S2). Participants with SSD also showed the highest

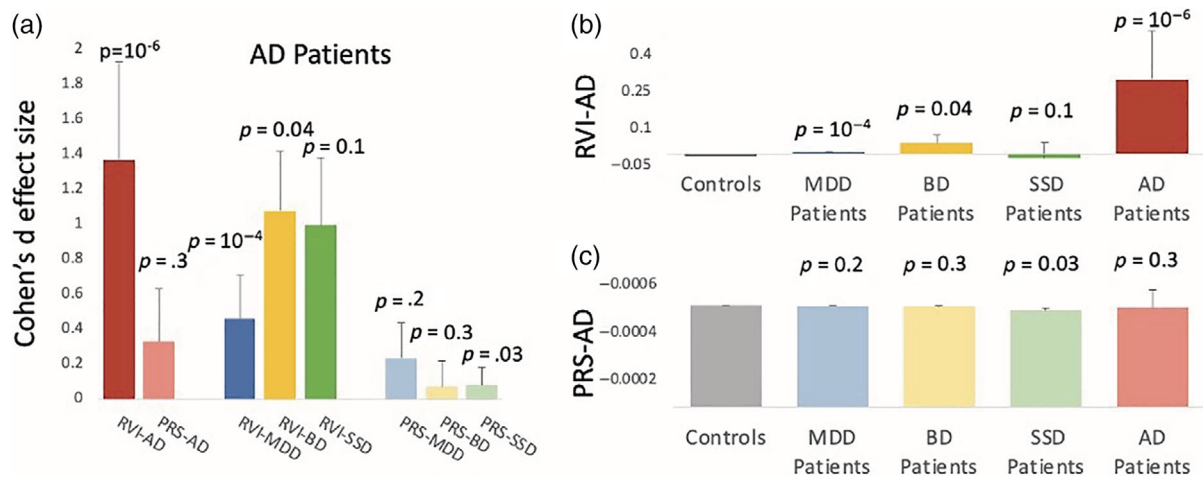


FIGURE 3 A comparison of the effect sizes for RVI and PRS values in UKBB participants with Alzheimer disease (AD). (a) RVI-AD had larger effect size than RVI-PRS compared with controls, while both RVI-AD and PRS-AD had larger effect sizes than RVI and PRS of any SMI. (b,c) A comparison of control, SMI, and AD participants on RVI-AD (b) and PRS-AD value (c). The p -values are based on statistical comparisons with controls. Error bars denote SE.

TABLE 2 The results of fitting Model 1 to evaluate the effects of genetics (PRS) and developmental environment (adverse childhood events: ACEs) on RVI for three the SMI

RVI	Full model	ACE	PRS	ACE × PRS
RVI-MDD	$F = 6.3, p = .002$	$t = 4.1, p = 7 \times 10^{-4}$	$t = 1.1, p = .3$	$t = 0.4, p = .6$
RVI-BD	$F = 1.9, p = .3$	$t = 1.5, p = .1$	$t = 0.2, p = .8$	$t = 0.3, p = .7$
RVI-SSD	$F = 8.6, p = 1 \times 10^{-5}$	$t = 1.9, p = .03$	$t = 3.7, p = 1 \times 10^{-4}$	$t = 0.2, p = .9$

Note: Bold values are significant after correcting for multiple comparisons

RVI-SSD compared with RVI-BD, MDD, and AD (Cohen's $d = 0.45$, 0.46 , and 0.37 , respectively) versus controls that were also comparable with UKBB findings. In comparison, these SSD participants did not show significant elevation in PRS-SSD scores ($d = 0.20$) or PRS scores for BD and MDD (0.24 and 0.08 , respectively) compared with controls (all $p < .1$), where the highest PRS scores were PRS-BD rather than PRS-SSD. Overall, the replication sample further suggests that the RVI findings were replicable while the PRS findings appeared more variable and less specific.

3.5 | Contribution of genetic and environmental risks to RVI

We used Model 1 to test the hypothesis that RVI as a brain anatomic vulnerability index is sensitive to both genetic and environmental risk factors in the combined UKBB sample. The ACE was the only significant predictor for the RVI-MDD model (Table 2). The RVI-BD model was not significant. For RVI-SSD, both PRS and ACE were significant and positive contributors to RVI-SSD (Table 2). In no models did we find a significant gene × environment interaction on RVI. Importantly, the adverse childhood event (ACE) score was not significantly correlated with any of the PRS scores (all $p > .1$), consistent with the environmental nature of these events.

Fitting Model 1 separately in patients with SMI and controls, we found that the model was not significant in combined SMI patients or any of the SMI separately. This may be due to the small sample sizes for these analyses. In controls, RVI-MDD showed only association with ACEs ($t = 2.9, p = .003$); RVI-BD was not significant; and the RVI-SSD showed significant associations with both PRS-SSD ($t = 3.6, p = 3 \times 10^{-4}$) and ACEs ($t = 3.8, p = 2 \times 10^{-4}$), suggesting that findings of ACE effects on RVI-MDD and genetic plus ACE effects on RVI-SSD were primarily driven by findings in non-neuropsychiatric controls. PRS-AD ($t = 3.5, p = 4 \times 10^{-5}$), but not ACEs ($t = 1.1, p = .2$), was a significant predictor of RVI-AD.

3.6 | Effects of RVI and PRS on cognition

SMI are known to be associated with cognitive impairments, and these cognitive deficits are present in the UKBB sample: individuals with SMI showed significantly poorer performance across the available cognitive tasks (Figure S3). For the majority of the tasks, the ranking of effect sizes of the impairment compared with controls followed the order of SSD > BD > MDD (Figure S3). If RVI and PRS are to be used as vulnerability markers in the general population, we hypothesized that being similar to SMI's brain and/or genetic patterns may be associated with impaired cognitive performance even when

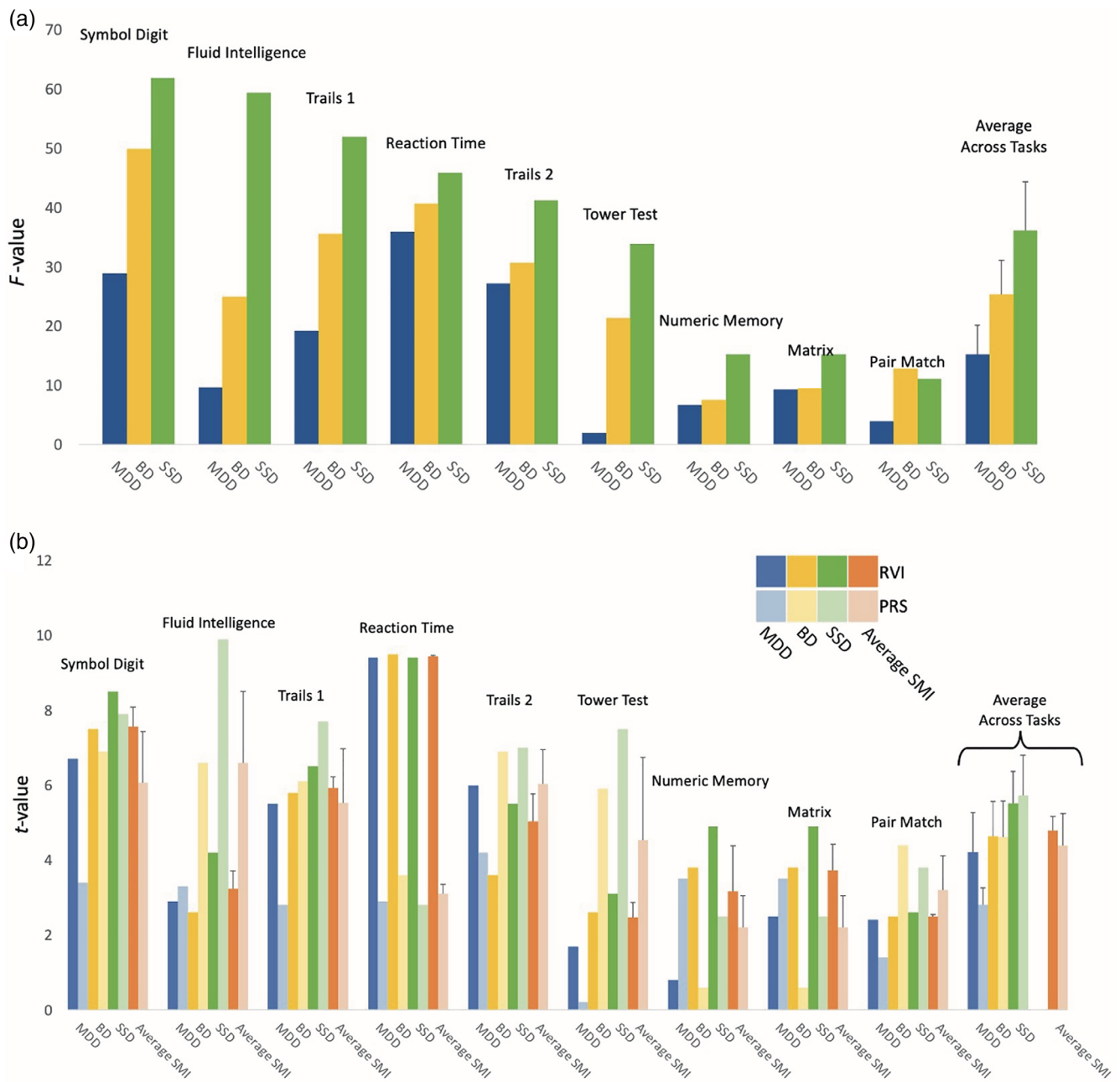


FIGURE 4 Contributions of RVI and PRS on cognition. (a) The model strength (*F*-values) of RVI and PRS association with cognition in non-neuropsychiatric controls. (b) The predictive strength (*t*-values) of RVI versus PRS association with cognition in non-neuropsychiatric controls. All comparisons are significant except the Tower test in MDD patients (Table S2). Error bars denote SE (for averaging the *F* or *t* values across the models, tasks, and/or disorders).

there is a lack of the symptoms necessary to make SMI diagnoses. Model 2 was used to test this, and we found that the model was significant for all but one cognitive measure for each SMI's RVI/PRS combination (Figure 4, Table S3).

The most robust models were observed for the Digit Symbol Substitution (for processing speed) and the Fluid Intelligence tests where RVI- and PRS-SSD were significant predictors ($F = 61.9$ and 59.4 , respectively, Figure 4a). Across all cognitive tests, brain and genetic similarities with SSD were associated with the highest model strength

($F = 37.3 \pm 6.5$), followed by BD (25.8 ± 4.8), while similarity to MDD had lower model strength ($F = 15.8 \pm 4.1$), all of which were statistically significant (Figure 4a), indicating that cognitive deficit severity levels known to be found in SMI patients, that is, $SSD > BD > MDD$, are also observed even in healthy controls, based on the corresponding whole-brain brain plus genomic vulnerability index.

The relative contributions from RVI and PRS were shown in Figure 4b. Overall, RVI and PRS showed similar strength of association with cognitive performance (Figure 4b, last panel). However, there

were task-specific contrasts. For instance, reaction time was explained more by RVI of all SMI, while Fluid Intelligence was explained more by PRS, specifically PRS-SSD. Again, RVI and PRS for SSD explained variance better across cognitive measures compared with BD and MDD. Additional analyses of RVI and PRS for AD were provided in the Table S3, where the highest associations were found in reaction time ($F = 24.1$, $p = 3 \times 10^{-10}$) followed by Digit Symbol test ($F = 21.2$, $p = 7 \times 10^{-10}$). In the case of AD, most of the variance on cognition was explained by RVI rather than PRS-AD (Table S3).

4 | DISCUSSION

The RVI was developed to define brain vulnerability based on the similarity in phenotypic patterns to those observed in the SMI. RVI was tested in the largest available imaging and genetics dataset by comparing to the PRS. Overall, with a few notable exceptions, the RVI was similar and complementary to PRS (1) in separating participants with SMI from non-neuropsychiatric controls, (2) in explaining disease specificity among SMI, and (3) in predicting cognitive performance in a nonpsychiatric population.

Both RVI and PRS showed similar effect sizes in separating participants with SMI from controls in the UKBB sample. The participants with MDD showed the smallest effects for both RVI and PRS and progressively higher effect sizes were observed for BD and SSD. As the UKBB sample contains only a few participants with SSD, we retested the hypothesis in another sample and found that the RVI-SSD effect sizes observed in UKBB were replicated in this independent sample of SSD patients. The differences in effect sizes among SMI approximate the clinical severity of these SMI where SSD is usually the most disabling, followed by BD and MDD. The results suggest a possibility that RVI based brain-wide indices can be as powerful as the PRS based genome-wide indices for individual-level clinical characterizations.

On specificity, MDD and SSD participants had the highest RVI scores for the respective illnesses. In the SSD replication sample, RVI-SSD also showed the largest effect size in SSD patients compared with RVI-MDD or RVI-BD. For PRS, the highest scores for MDD and BP were not found in the respective illnesses; and although the highest PRS scores for SSD were found in SSD patients in the UKBB sample, although even this was not replicated in the SSD replication sample. In this regard, the RVI performed better for SMI disorder-related specificity. However, neither RVI nor PRS achieved optimal performance, as even for RVI, the highest RVI for BD were not observed in participants with the corresponding illness and the separations between some of the RVI values were small. For instance, subjects with BD had significant elevation in RVI-SSD and subjects with SSD showed significantly higher RVI-BD. This finding supports the long going discussion on the continuum of mental illness versus existing of distinct diagnostic categories. The cross-elevation of RVI for subjects with mental illness, especially between SSD and BD, parallels the findings of overlap in risk factors and genetics of two illnesses (Lichtenstein et al., 2009; Purcell et al., 2009), and the patterns brain

structural deficits (Anderson et al., 2013; Hulshoff Pol et al., 2012; McIntosh et al., 2008; Rimol et al., 2010; Squarcina et al., 2017).

We further used a common neurological brain illness AD as a “positive control” comparison to evaluate specificity of RVI and PRS. The UKBB AD participants had the highest RVI- and PRS-AD compared with SMI patients or controls, although RVI provided more robust separation from controls than PRS (Figure 3). While AD patients also had elevated RVI and PRS for SMI, there were numerically smaller than RVI and PRS for AD. These data support RVI and PRS's disease specificity beyond SMI. As the sharing of the underlying neurodegeneration mechanism in mental disorders and AD has been debated since Kraepelin's definition of schizophrenia as *dementia praecox*, or premature dementia (Hippius & Neundorfer, 2003), the elevated RVI-SMI (Figure 3a) and to an even smaller extent the elevated RVI-AD in SMI (Figure 3b) may suggest some similarities in deficit patterns, including deficits in the temporal and parietal regions, hippocampus, and white matter (Crossley et al., 2014; Kochunov, Zavaliangos-Petropuli, et al., 2020) despite many clear differences between SMI and AD. Overall, comparing SMI to neurological illness AD, RVI still showed strong validity and provided similar or better sensitivity and specificity than PRS.

RVI is a phenotypic similarity measure of brain patterns and we hypothesized that RVI may act as an intermediate phenotype in gene-brain-illnesses axis. RVI likely incorporates both genetic and environmental effects on the brain and thus may be more robust for identifying disease-related features versus PRS. RVI-SSD had significant associations with both PRS and adverse childhood events (ACE). SSD is a highly heritable disorder with ~40%–80% of the diagnostic variance explained by additive genetic factors (Hilker et al., 2018; Lee et al., 2013), and has complex environmental risk factors including prenatal and perinatal complications and cumulative developmental and lifetime stress (Anglin et al., 2021; Barzilay et al., 2019; Grattan et al., 2019). The RVI may have captured the brain consequence of the aggregated genetic and early life adversity factors for SSD. In contrast, MDD has low-to-modest heritability (reported h^2 values range from 5% to 50%) and environmental and other etiologies play proportionally more prominent roles (Colodro-Conde, Couvy-Duchesne, Zhu, et al., 2018; Kvarta et al., 2021). This may explain why ACE was the only significant contributor to RVI-MDD. RVI-BD showed no significant association with either PRS-BD or ACE. BD has high genetic contributions—heritability is estimated at 70%–90% (Barnett & Smoller, 2009; Gordovez & McMahon, 2020; Smoller & Finn, 2003). This may explain the lack of significant contributions of childhood adversity but the lack of association with PRS-BD is still unexplained. Finally, AD is known to have a strong genetic component that was confirmed by the significant association between RVI-AD and PRS-AD with no association with childhood adversity.

The extension of the RVI- and PRS to explain potential vulnerabilities in general population was supported by findings of these indices' effects on cognition in nonpsychiatric controls. Cognitive deficits are common and contribute to functional disability in patients with SMI (Sheffield et al., 2018). Higher RVI and PRS were negatively associated with cognitive performance in all nine cognitive measures but with

significant variability across the indices (Figure 4). First, the PRS- and RVI-SSD showed greater predictive power in explaining cognitive variance compared with the BD and MDD indices (the association between MDD and the Tower test was not significant), replicating the clinically observed SSD > BD > MDD cognitive deficit patterns. Cognitive deficits in SSD are persistent and debilitating (Barch & Sheffield, 2014; Fusar-Poli et al., 2012; Semkovska et al., 2019; Sheffield et al., 2018; Terachi et al., 2017), conversely, cognitive deficits in MDD show partial-to-full remission between depressive episodes and cognitive deficits in BD show intermediate findings (Ahern & Semkovska, 2017; Semkovska et al., 2019; Zaninotto et al., 2015). Across the cognitive tasks, RVI- and PRS-SSD explained the most variance in information processing speed and learning tasks: Digit Symbol, Fluid Intelligence, Trails A, and Reaction Time. This mirrors the reports in SSD where lower information processing speed and impaired working memory abilities are the core of cognitive disabilities in SSD (Dickinson et al., 2007; Faraone et al., 2000; Keefe et al., 2005; Keefe et al., 2004; Knowles et al., 2010; Kochunov et al., 2017). Our findings suggest that similarity to the SSD-and other SMI related brain and genetic patterns without SMI diagnoses still confers risk for cognitive deficits. As cognitive performance and brain structures in controls are not affected by psychiatric illness processes or psychotropic medications, these observations further support the validity of RVI in indexing individual level vulnerability by their anatomic similarity to SMI (Liebers et al., 2016). Overall, the brain and genetic signatures for SMI may confer cognitive risks directly, rather than being secondary effects of the active illness.

4.1 | Limitations

RVI is a simple concept that measures the linear similarity between deficit pattern of a given individual to the disruption pattern estimated from an independent case-control comparison. Therefore, it lacks a topographical characterization for detailed brain regions and may ignore heterogeneity across patients with the same disorder. This study should stimulate research into more complex machine learning approaches that could capture nonlinear topography of the effects of illness on the brain. *The UKBB recruitment is biased toward healthy volunteer, reducing the number of participants with SMI as compared with the population prevalence* (Fry et al., 2017). Furthermore, *the diagnostic information provided in UKBB is based on self-report and hospitalization records and maybe susceptible to misclassifications* (Bycroft et al., 2018). These factors likely affected the ability to perform SMI-related comparisons. However, the RVI-SSD findings in UKBB were readily replicated in an independent sample of SSD patients and controls, suggesting that this may not be a critical limitation. The elevated PRS-SSD values failed to reach significance in the replication sample. However, the PRS effect size in that sample ($d = 0.20$) is more similar to d -values reported in the literature for SSD ($d = 0.01-0.4$) (He et al., 2021; Richards et al., 2019; Xavier et al., 2018), suggesting the findings of high PRS for SSD in UKBB maybe an artifact of the small number of SSD patients. Also in the AD group, the patients were

significantly older than the average UKBB age, while the replication sample of SSD were much younger. As such some of the changes in the brain could be attributed to age related changes. The MDD diagnosis group was also not divided into severe and more mild groups for the analyses. Recent studies have found large difference in brain morphology between BD patients with psychosis and without psychosis (Anticevic et al., 2013), indicating a potential avenue of future research in RVI, as it has already proven adept at predicting treatment resistance in SSD. Another important limitation is that PRS analysis was restricted to Caucasians given the ancestry related biases if performed in ethnically diverse cohorts (Chatterjee et al., 2016; Torkamani et al., 2018). There is a need to assemble large non-Caucasian samples to validate these observations across ethnicities. *In addition, imputation protocols differed between UKBB and replication protocols and this may have affected the calculation of PRS between protocols.* Finally, the proposed validity of RVI in comparison to the widely used PRS must be further tested beyond the cross-sectional data used in this study, for example in longitudinal follow-up and also in other brain diseases.

To summarize, the novel vulnerability construct, the regional vulnerability index, demonstrates the ability to transfer big data neuroimaging findings to the individual level and may play a complementary role to a similar approach in genetics, the polygenic risk score, for characterizing the vulnerability for SMI in both clinical and nonclinical samples. These whole-brain and whole-genome level RVI and PRS indices together should provide an even more powerful tool than PRS alone in our search for the gene-to-brain-to-severe mental illness pathways.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the UK BioBank. Restrictions apply to the availability of these data, which

were used under license for this study. Data are available from at <https://biobank.ndph.ox.ac.uk/showcase/> with the permission of the UK BioBank.

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