

A Brainwide Risk Score for Psychiatric Disorder Evaluated in a Large Adolescent Population Reveals Increased Divergence Among Higher-Risk Groups Relative to Control Participants

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ABSTRACT

BACKGROUND: Accurate psychiatric risk assessment requires biomarkers that are both stable and adaptable to development. Functional network connectivity (FNC), which steadily reconfigures over time, potentially contains abundant information to assess psychiatric risks. However, the absence of suitable analytical methodologies has constrained this area of investigation.

METHODS: We investigated the brainwide risk score (BRS), a novel FNC-based metric that contrasts the relative distances of an individual's FNC to that of psychiatric disorders versus healthy control references. To generate group-level disorder and healthy control references, we utilized a large brain imaging dataset containing 5231 total individuals diagnosed with schizophrenia, autism spectrum disorder, major depressive disorder, and bipolar disorder and their corresponding healthy control individuals. The BRS metric was employed to assess the psychiatric risk in 2 new datasets: Adolescent Brain Cognitive Development (ABCD) Study ($n = 8191$) and Human Connectome Project Early Psychosis ($n = 170$).

RESULTS: The BRS revealed a clear, reproducible gradient of FNC patterns from low to high risk for each psychiatric disorder in unaffected adolescents. We found that low-risk ABCD Study adolescent FNC patterns for each disorder were strongly present in over 25% of the ABCD Study participants and homogeneous, whereas high-risk patterns of each psychiatric disorder were strongly present in about 1% of ABCD Study participants and heterogeneous. The BRS also showed its effectiveness in predicting psychosis scores and distinguishing individuals with early psychosis from healthy control individuals.

CONCLUSIONS: The BRS could be a new image-based tool for assessing psychiatric vulnerability over time and in unaffected individuals, and it could also serve as a potential biomarker, facilitating early screening and monitoring interventions.

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Mental disorders are major contributors to morbidity and mortality, with an estimated 1 in 5 adults in the United States affected (1). Screening high-risk adolescents is an important step toward early-stage intervention. Methods have been developed for decades to quantify the risk of multiple psychiatric disorders. Structured interview-based criteria for clinical high-risk states, such as the Scale of Psychosis-Risk Syndromes (2), are useful for diagnosing prodromal psychosis. The rate of developing psychosis within 2 years of being identified as clinical high risk was estimated at between 20% and 35% in a 2011 meta-analysis (3). Nevertheless, the accuracy of the results is influenced by factors such as the doctor's expertise, language, and culture. In addition, the interview-based criteria are not able to delineate the fundamental mechanisms of

dysfunction. Apart from interview-based criteria, polygenic risk score (PRS) (4) is another widely used metric for psychiatric risk assessment. The PRS is derived from genome-wide association studies' summary statistics, which aggregate and quantify the effects of numerous common genome variants (5). However, these genetic factors contribute only to a small part of the risk, and PRSs capture only part of the genetic contribution (6), causing few reproducible genetic psychiatric risk factors to be identified through linkage analysis, candidate gene analysis, or by genome-wide association studies (7). In addition, the PRS is a static metric that does not capture the changes in brain developmental trajectories that are unique to a child's life circumstances including those that might contribute to psychiatric disorders [i.e., prenatal cannabis exposure (8)].

SEE COMMENTARY ON PAGE e17

An ideal metric for longitudinally assessing psychiatric risk in adolescents should be: 1) reproducible and adaptable to environmental factors, 2) related to the underlying mechanisms of psychiatric disorders, 3) consistent with clinical symptoms, and 4) able to distinguish patients with mental disorders from healthy control participants.

In contrast to the Scale of Psychosis-Risk Syndromes and PRSs, the functional connectivity (or its network analog, functional network connectivity [FNC]) profile from resting functional magnetic resonance imaging (fMRI) data is highly unique but also exhibits temporal variability (9–12), making it a viable option for evaluating the developmental trajectory in adolescents. According to a previous study that utilized data from the Adolescent Brain Cognitive Development (ABCD) Study, the FNC profile was able to identify a particular child from a large group with high accuracy (>90%) (10). FNC also demonstrates excellent capability in identifying mental disorders (13) and predicting clinical symptoms (14). Nevertheless, the application of FNC for assessing psychiatric risk faces several challenges, including small sample sizes and incompatible image-processing pipelines (15,16). In addition, there is evidence indicating that resting-state networks are not confined to specific regions but rather encompass large-scale networks that span the entire brain (17,18). To address the above issues, we propose the use of large clinical cohorts and a standard fMRI processing pipeline (17) that combines a data-driven decomposition adapted to individual participants with a spatial constraint to ensure interparticipant correspondence between networks.

Here, leveraging large population neuroimaging datasets and a standardized image-processing pipeline, we investigated a novel functional imaging-based psychiatric risk assessment system, brainwide risk score (BRS), which contrasts the relative distances of an individual's FNC to that of psychiatric disorders versus healthy control references. To accomplish this, we planned to preprocess all fMRIs using

NeuroMark (17), a fully automated independent component analysis (ICA) pipeline that is robust even when utilizing short data collection times (19). Having derived BRS in the clinical population, we then planned to use it for assessing signatures of psychiatric risk (i.e., functional brain patterns showing more similarity to a chronic patient cohort vs. control groups) in the ABCD Study adolescents. Considering the fact that the images were obtained when the ABCD Study adolescents were between 9 and 13 years of age, too early for the typical emergence of schizophrenia (SCZ) or bipolar disorder (BPD), we also planned to utilize the Human Connectome Project Early Psychosis (HCP-EP) dataset to evaluate the robustness, predictability, and classification performance of the BRS.

METHODS AND MATERIALS

The workflow of the study is illustrated in Figure 1. We utilized fMRI samples from 7 clinical studies ($n = 5231$) of individuals diagnosed with SCZ, autism spectrum disorder (ASD), major depressive disorder (MDD), BPD, and of healthy control participants. fMRIs were analyzed with NeuroMark, a spatially constrained ICA pipeline, to extract FNC features. We then obtained references for a given disorder and its corresponding healthy control group by averaging the FNCs of patients and control participants within each clinical group and computing the difference. Subsequently, the references from each clinical group were compared with the FNC of each individual from the ABCD or the HCP-EP dataset. Specifically, for each individual in the ABCD or HCP-EP dataset, the BRS was determined by calculating the Euclidean distance between their FNC to disorder reference and to the corresponding control reference. A more detailed calculation can be found in the [BRS Calculation](#) section. Further analysis, such as FNC gradient visualization, prodromal score prediction, and early psychosis classification were conducted based on the obtained BRS.

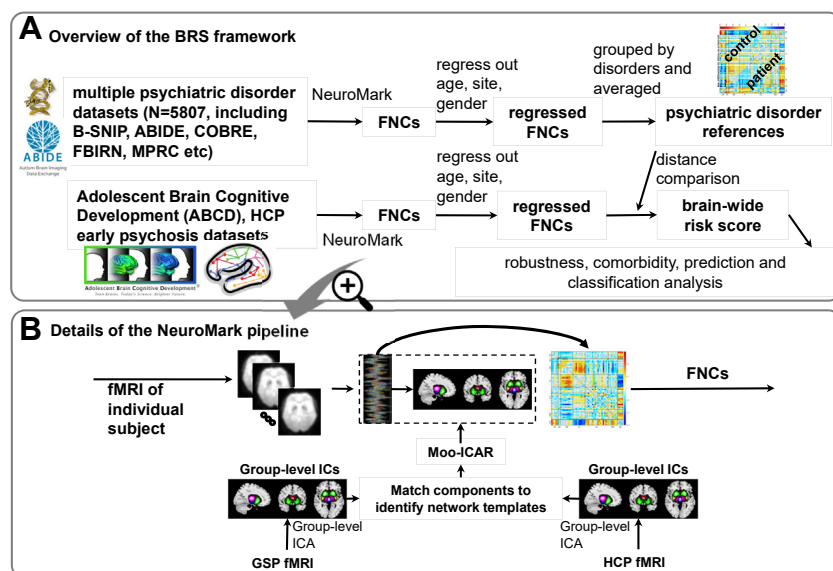


Figure 1. Workflow of the study. **(A)** Psychiatric disorder references were constructed using 7 clinical studies. All functional magnetic resonance images (fMRIs) were processed using NeuroMark to obtain comparable functional network connectivities (FNCs). The FNCs were categorized according to diagnosis and were averaged to build references. After preprocessing, the Adolescent Brain Cognitive Development (ABCD) Study and Human Connectome Project (HCP) Early Psychosis FNCs from individual participants were compared with references to obtain brainwide risk scores. **(B)** Details of the NeuroMark pipeline, which utilizes a spatially constrained independent component analysis (ICA) approach to generate comparable and reproducible FNCs. ABIDE, Autism Brain Imaging Data Exchange; B-SNIP, Bipolar & Schizophrenia Network on Intermediate Phenotypes; COBRE, Center for Biomedical Research Excellence; FBIRN, Function Biomedical Informatics Research Network; GSP, Genomics Superstruct Project; Moo-ICAR, multiobjective optimization ICA with reference; MPRC, Maryland Psychiatric Research Center.

Table 1. Baseline Demographic Information of Multiple Psychiatric Datasets

Disorders	Categories	Age, Years, Mean \pm SD	Gender, Female/Male, <i>n</i>	Dataset (Sample Size)
SCZ, <i>n</i> = 2615	Patients, <i>n</i> = 1302	35.8 \pm 12.6	487/815	B-SNIP (429), COBRE (68), FBIRN (151), MPRC (147), 754-sample SCZ (507)
	Control Participants, <i>n</i> = 1313	34.2 \pm 11.7	679/634	B-SNIP (576), COBRE (89), FBIRN (160), MPRC (241), 754-sample SCZ (247)
ASD, <i>n</i> = 1735	Patients, <i>n</i> = 796	16.7 \pm 9.2	110/686	ABIDE (796)
	Control Participants, <i>n</i> = 939	16.2 \pm 8.6	229/710	ABIDE (939)
MDD, <i>n</i> = 585	Patients, <i>n</i> = 278	33.4 \pm 11.2	169/109	585-sample MDD (278)
	Control Participants, <i>n</i> = 307	31.3 \pm 10.4	191/116	585-sample MDD (307)
BPD, <i>n</i> = 872	Patients, <i>n</i> = 296	35.4 \pm 12.1	192/104	B-SNIP (296)
	Control Participants, <i>n</i> = 576	36.2 \pm 12.5	341/235	B-SNIP (576)

ABIDE, Autism Brain Imaging Data Exchange; ASD, autism spectrum disorder; BPD, bipolar disorder; B-SNIP, Bipolar & Schizophrenia Network on Intermediate Phenotypes; COBRE, Center for Biomedical Research Excellence; FBIRN, Function Biomedical Informatics Research Network; MDD, major depressive disorder; MPRC, Maryland Psychiatric Research Center; SCZ, schizophrenia.

Participants and Data Acquisition

Multiple Psychiatric Datasets for Building References. Table 1 shows the demographic information for the samples that were used for constructing references obtained from 7 clinical studies including the Bipolar & Schizophrenia Network on Intermediate Phenotypes (B-SNIP) (20), Center for Biomedical Research Excellence (COBRE) (21), Function Biomedical Informatics Research Network (FBIRN) (22), Maryland Psychiatric Research Center (MPRC) (23), a 754-sample SCZ dataset (13), Autism Brain Imaging Data Exchange (ABIDE) (24), and a 585-sample MDD dataset (25). Additional information regarding the demographics of the datasets can be found in Tables S1–S7. Participant inclusion criteria required all participants with head motion $\leq 3^\circ$ and ≤ 3 mm and with functional data providing near full brain successful normalization (by comparing the individual mask with the group mask, see the Supplement). This criterion yielded a total of 5231 participants, with SCZ (*n* = 2615, comprising 1302 patients and 1313 control participants), ASD (*n* = 1735, 796 patients and 939 control participants), MDD (*n* = 585, 278 patients and 307 control participants), and BPD (*n* = 872, 296 patients and 576 control participants) datasets. All clinical participants were diagnosed based on conventional DSM-derived diagnosing criteria.

ABCD and HCP-EP for Assessment. The ABCD Study is the most extensive longitudinal and observational study conducted to date, exploring brain development and child health starting at age 9 to 10 and initiated in 2016 in 21 sites across the United States (26). The ABCD Study database includes around 11,800 participants, with multiple scans obtained from different longitudinal sessions. This dataset contains a comprehensive range of metrics related to mental health, cognition, and other health-related backgrounds (27) that have allowed researchers to explore the relationship between adolescent behaviors and brain functions and how these are influenced by socioeconomic and genetic factors (28). The demographic characteristics of the ABCD Study samples that were used in this study are shown in Table S8.

As part of the Human Connectome Project, the HCP-EP imaged individuals within the first 5 years of the emergence of psychotic symptoms (early-phase psychosis). It includes

183 participants with confirmed psychiatric diagnoses as well as healthy individuals. The affective group encompassed individuals diagnosed with MDD with psychosis (single or recurrent episodes) or BPD with psychosis (including most recent episode depressed and manic types). The nonaffective group consisted of individuals diagnosed with SCZ, schizophreniform, schizoaffective, psychosis not otherwise specified, delusional disorder, or brief psychotic disorder. Individuals in the control group did not meet the diagnostic criteria for any mental disorder. The demographic characteristics of the HCP-EP samples used in this study are shown in Table S9.

Data Preprocessing

NeuroMark Pipeline. To capture reliable intrinsic connectivity networks and their corresponding time courses for each fMRI scan, NeuroMark (17) was applied to the ABCD Study data using the NeuroMark_fmri_1.0 templates (available in the group ICA of fMRI toolbox at <https://trendscenter.org/software/gift/> or <https://trendscenter.org/data/>). In contrast to the region of interest-based approaches that typically assume fixed brain regions across participants, NeuroMark can identify brain networks that are comparable across participants while adapting single-participant variability with the networks. Previous studies have demonstrated the efficacy of NeuroMark in identifying a variety of brain markers and abnormalities in different populations (29,30) and have also shown consistent sensitivity to group difference patterns and preservation of individual classification accuracy for a relatively short period (19). Further information about the NeuroMark network parcellation can be found in Figure S1 and Table S10.

FNC Postprocessing. Four additional postprocessing steps were performed to further reduce artifacts/noise in the time courses: 1) detrending to eliminate linear, quadratic, and cubic trends, 2) despiking temporal outliers, 3) low-pass filtering with a cutoff frequency of 0.15 Hz, and 4) regressing out 6 head motion parameters and their temporal derivatives. Pearson correlation coefficients between postprocessed time courses were calculated to obtain the FNCs for each scan. To mitigate and remove confounds when building the specific psychiatric disorder FNC references, the biological (i.e., age, gender) and technical (i.e., scanner, sites) covariates were

regressed out for each disorder. Detailed data processing procedures can be found in the [Supplement](#).

BRS Calculation

To obtain the averaged group references, FNCs of the patients and the corresponding healthy control participants in the same project were averaged for each psychiatric disorder. For the FNC of i_{th} testing participant T_i from the ABCD or HCP-EP dataset, we calculated the Euclidean distance $d_i^{patient}$ between T_i and patient reference ($R_{patient}$) and the Euclidean distance $d_i^{control}$ between T_i and control reference ($R_{control}$):

$$d_i^{patient} = \sum_{j=1}^n \|T_i^j - R_{patient}^j\|^2, d_i^{control} = \sum_{j=1}^n \|T_i^j - R_{control}^j\|^2 \quad (1)$$

where j represents the index of the FNC feature, and n is the total number of FNC features ($n = 1378$).

The distance between a testing individual with the patient reference ($d_i^{patient}$) and with the control reference ($d_i^{control}$) was further calculated to quantify the BRS:

$$BRS = d_i^{control} - d_i^{patient} \quad (2)$$

As defined, a smaller BRS implies a lower risk of developing a psychiatric disorder.

RESULTS

BRS Reveals a Reproducible Gradient of FNC Dissociation From Low-Risk to High-Risk Adolescents

As shown in [Figure 2A](#), the FNC references of mental disorders are in the lower triangle, and healthy control participants are in the upper triangle. The FNC of ABCD Study samples used in this study was the same as our previous study (10), which revealed that the accuracy of identifying an individual's FNC at the second year from the FNC collected at baseline was over 90%. The FNC quartiles, shown in [Figure 2B](#), demonstrate the trajectories from low-risk to high-risk samples for each mental disorder in ABCD Study adolescents. Specifically, all ABCD Study samples were sorted in ascending order of their BRS, with the lowest-risk samples averaged to be the first FNC in each column and the highest-risk samples averaged to be the fourth FNC. Similar results were replicated on the second-year follow-up ABCD Study samples, as shown in [Figure S2](#). Head motion showed no significant effects on BRS ([Figure S3](#)).

As shown in [Figure 2C](#), 2 groups of networks, a sensorimotor (SM) hub and a cerebellar (CB) hub, were identified that indicate the psychiatric risk in a healthy population. We found that low-risk ABCD Study adolescents were alike regardless of the reference used, but high-risk adolescents differentiated toward each psychiatric disorder. Specifically, for the SM hub, negative connectivity within the SM and between SM and visual and positive connectivity between SM and subcortical (SC) networks were related to increased psychiatric risk for all mental disorders. For the CB hub, negative connectivity between CB and SC and between CB and cognitive control (CC) networks and positive connectivity between CB and visual networks were related to increased risk of SCZ and autism.

Autism also showed a positive connection between CC and SM when risk increased. In contrast, high-risk MDD did not exhibit an obvious CB hub-related connectivity change. High-risk BPD did not show an obvious change between CB and visual networks.

The high similarity and strongly present FNC patterns showed in more than one-quarter of ABCD Study participants, indicating a presumed protective pattern, whereas the patient-like patterns were not strongly visible until we “zoomed in” to the upper 1% of the high-risk participants ([Figure 2C](#)). Considering that the global age-standardized prevalence of most mental disorders is <1% (31), to quantify the divergence of participants at different psychiatric risk levels, we used cross-correlation among 4 psychiatric-risk groups within the 1% lowest-risk and 1% highest-risk ABCD Study participants (Note: the cross-correlation among all ABCD Study participants is shown in [Figure S4](#), and the demographic information of 1% lowest-risk and 1% highest-risk ABCD Study participants is shown in [Table S11](#)). As shown in [Figure 3A](#), the 1% of lowest-risk adolescents showed high similarity ($r \approx 1$), and the 1% of highest-risk showed low similarity. We also quantified the averaged correlation distance (1 minus averaged correlation coefficients) at 2 risk levels. The averaged distance among disorders at the low risk level (mean \pm SD: 0.05 ± 0.02) was much smaller than that at the high-risk level (mean \pm SD: 0.79 ± 0.36), demonstrating increased divergence among higher-risk groups relative to the control groups.

Comorbidity of Psychiatric Disorders Measured Using BRS

[Figure 3A](#) shows an increased divergence among higher-risk groups relative to control groups. To further investigate how the BRS could facilitate the study of psychiatric comorbidity, we calculated the overlaps of high-risk ABCD samples for each mental disorder. [Figure 3B](#) shows a Venn diagram of the top 25% risk ABCD samples for each psychiatric disorder. Overlap between individuals with high-risk SCZ and ASD BRS (29.6%) and SCZ and BPD BRS (28.9%) was greater than pairwise overlap with other disorders (SCZ and MDD: 21.6%, ASD and MDD: 14.9%, ASD and BPD: 21.3%, MDD and BPD: 19.3%). SCZ also showed the least number of individuals with no shared high-risk categories (3.1%); MDD showed the most uniqueness (18.6%), followed by ASD (12.3%) and BPD (10.3%), consistent with the high prevalence of comorbidity of SCZ with other mental disorders (32). In addition, 7.7% of individuals showed shared overlap among all 4 disorders. As shown in [Figure 3C](#), all ABCD Study participants are visualized on a 2-dimensional plane. The top 1% risk samples of each psychiatric disorder were selected and highlighted based on their BRSs. Results show that high-risk SCZ (red dots) and high-risk ASD (yellow dots) have a greater degree of overlap than the other disorders (blue and green dots).

Correlation Between BRS and Clinical Symptoms

Skewness is a metric that evaluates the asymmetry of a random variable's probability distribution relative to its mean. For the BRS histogram of each disorder, a negative skew indicates that the tail is situated on the left side of the distribution, which is indicative of control references, whereas a

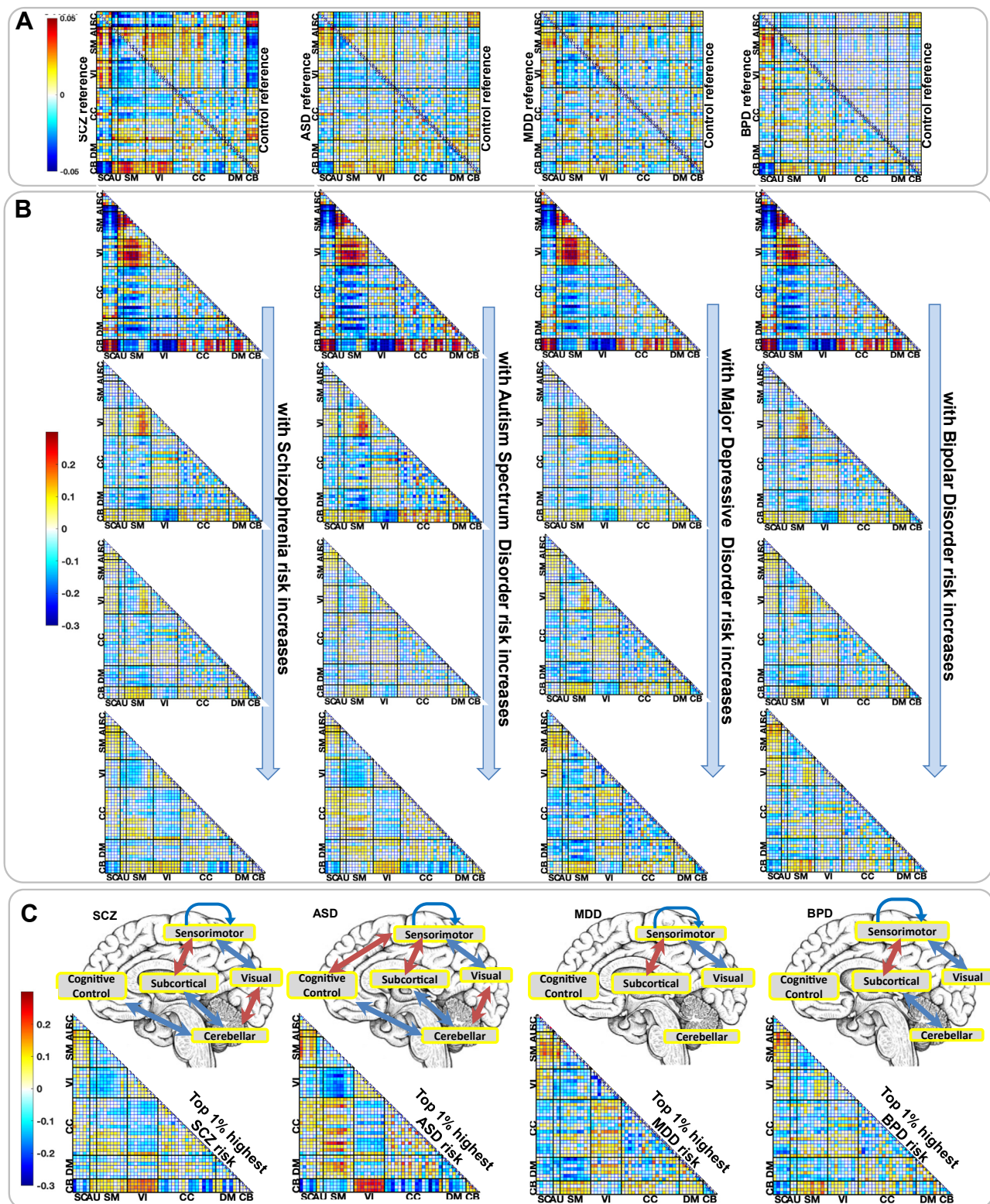


Figure 2. (A) Functional network connectivity (FNC) references generated for each psychiatric disorder. Each figure displays the FNC of a psychiatric disorder in the lower triangle and the FNC of the control group in the upper triangle. (B) The FNC of Adolescent Brain Cognitive Development (ABCD) Study baseline quartile, arranged from low risk (top) to high risk (down). All participants are ranked according to their scores for psychiatric risk. Each FNC represents the averaged FNC of 5% of the ABCD Study samples (from left to right, 0% ~ 5%, 20% ~ 25%, 70% ~ 75%, and 95% ~ 100%, respectively). (C) Upper: The

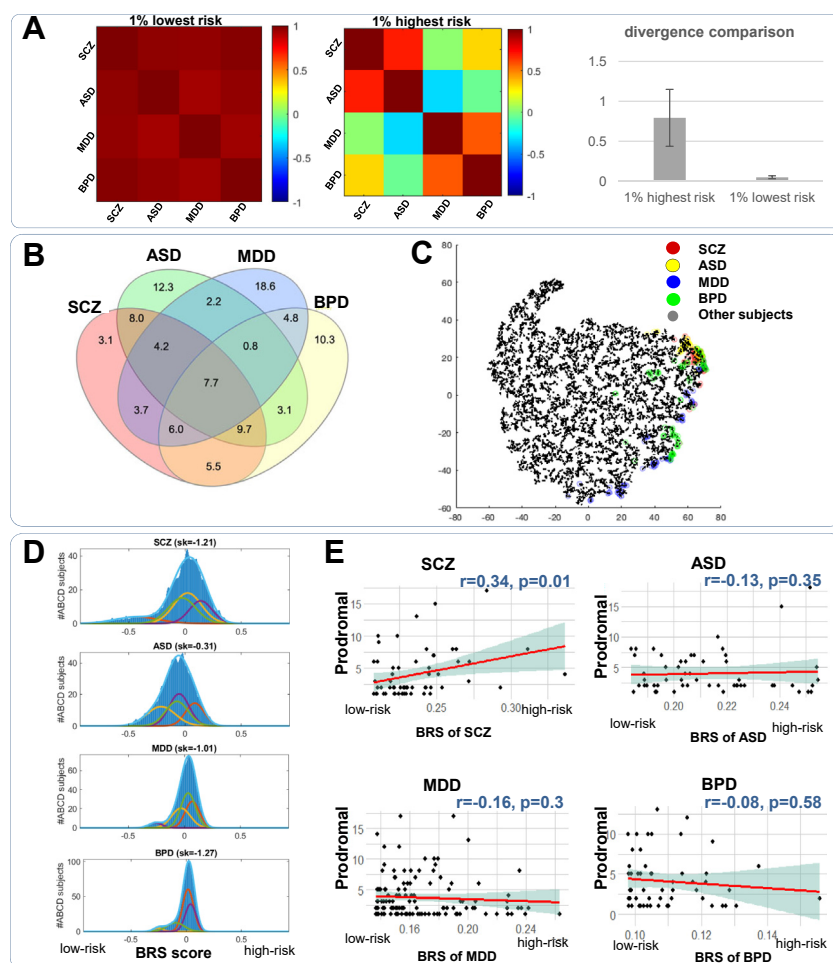


Figure 3. (A) Left: Cross-correlation among 4 psychiatric risk groups within the 1% lowest-risk Adolescent Brain Cognitive Development (ABCD) Study participants; middle: cross-correlation among 4 psychiatric-risk groups within the 1% highest-risk ABCD Study participants; right: the divergence comparison between the high-risk level and low-risk level. (B) Venn diagram of the ABCD Study top 25% high-risk samples for various psychiatric disorders. Each number represents the ratio of samples that belong to a distinct area. The individuals with high-risk schizophrenia (SCZ) and autism spectrum disorder (ASD) brainwide risk scores (BRSs) showed greater overlap than individuals with other disorders. (C) T-distributed stochastic neighbor embedding visualization of all ABCD Study baseline samples ($n = 8191$). The highlighted dots note the top 1% high-risk samples for each disorder. The ABCD Study participants who exhibited risks of SCZ and ASD had the greatest degree of overlap, consistent with the comorbidity of the 2 disorders. (D) The BRS distributions of ABCD Study baseline samples for each psychiatric disorder. The color curves represent the 4 components derived using Gaussian mixture model. (E) Spearman correlations between the BRS and prodromal scores for the top 1% risk ABCD Study participants ($n = 82$) in each disorder. BPD, bipolar disorder; MDD, major depressive disorder; sk, skewness.

positive skew indicates that the tail is situated on the right, which is indicative of patient references. As shown in Figure 3D, the BRS histogram of ABCD Study individuals relative to all 4 references showed a strong negative skewness, indicating a higher similarity to the control reference.

We also evaluated whether the BRS predicted prodromal scores in the ABCD Study. Because the ABCD Study mainly includes very young adolescents, we first chose the participants with the top 1% of BRSs, which we reasoned would be the ones most likely to present prodromal symptoms (33), to build linear regression models. As shown in Figure 3E, a significant positive correlation (Spearman correlation, $r = 0.34$, $p = .01$) was observed between BRS SCZ and the prodromal score. Similarly, we also analyzed the correlation between the PRS (4) for SCZ and prodromal symptoms (Figure S5), and the

results showed no significant correlations between PRS and prodromal scores. In addition, a significant positive correlation (Spearman correlation, $r = 0.34$, $p = .0002$) was observed between BRS MDD and `cbcl_scr_dsm5_depression_t` (Figure S6).

Performance of BRS to Distinguish Psychiatric Disorders From Healthy Control Participants

Major psychiatric disorders such as SCZ and BPD typically emerge during the late teens and early 20s. However, the images from the ABCD Study adolescents that we analyzed were obtained between 9 and 13 years of age, too early for the typical emergence of the disorder. Therefore, we utilized the HCP-EP dataset to further test the performance of the BRS in identifying psychiatric disorders. As shown in Figure 4A, the

network connectivity changes, which increase psychiatric risk for each disorder. Blue arrows represent the flip from positive to negative connectivity, while orange arrows represent the flip from negative to positive. Lower: The averaged FNC of the top 1% of high-risk ABCD Study samples for each disorder. The color bars in each panel represent the functional connectivity strength. ASD, autism spectrum disorder; AU, auditory domain; BPD, bipolar disorder; CB, cerebellar domain; CC, cognitive-control domain; DM, default mode domain; MDD, major depressive disorder; SC, subcortical domain; SCZ, schizophrenia; SM, sensorimotor domain; VI, visual domain.

mean BRS of the control groups was less than that of the patient groups, indicating that their brain patterns were more similar to the control references. We also tested whether the BRSs could predict patients who were diagnosed with early psychosis. For this purpose, every participant in the HCP-EP was represented with a 4-dimensional BRS vector to train support vector machine (SVM) classifiers to distinguish patients with early psychosis from healthy control participants. The performance of the SVM classifiers with Gaussian kernels was assessed by using 5-fold cross-validation. The classification performance was also compared with the SVM trained on the original FNC, which contained 1378 connectivity features. The results showed that the 4-dimensional BRS vectors had similar classification performance to the original FNC features, suggesting that the low-dimensional BRS preserved disorder-discriminating information that was useful to distinguish patients with psychotic disorders from control participants.

DISCUSSION

Assessing individual risk for a particular psychiatric disorder is essential for providing effective interventions at an early stage. In this work, we investigated the use of the BRS, a novel neuroimaging-based metric, to quantify the psychiatric risk of individuals by comparing the relative distances to FNC references derived from multiple large cohort neuroimaging studies. Our results showed that the BRS displayed 3 important capabilities: 1) BRS revealed connectome trajectories from low-risk to high-risk for each disorder, providing brain network information relevant to the underlying mechanisms of psychiatric disorders and comorbidity; 2) BRS was sensitive to

the presence of prodromal symptoms of psychosis and contained useful information to differentiate patients with psychiatric disorders from healthy control participants; and 3) the FNC patterns within the low-risk categories were present in at least 25% of the ABCD Study participants and were highly similar, suggestive of a protective pattern, whereas those within the high-risk categories diverged from one another.

Despite numerous attempts, the “Holy Grail” of clinical applications of neuroimaging to psychiatric disorders via personalized biomarkers has remained mostly elusive (34). A significant challenge hindering the utilization of data-driven approaches for biomarker discovery is that the results can be difficult to compare across individuals. The NeuroMark framework utilized in the BRS provides a solution for processing all fMRI samples using a standardized pipeline, which leverages the advantage of large datasets and avoids site effects. In comparison to seed-based approaches, NeuroMark, which utilized spatially constrained ICA, has been shown to provide improved control over head motion effects (35). This spatially constrained ICA was implemented using a template derived from external data, and it was applied to each participant individually, thus eliminating any risk of motion-related interparticipant contamination. While stringent head motion standards can enhance data quality, overly rigid criteria may lead to excessive data exclusion and potentially introduce study biases (36). In the current study, we set a 3-mm threshold against pronounced head motion, aiming to retain the maximum number of participants. The strong correlation between the PRS with and without regressing out the mean framewise displacement suggested that the influence of head motion on the PRS was minimal. Moreover, the high accuracy of identifying a child’s FNC across years demonstrated the

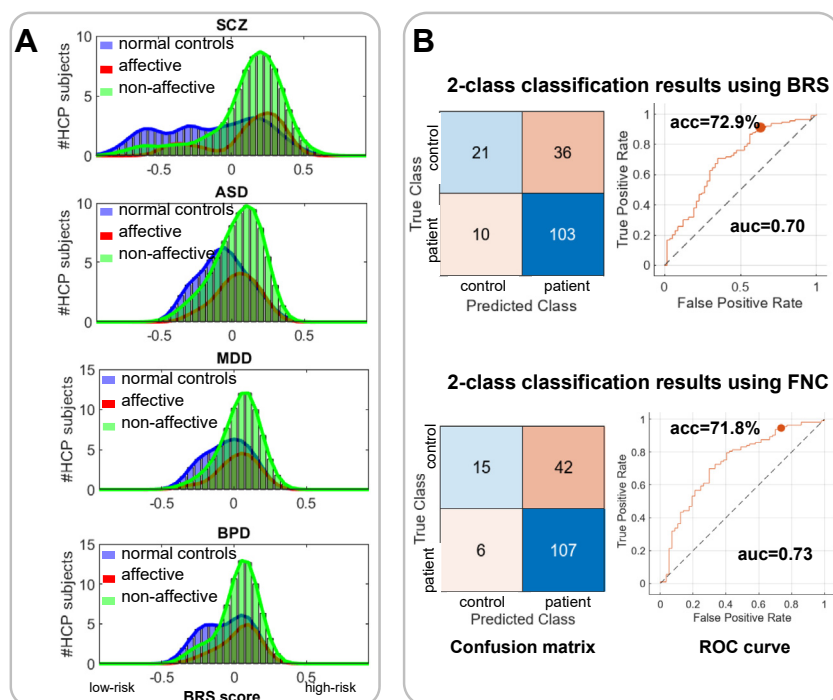


Figure 4. (A) Brainwide risk score (BRS) distributions of the Human Connectome Project (HCP) Early Psychosis dataset for each psychiatric disorder. (B) Confusion matrix and receiver operating characteristic (ROC) curve for control participant vs. patient classification. Even with limited feature dimensions, the BRS (accuracy [ACC] = 72.9%) outperforms functional network connectivity (FNC) (ACC = 71.8%) in differentiating patients with early psychosis from healthy control participants. ASD, autism spectrum disorder; AUC, area under the ROC curve; BPD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia.

robustness of FNC, highlighting its potential for longitudinally monitoring developmental factors (10).

The BRS revealed reproducible psychiatric trajectories from low to high risk for mental disorders. As the psychiatric risk increased in adolescents, 2 network systems, the SM hub and CB hub, showed the most significant alterations. Nevertheless, the transformations of various psychiatric disorders differed, indicating distinct pathologies among the disorders. Moreover, the BRS contains abundant information specific to psychiatric disorders, thereby enabling the accurate prediction of clinical symptoms, such as prodromal scores, as well as the precise differentiation between patients with psychiatric disorders and healthy control participants. The increased subcortical-somatosensory connectivity pattern found in high-risk ABCD Study samples was reported shared across SCZ, BPD, and MDD (37–42). The cerebellar-thalamic connectivity deficits found in high-risk ABCD Study samples support the cognitive dysmetria theory that cerebello-thalamo-cortical circuitry disruptions lead to impairments in the coordination of mental processes in SCZ. Disruptions in the cerebellar circuitry, a critical component in overall brain function, have also been reported in conditions such as BPD (43), MDD (44), and ASD (45). Evidence has demonstrated that connectivity between the thalamus and cerebellum is a recurring biological mechanism that underlies multiple psychiatric disorders, particularly psychotic disorders (46).

In comparison to the PRS (47), which is a static metric throughout the life span, the BRS is more suitable for observing dynamic changes linked to brain development. Considering the substantial effect of environmental factors on brain development and mental disorders, the use of such a functional measure is advantageous. The BRS performs better in capturing syndrome-related features (e.g., prodromal score) than the PRS. The BRS framework, with its capacity to illustrate the risk trajectory for a psychiatric disorder, may also be suited for tracing illness progression in an individual.

The BRS also provides a novel neuroimaging perspective for studying the comorbidities of psychiatric disorders. Due to the presence of shared symptoms across various psychiatric disorders, diagnostic comorbidity is generally the rule rather than the exception, and patients frequently have more than one psychiatric diagnosis. It remains unclear whether this apparent comorbidity arises from commonalities in underlying biology or simply reflects a classification system that is ill-suited to capturing the full complexity of human behavior and brain neuropathology (1). Given the shared clinical manifestations of the 2 disorders (48,49), SCZ and ASD are comparable in many ways. For example, in one study, the prevalence of SCZ was significantly higher in individuals with ASD than in control participants (50). Nearly 30% of youths diagnosed with childhood-onset SCZ in a large National Institutes of Health cohort had a comorbid diagnosis of ASD (51). Genome-wide association analysis also supports the notion that ASD and SCZ share similar risk factors (52). The BRS is helpful to explain comorbidity from the connectome perspective. The integration of genetic and demographic information with the BRS will facilitate a better understanding of biology in the future.

The current work has several limitations. Firstly, given that the ABCD Study participants are currently healthy

adolescents, the BRS requires validation through follow-up in the sample as they reach their late teens, by which point a significant proportion of those who will ultimately develop a psychotic illness are likely to manifest more overt symptoms. We chose the averaged Euclidean distance as the metric of evaluation considering the tradeoff between accuracy and feasibility, and a similar BRS was replicated using correlation distance (Figure S7). In the future, more optimized metrics can be explored by considering the functional connectivity modules. In addition, even though a large cohort of samples were collected and analyzed for constructing the references, the diversity of age and race remains inadequate. Family status was not incorporated into the current study; in the future, utilizing multisite datasets comprising different races, age ranges, and siblings would further enhance the representation of the BRS framework (Figure S8). Moreover, the BRS is currently calculated solely based on functional neuroimaging. In the future, the BRS can be integrated with other imaging modalities to identify presumptively more predictive and robust biomarkers. Future studies could also explore whether integrating a PRS with clinical interviews and the BRS would be even more successful in identifying at-risk individuals. Finally, the extent to which the BRS captures information relevant to mood disorders without psychotic symptoms or its relevance to other nonserious mental disorders (i.e., attention-deficit/hyperactivity disorder, eating disorders, anxiety disorders) require further investigation.

In this work, for the first time, by leveraging large neuroimaging datasets and a standardized image-processing pipeline, we investigated a novel neuroimaging-based metric, the BRS, to quantify psychiatric risk in adolescents. The BRS demonstrated significant capability in assessing risks of psychiatric disorders, elucidating mental disorder comorbidity, predicting psychiatric symptoms, and distinguishing patients with disorders from healthy control participants. The BRS exhibits potential as a biomarker for early screening and mentoring interventions, either as a standalone tool or in combination with polygenic scores and clinical assessment tools.

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Data can be obtained from a third party and are not publicly available. They can be requested from the authors. Please email weizheng.yan@nih.gov and vince.calhoun@ece.gatech.edu for data and codes.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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