Schizophrenia Imaging Signatures and Their Associations With Cognition, Psychopathology, and Genetics in the General Population

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Objective: The prevalence and significance of schizophrenia-related phenotypes at the population level is debated in the literature. Here, the authors assessed whether two recently reported neuroanatomical signatures of schizophrenia—signature 1, with widespread reduction of gray matter volume, and signature 2, with increased striatal volume—could be replicated in an independent schizophrenia sample, and investigated whether expression of these signatures can be detected at the population level and how they relate to cognition, psychosis spectrum symptoms, and schizophrenia genetic risk.

Methods: This cross-sectional study used an independent schizophrenia-control sample (N=347; ages 16–57 years) for replication of imaging signatures, and then examined two independent population-level data sets: typically developing youths and youths with psychosis spectrum symptoms in the Philadelphia Neurodevelopmental Cohort (N=359; ages 16–23 years) and adults in the UK Biobank study (N=836; ages 44–50 years). The authors quantified signature expression using support-vector machine learning and compared cognition, psychopathology, and polygenic risk between signatures.

Results: Two neuroanatomical signatures of schizophrenia were replicated. Signature 1 but not signature 2 was significantly more common in youths with psychosis spectrum symptoms than in typically developing youths, whereas signature 2 frequency was similar in the two groups. In both youths and adults, signature 1 was associated with worse cognitive performance than signature 2. Compared with adults with neither signature, adults expressing signature 1 had elevated schizophrenia polygenic risk scores, but this was not seen for signature 2.

Conclusions: The authors successfully replicated two neuroanatomical signatures of schizophrenia and describe their prevalence in population-based samples of youths and adults. They further demonstrated distinct relationships of these signatures with psychosis symptoms, cognition, and genetic risk, potentially reflecting underlying neurobiological vulnerability.

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Schizophrenia is a neuropsychiatric disorder that imposes a significant personal and socioeconomic burden (1). Understanding the neuropathological processes underlying schizophrenia has been hampered by the disorder's neurobiological heterogeneity (2, 3), which has confounded case-control studies and impeded progress in treatment development (4). There is a pressing need for quantitative phenotypes and precision diagnostics, which could help define optimal personalized interventions according to a patient's neurobiological and clinical profile. Machine learning applied to neuroimaging has emerged as a valuable tool to establish precise and quantitative imaging phenotypes. Our recent study from the PHENOM (Psychosis Heterogeneity Evaluated Via Dimensional Neuroimaging) consortium revealed the presence of two statistically optimal and distinct neuroanatomical signatures in schizophrenia (5). The first was characterized by widespread reductions in white matter and gray matter volume correlating with illness duration and

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worse premorbid functioning, and the second was associated with overall normal brain structure except for enlarged striatal and internal capsule volumes. This suggests two different underlying neuropathological mechanisms and highlights the need to both replicate these signatures in independent schizophrenia samples and to investigate these signatures in population-based samples without schizophrenia.

Intensive efforts are now focused on understanding the pathophysiology of early stages of psychosis (6, 7), which will be essential for prevention and early intervention and has the additional advantage of studying patients in the absence of the effects of chronic illness or treatment. Most psychosis risk research examines "clinical high-risk" groups, which are typically help-seeking and identified in clinical settings (8). However, long-standing theories of schizotaxia (biological vulnerability to schizophrenia) and schizotypy (the wide spectrum of psychological manifestations of that vulnerability) argue that biological vulnerability to schizophrenia is expressed in a substantial proportion of the general population, many of whom will never develop psychosis (9, 10). Examination of schizophrenia-related neurostructural phenotypes in population-based samples is therefore critical to lay the groundwork for primary prevention efforts that incorporate stratification based on critical factors driving heterogeneity (6, 7). Previous work in population-based samples has demonstrated that psychosis spectrum symptoms are associated with increased risk of psychotic conversion (~10% convert) (11, 12). Schizophrenia-associated structural brain abnormalities are also linked to psychosis spectrum symptoms in population samples (13). Whether the two schizophrenia imaging signature expressions ("signature 1" and "signature 2") are detectable in population-based samples with psychosis spectrum symptoms is unknown. Even in healthy populations, schizophrenia genetic risk is associated with regional brain differences resembling signature 1 (fronto-temporal reductions) or signature 2 (basal ganglia enlargement) (14, 15); however, whether these signatures are associated with schizophrenia polygenic risk scores (PRSs) in population-based samples is unknown. To address these gaps, in the present study we replicated the signatures in schizophrenia and then leveraged two independent population-level (non-help-seeking) cohorts. First, the Philadelphia Neurodevelopmental Cohort (PNC) (13), which offers rich cognition and psychopathology data in psychosis spectrum symptoms and typically developing youths, was analyzed to investigate the presence of signature 1 and signature 2 expressions and their clinical and cognitive correlates. Second, the UK Biobank (16), which offers limited cognition and rich genetics data in adults, was analyzed to explore the prevalence of these signatures and their cognitive and genetic correlates.

We hypothesized that schizophrenia neuroanatomical signatures would be replicated in independent schizophrenia samples and would be more common and prominent in the psychosis spectrum group from the non-help-seeking PNC youth sample. We expected signature 1 but not signature 2 to be associated with poorer cognition, based on the known relationship between reduced gray matter volume (observed only in signature 1) and worse cognition (17–19). Given that schizophrenia PRS was defined using a large schizophrenia sample encompassing all potential subtypes (20, 21), we hypothesized that both signatures would be associated with elevated schizophrenia PRSs. However, we hypothesized that this elevation would be stronger in signature 1 than signature 2, because PRS is most strongly elevated in schizophrenia associated with early neurodevelopmental insults (22), and is also associated with fronto-temporal cortical reductions (14) and cognitive impairment (23), and because we observed signature 1 to be more prevalent than signature 2 in schizophrenia, likely influencing the allelic composition of the PRS.

METHODS

Study Sample

This study included data from a total of 2,213 participants from the PHENOM consortium (N=671), replication data (N=347), the PNC (N=359, typically developing youths and youths with psychosis spectrum symptoms), and the UK Biobank (N=836). The PHENOM sample includes participants with established schizophrenia (N=307) and healthy control subjects (N=364). The PNC is a large-scale community-based study, and after restricting our sample to participants age 16 or older (to ensure overlapping age with the PHENOM sample, so that machine learning models can be applied appropriately), there were 181 individuals with psychosis spectrum symptoms and 178 typically developing individuals. The UK Biobank is a large-scale open-access resource for neuroimaging, genetic, and limited cognitive data sets. The subsample of UK Biobank healthy participants age 50 or younger were analyzed. Details on the samples are provided in the online supplement.

Image Acquisition and Preprocessing

A multi-atlas region segmentation utilizing ensembles of registration algorithms and parameters, and locally optimal atlas selection (MUSE) (24) was used to segment each individual's T_1-weighted images into 145 anatomical regions of interest from gray matter, white matter, and cerebrospinal fluid (see Table S1 in the online supplement). Voxel-wise volumetric maps for gray matter and white matter were generated by deformable registration of skull-stripped T_1 images to common space (see the online supplement).

Identifying the Presence of Schizophrenia Imaging Signatures and Defining Subgroups

Heterogeneity through discriminative analysis (HYDRA) (25) was used to identify the presence and expression strength of schizophrenia imaging signatures. In contrast to unsupervised or fully supervised clustering techniques, HYDRA is a semisupervised machine learning method and uses prespecified patient and control labels but then uses a data-driven approach to simultaneously perform classification and clustering within the patient group. Rather than

forcing patient data into a single common discriminative pattern, HYDRA allows for the separation of distinct patient groups. The HYDRA parameters derived from PHENOM (5) were applied to harmonized PNC and UK Biobank data using support-vector machine learning (25, 26) to estimate neuroanatomical signature expression strength (E_1 and E_2). Since control subjects are assigned "−1" and schizophrenia "+1" during HYDRA training, E (>0) represents signature presence while E (<0) represents its absence. Thus, each participant was assigned to one of these subgroups: signature 1 ($E_1>0$, $E_2<0$), signature 2 ($E_1<0$, $E_2>0$), neither signature ($E_1<0$, $E_2<0$), and both signatures ($E_1>0$, $E_2>0$) (see the online supplement). These subgroups were compared for clinical, cognitive, genetic, and voxel-wise analyses. Signature expression strengths were also compared between typically developing and psychosis spectrum groups in the PNC, and between healthy control subjects and schizophrenia patients in PHENOM.

Voxel-Wise Volumetric Analyses

To visualize voxel-wise volumetric differences between signatures, we used multivariate discriminative statistical mapping (MIDAS) (27). MIDAS determines the optimal regional smoothing and provides higher sensitivity and specificity in identifying group alterations compared to other methods (see the online supplement).

Clinical and Cognitive Measures

To assess clinical profiles, we used psychopathology scores derived from the PNC structured interview (28). To evaluate cognition in the PNC sample, we utilized the Penn Computerized Neurocognitive Battery, analyzing summary z-score measures of factors capturing overall accuracy, speed, and efficiency (29). Primary analyses of cognition in the UK Biobank were limited to fluid intelligence (30) and the Trail Making Test, part B (Trails B) (31) based on their availability in larger samples (further details are available in the online supplement).

Genetic Measures

Since the schizophrenia PRS is only valid for the European-ancestry population used to derive it (32), we limited PRS calculation to the UK Biobank European-ancestry cohort (N=671). We used validated schizophrenia PRS weights from the Polygenic Score Catalog (20) generated from 284,262 SNPs (21). The LiftOver tool was used to convert SNPs to build GRCh38 (33), and PLINK, version 1.9, was used to calculate schizophrenia PRSs (34).

Statistical Analysis

The proportions of participants expressing each of the signatures were compared between groups using a chi-square test. A two-sided Wilcoxon rank sum test compared cognitive, clinical, and PRS measures. Spearman correlations were used to examine associations between dimensional signature expression strength and cognition or PRS. We applied nonparametric tests across comparisons because some measures, especially Trails B, were not normally distributed even after applying transformation. The covariates age and sex were controlled in all analyses. Ancestry principal components were also controlled in genetic analyses. All p values were corrected for multiple comparisons using the false discovery rate (FDR), requiring an FDR-corrected p-value threshold of 0.05.

RESULTS

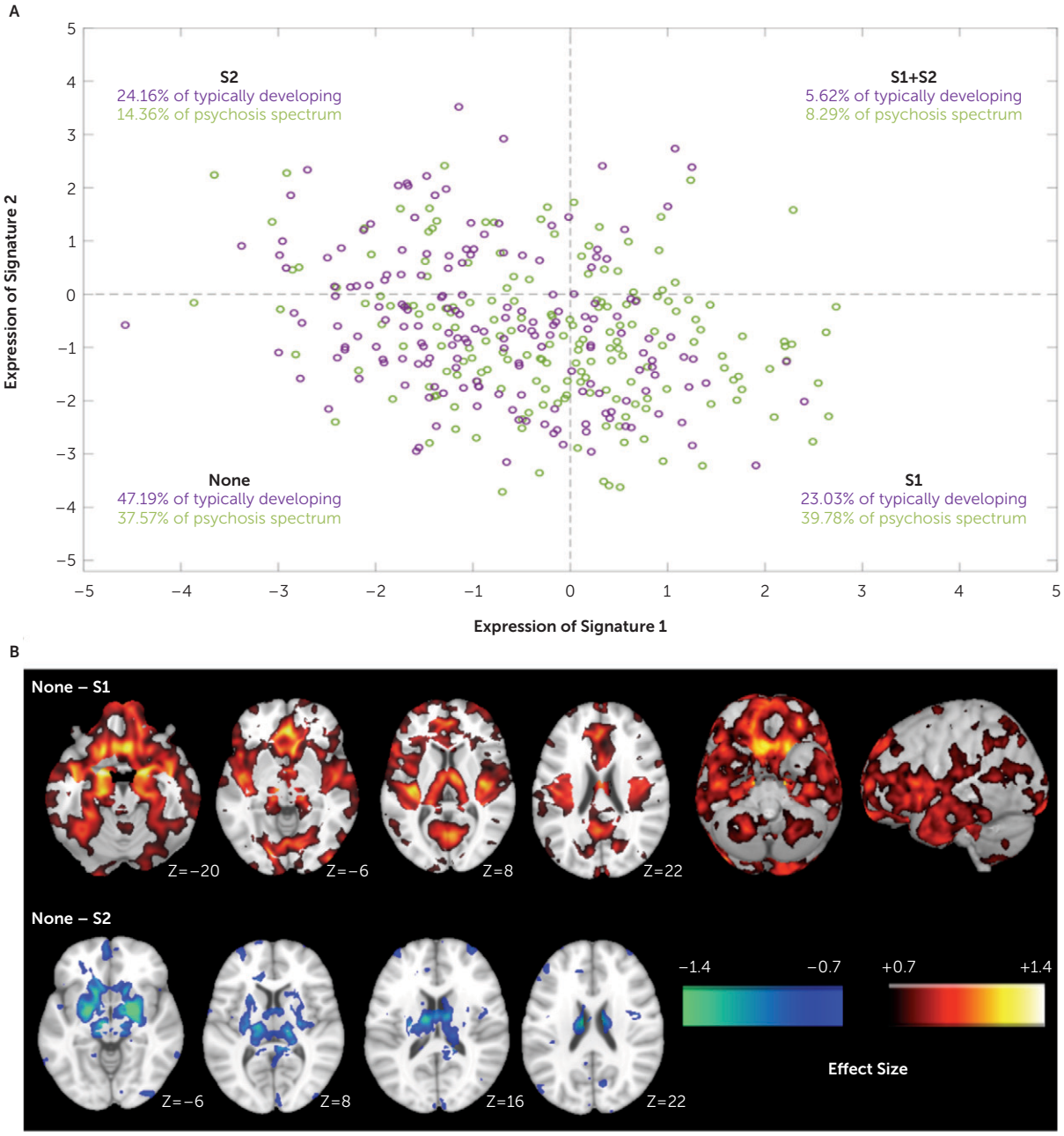
Replication of Schizophrenia Neuroanatomical Subtypes

Schizophrenia neuroanatomical subtyping using HYDRA replicated the same two subtype profiles in the independent schizophrenia sample (see Figures S1 and S2 in the online supplement), with proportions similar to those in the original PHENOM sample (58.39% signature 1, 41.61% signature 2).

Prevalence of Schizophrenia Imaging Signatures in the PNC

In typically developing youths, the prevalences of schizophrenia signature 1, signature 2, both signatures, and neither signature ("none") were 23.03%, 24.16%, 5.62%, and 47.19%, respectively (Figure 1A). In psychosis spectrum youths, the prevalences of signature 1, signature 2, both signatures, and "none" were 39.78%, 14.36%, 8.29%, 37.57%, respectively. Psychosis spectrum youths displayed significantly higher signature 1 prevalence than typically developing youths ($\chi^2=11.67$, df=1, $p<0.05$), whereas the frequency difference between the typically developing and psychosis spectrum groups was not significant for signature 2, both signatures, or "none." Descriptive voxel-wise group comparisons were carried out between signature 1 or signature 2 and "none" in order to visually illustrate the signature patterns. Signature 1 was characterized by widespread reductions in gray matter and white matter volumes, and signature 2 was characterized by generally normal regional brain volumes except for markedly increased striatal and internal capsule volumes (Figure 1B; see also Figures S3 and S4 in the online supplement; Cohen's d effect sizes were ~1.4 in regions showing the most prominent differences). Within the signature 1 and signature 2 groups, the pattern of gray matter volume did not differ significantly between the psychosis spectrum or schizophrenia groups and their respective control groups (see Figure S5 in the online supplement; for exploratory comparisons, see Figure S6 in the online supplement). However, the expression strength of signature 1 and signature 2 was higher for individuals with schizophrenia than for healthy control subjects, without a statistical difference between the typically developing and psychosis spectrum groups (see Figure S7 in the online supplement). Exploratory analyses in the separate PNC subsamples with other psychopathology are presented in the online supplement (see the section "Schizophrenia signature prevalence in other psychopathology"); exploratory analyses in typically developing and psychosis spectrum participants ages ≥10 years and <16 years are also presented (see the section "Schizophrenia signature prevalence in PNC younger participants").

FIGURE 1. Presence of signature 1 (S1) and signature 2 (S2) expressions in the Philadelphia Neurodevelopmental Cohort data set[a]

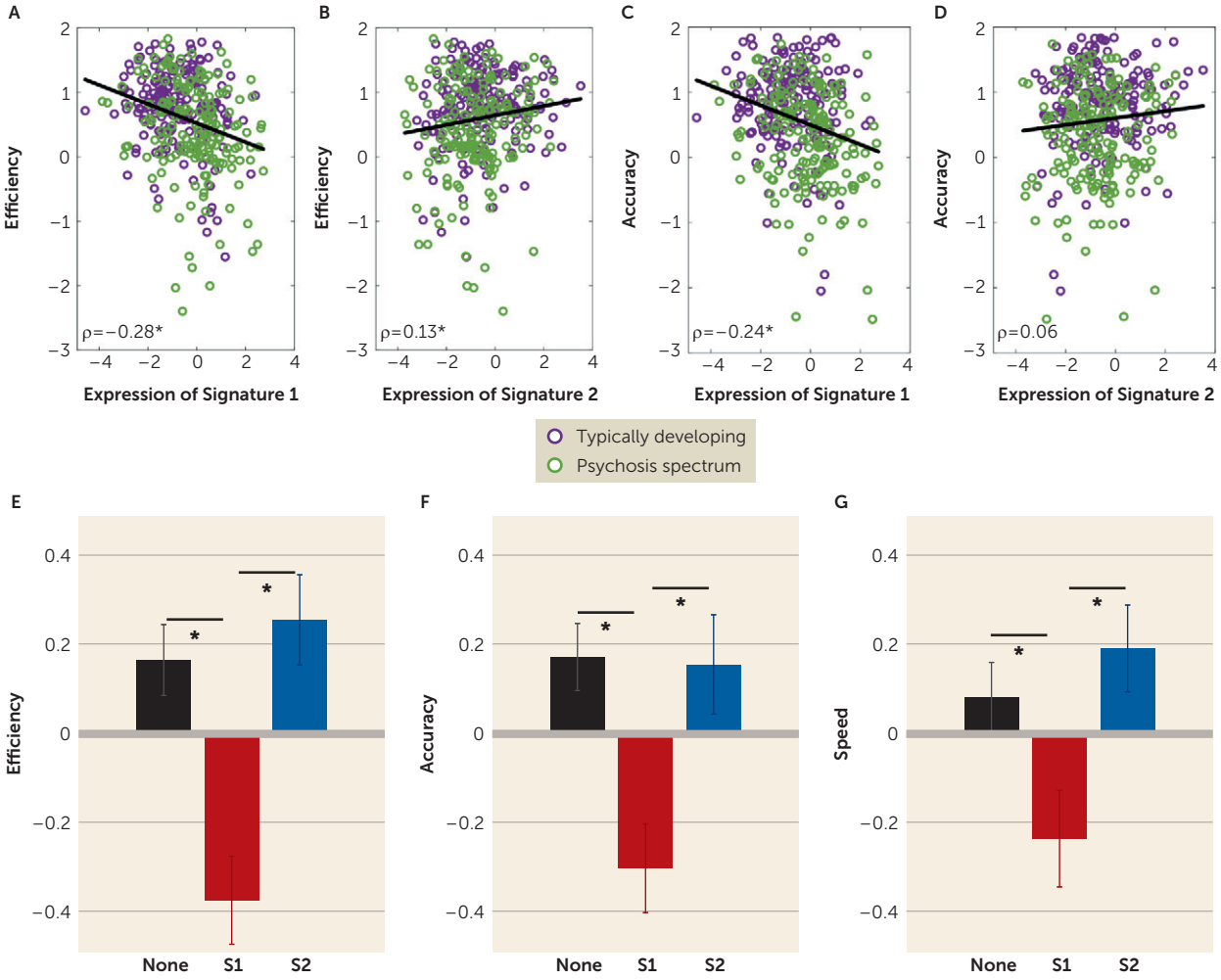


[a] In panel A, dimensional expression strength was visualized in a two-axis (E_1, E_2) framework, with typically developing and psychosis spectrum individuals across S1, S2, both signatures (S1+S2), and neither signature ("none"). S1 was significantly more common in the psychosis spectrum group than in the typically developing group ($\chi^2=11.67$, df=1, $p<0.05$, corrected for multiple comparisons), but other combinations were similar between the typically developing and psychosis spectrum groups ($p>0.05$). In panel B, voxel-based comparisons of regional gray matter volumes between individuals expressing primarily S1 (top) or S2 (bottom), compared with individuals expressing neither of these two signatures, are displayed for visualization purposes. Individuals with S1 were characterized by significantly reduced gray matter volumes, especially in prefrontal, temporal, and peri-Sylvian regions, whereas those with S2 were characterized by markedly increased striatal volumes and normal to mildly enlarged cortical volumes compared with the "none" subgroup. Cohen's d (effect size) maps were generated by masking MIDAS results after false discovery rate correction over voxels at $p<0.05$, and the largest effect sizes (~1.4) were observed in the thalamus, nucleus accumbens, and medial temporal, medial prefrontal/frontal, and insular cortices for S1 and in the striatal region for S2. (See Figure S3 in the online supplement for visualization of white matter comparison.)

Associations Between Signature 1, Signature 2, Cognition, and Psychosis Spectrum Symptoms in the PNC

Across the full PNC data set (typically developing and psychosis spectrum participants) (Figure 2A–D), signature 1 expression was inversely correlated with cognitive efficiency (combination of accuracy and speed) (Spearman's correlation: $\rho=-0.28$, $p<10^{-4}$), accuracy ($\rho=-0.24$, $p<10^{-4}$), and speed ($\rho=-0.16$, $p<0.05$), whereas stronger signature 2 expression was positively correlated with efficiency ($\rho=0.13$, $p<0.05$) or speed ($\rho=0.13$, $p<0.05$) without significant

FIGURE 2. Cognitive profiles of signature 1 (S1) and signature 2 (S2) in the Philadelphia Neurodevelopmental Cohort data set[a]



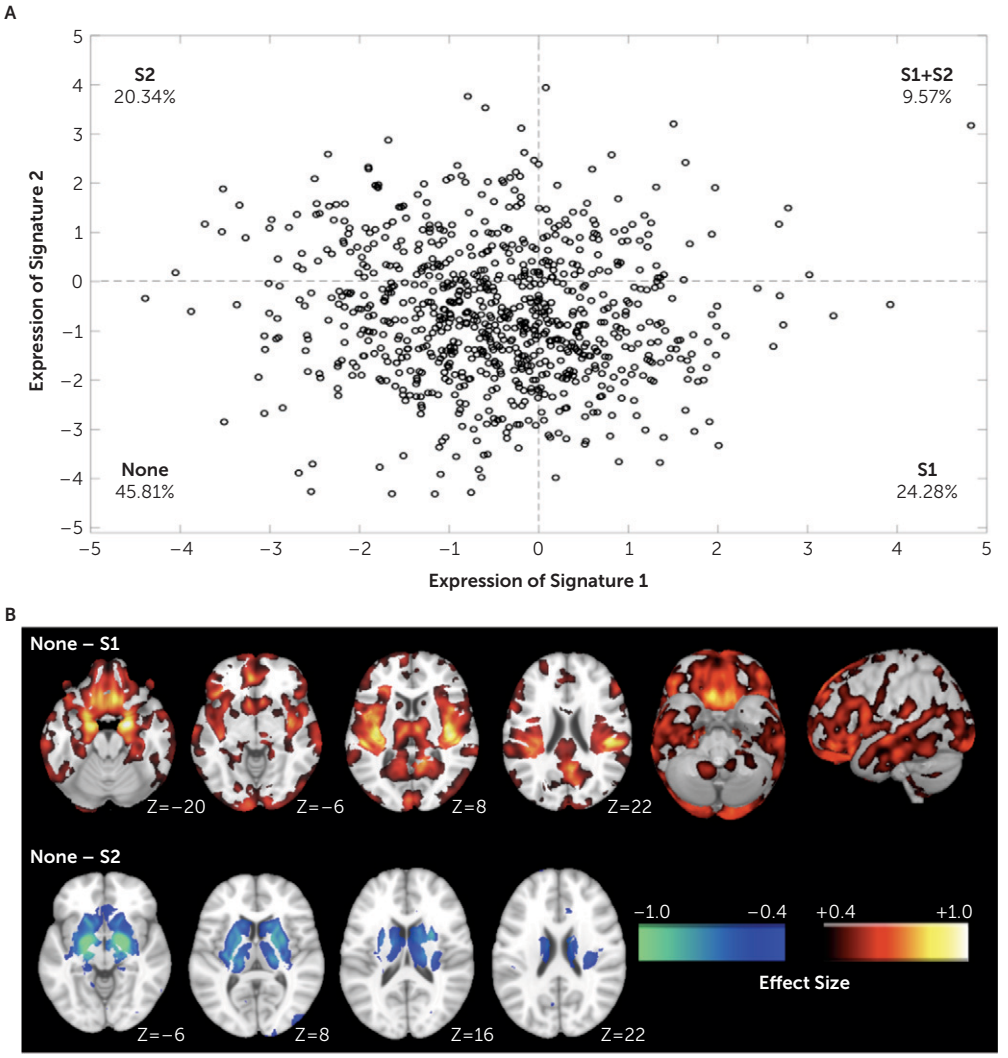
[a] In panels A–D, S1 expression across the full sample was inversely correlated with global cognitive performance efficiency (combination of accuracy and speed) (Spearman's rank correlation, $\rho=-0.28$, $p<10^{-4}$) and accuracy ($\rho=-0.24$, $p<10^{-4}$), whereas stronger S2 expression was correlated with higher efficiency ($\rho=0.13$, $p<0.05$), and S2 expression was not significantly associated with accuracy ($\rho=0.06$, $p>0.05$). In panels E–G, individuals with S1 had worse efficiency (Wilcoxon rank sum test, $z=-4.64$, $p<10^{-4}$), accuracy ($z=-3.38$, $p<0.05$), and speed ($z=-2.71$, $p<0.05$) than those with S2. The S1 subgroup also had worse efficiency ($z=-4.50$, $p<0.05$), accuracy ($z=-3.91$, $p<0.05$), and speed ($z=-2.53$, $p<0.05$) than the "none" subgroup. Error bars indicate standard error of the mean over subjects; asterisks indicate $p<0.05$, corrected for multiple comparisons.

accuracy correlation. Compared with PNC youths with signature 2, those with signature 1 had lower efficiency (Wilcoxon test: $z=-4.64$, $p<10^{-4}$), accuracy ($z=-3.38$, $p<0.05$), and speed ($z=-2.71$, $p<0.05$) (Figure 2E–G). Compared with individuals with neither schizophrenia signature, those with signature 1 also had lower efficiency ($z=-4.50$, $p<0.05$), accuracy ($z=-3.91$, $p<0.05$), and speed ($z=-2.53$, $p<0.05$). Consistent results were found after excluding individuals with threshold-level psychosis ratings (see the section "Schizophrenia signatures excluding participants who endorse full psychotic-level symptoms" in the online supplement). Exploratory results for individual Penn Computerized Neurocognitive Battery tasks are presented in Figure S8 in the online supplement. Typically developing and psychosis spectrum youths were also analyzed separately, and similar signature-cognition relationships were found (see Figure S9 in the online supplement). Exploratory results for available dimensional clinical measures are shown in Tables S2 and S3 in the online supplement. There was an inverse relationship between signature 1 and signature 2 expression strength ($\rho=-0.28$, $p<10^{-4}$).

Prevalence of Schizophrenia Imaging Signatures in the UK Biobank

In UK Biobank adults, prevalences of signature 1, signature 2, both signatures, and "none" were 24.28%, 20.34%, 9.57%, and 45.81%, respectively (Figure 3A). Signature 1 was characterized by widespread reductions in gray matter and white matter volumes (compared with "none"), while signature 2 was associated with markedly increased striatal and internal capsule volumes (Figure 3B; see also Figure S10 in the online supplement; Cohen's d effect sizes were ~1.0 in regions showing the most prominent differences). Exploratory analyses in the UK Biobank participants up to age 55 are also presented in the

FIGURE 3. Presence of signature 1 (S1) and signature 2 (S2) expressions in the UK Biobank data set[a]



[a] In panel A, dimensional expression strength was visualized in a two-axis (E_1, E_2) framework, with individuals across S1, S2, both signatures (S1+S2), and neither signature ("none"). In panel B, voxel-based comparisons of regional gray matter volumes between individuals expressing primarily S1 (top) or S2 (bottom), compared with individuals expressing neither of these signatures, are displayed for visualization purposes. Individuals with S1 were characterized by significantly reduced gray matter volumes, especially in prefrontal, temporal, and peri-Sylvian regions, whereas those with S2 were characterized by markedly increased striatal volumes compared to the "none" subgroup. Cohen's d (effect size) maps were generated by masking MIDAS results after false discovery rate correction over voxels at $p<0.05$. (See Figure S10 in the online supplement for visualization of white matter comparison.)

online supplement (see the section "Schizophrenia signature prevalence in UK Biobank older participants").

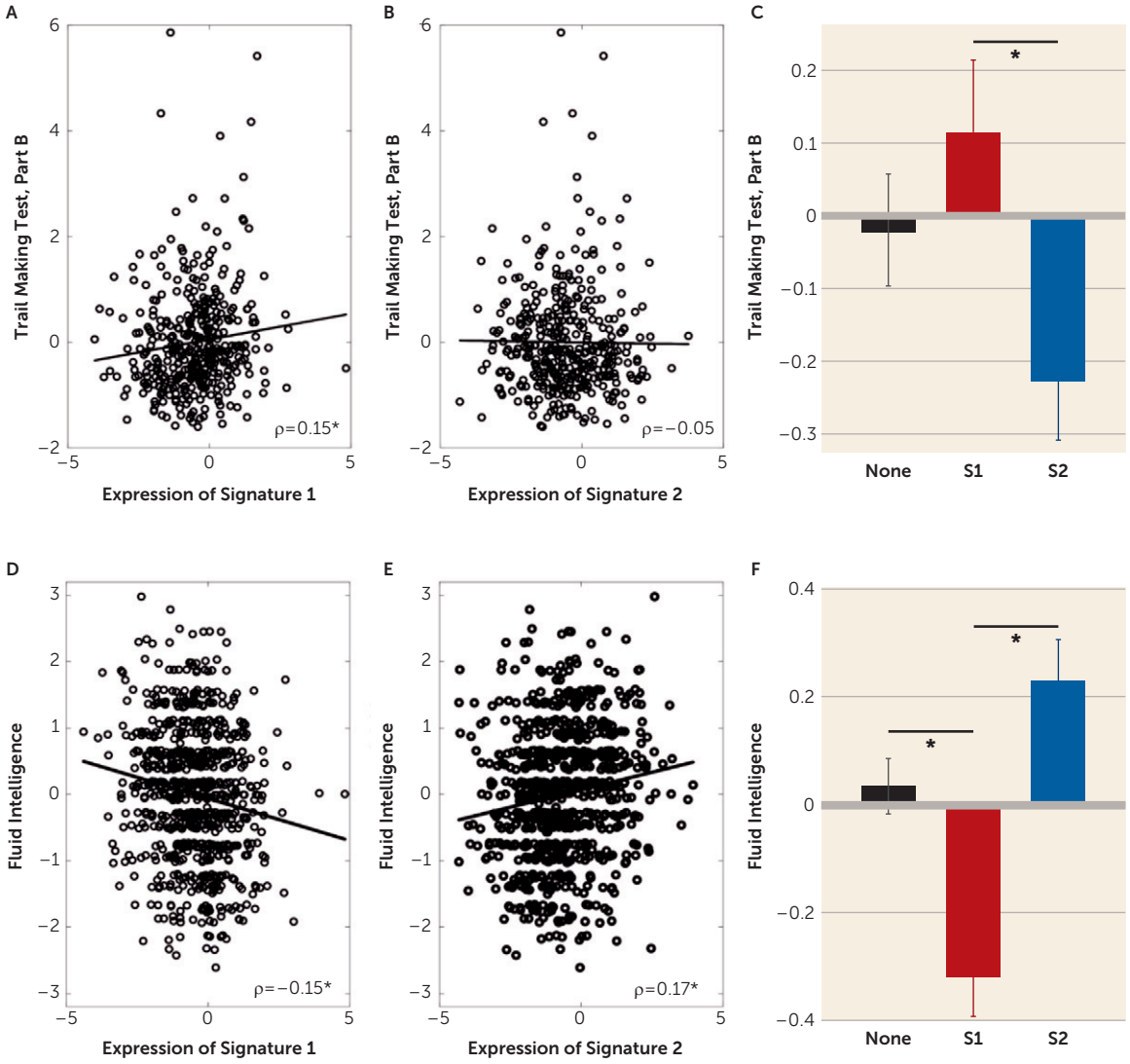
Associations Between Signature 1, Signature 2, and Cognition in the UK Biobank

In UK Biobank adults, greater signature 1 expression was correlated with worse cognitive performance on the Trails B task ($\rho=0.15$, $p<0.05$), with a nonsignificant correlation for signature 2 expression (Figure 4A,B). Signature 1 was associated with worse Trails B performance than signature 2 ($z=2.85$, $p<0.05$) (Figure 4C; see also Figure S11 in the online supplement). Fluid intelligence was negatively correlated with signature 1 expression ($\rho=-0.15$, $p<10^{-4}$) but positively with signature 2 expression ($\rho=0.17$, $p<10^{-4}$) (Figure 4D,E), and fluid intelligence was lower in signature 1 than signature 2 ($z=-5.16$, $p<10^{-4}$) and "none" ($z=-3.89$, $p<0.05$). Exploratory results for available dimensional clinical and other cognitive measures are shown in Table S4 and Figure S12 in the online supplement. Expressions of signature 1 and signature 2 were inversely associated ($\rho=-0.11$, $p<0.05$).

Genetic Associations of Signature 1 and Signature 2 in the UK Biobank

In the UK Biobank, signature 1 was associated with significantly higher schizophrenia PRS compared with "none" (Wilcoxon test; $z=2.69$, $p<0.05$), but this was not seen for signature 2 (Figure 5; see also Figure S13 in the online

FIGURE 4. Cognitive profiles of signature 1 (S1) and signature 2 (S2) in the UK Biobank data set[a]



[a] In panel A, stronger S1 expression across the full sample was associated with worse cognitive performance on the Trail Making Test, part B (Trails B; higher Trails B time reflects worse performance) ($\rho=0.15$, $p<0.05$), whereas in panel B, S2 expression was not significantly correlated with Trails B ($\rho=-0.05$, $p>0.05$). In panel C, the S1 subgroup had worse cognitive performance on Trails B than the S2 subgroup ($z=2.85$, $p<0.05$). In panel D, stronger S1 expression across the full sample was correlated with worse cognitive performance on the fluid intelligence test ($\rho=-0.15$, $p<10^{-4}$), whereas in panel E, S2 expression was positively correlated with the fluid intelligence test ($\rho=0.17$, $p<10^{-4}$). In panel F, the S1 subgroup had worse cognitive performance on the fluid intelligence test than the S2 subgroup ($z=-5.16$, $p<10^{-4}$) and the "none" subgroup ($z=-3.89$, $p<0.05$). Error bars indicate standard error of the mean over subjects; asterisks indicate $p<0.05$, corrected for multiple comparisons.

supplement; for dimensional associations between signature expression and schizophrenia PRS, see Figure S14 in the online supplement).

DISCUSSION

In this study, we replicated our recent findings of two novel neuroanatomical signatures of schizophrenia (5), in an independent schizophrenia sample. We then examined the expression of these signatures in separate youth and adult population-based cohorts to measure signature prevalence, quantitative expression strength, and associations with psychosis spectrum status, cognition, and genetics. Overall, moving from control subjects to those with psychosis spectrum symptoms to those with schizophrenia, the prevalence of both schizophrenia signatures trended upward, consistent with these signatures reflecting psychosis spectrum pathophysiology. Signature 1, marked by lower cortical gray matter and white matter volumes, was associated with psychosis spectrum status in PNC youths and with impaired cognition in both PNC youths and UK Biobank adults. In contrast, signature 2, marked by larger striatal and internal capsule volumes and normal to mildly larger cortical gray matter and white matter volumes, was not significantly associated with psychosis spectrum symptoms and showed a positive association with cognitive performance. Schizophrenia PRS was

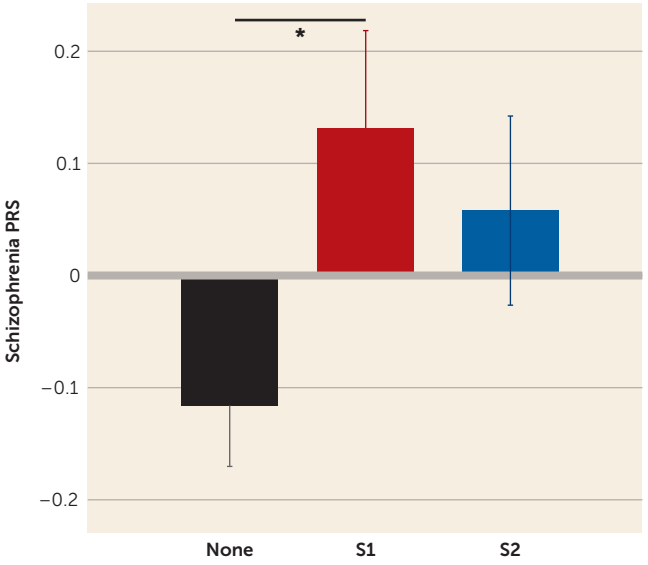
not significantly different between individuals with signature 1 and signature 2, and only those with signature 1 had significantly higher polygenic risk compared with those without either signature. A small fraction of healthy individuals (5%–10%) expressed both signature 1 and signature 2, with somewhat higher percentages in psychosis spectrum youths than in typically developing youths. Thus, signature 1 and signature 2 capture distinct neurostructural dimensions, creating a novel two-axis framework for investigating the neuroanatomy of psychosis risk.

Prevalence of Schizophrenia Neuroanatomical Signatures and Their Significance

As expected for dimensional brain imaging signatures, a substantial proportion of healthy individuals expressed them to some degree. The presence of schizophrenia-related neuroanatomical signatures in healthy individuals raises the question of their clinical significance. It is possible that these signatures, particularly signature 1, reflect neuroanatomical correlates of schizotaxia, a putative neurobiological state conferring risk for schizophrenia (10, 35). Meehl, who developed the concept of schizotaxia (9), predicted that ~10% of healthy individuals have schizotaxia. The idea that biological vulnerability to schizophrenia is present in a substantial fraction of individuals even in the absence of a detectable pathological behavioral phenotype is highly plausible and is supported by our findings here. Nonetheless, it is likely that only a minority of healthy participants identified here as expressing schizophrenia-related signatures would have a substantially elevated risk of schizophrenia. One possibility is that the signatures are truly dimensional, and that the lowest levels of expression are common but reflect negligible levels of pathophysiology or risk. Another possibility is that low levels of expression reflect normal variation in brain structure, which is etiologically unrelated to schizophrenia, whereas at higher expression levels, perhaps above a specific threshold, their association with pathophysiology and vulnerability would be much stronger. Here we do see that the strength of signature 1 and signature 2 expression is greater in patients with schizophrenia than in control subjects identified by the same binarized signature definitions. Yet another possibility is that healthy individuals expressing these signatures have other protective or compensatory structural or functional brain characteristics.

Thus, the neuroanatomical signatures we identified in order to help parse the heterogeneity of schizophrenia are themselves likely to have heterogeneity with respect to underlying etiological and microstructural contributors, coincidence of other biological and environmental factors, and, hence, pathophysiological significance. Even at a given level of expression, it is likely that the clinical significance of these signatures would depend on the population—for example, varying by age and prevalence of various medical or psychiatric conditions, as these signatures are less robust at distinguishing psychosis spectrum from typically developing youths than schizophrenia from control subjects among adults. We note that the complexity of neuroanatomical signatures of risk is not substantially different from psychosis risk approaches focused on subthreshold symptoms; population samples reveal such symptoms in 10%–15% of youths, most of whom will not go on to develop a frank psychotic disorder (11, 36). While more work is needed to clarify these issues, having a neurostructural approach to assess schizophrenia risk complements the current symptom-based approach, and a combination of these (together with genetic and other biomarkers) is likely to optimize sensitivity and specificity for determining risk, establishing diagnosis, or predicting outcomes (37).

FIGURE 5. Genetic profiles of signature 1 (S1) and signature 2 (S2) in the UK Biobank data set[a]



[a] Only the S1 subgroup had significantly higher polygenic risk scores (PRSs) for schizophrenia compared with the "none" subgroup (Wilcoxon rank sum test, $z=2.69$, $p<0.05$). Error bars indicate standard error of the mean over subjects; asterisks indicate $p<0.05$, corrected for multiple comparisons.

Differences Between Signatures

Signature 1 was associated with psychosis spectrum status and with poorer cognition across groups, consistent with previous work linking reduced brain volume, especially in fronto-temporal regions, to worse cognitive performance, and with evidence of impaired cognition in schizophrenia and at-risk states (17–19). Overall, signature 1 captures a more typical or prevalent schizophrenia-related signature that is also more closely linked to known clinical risk factors in the general population. However, in PHENOM, signature 2 was present in about one-third of individuals with established schizophrenia, and these individuals did not differ dramatically in clinical features from schizophrenia with signature 1 (aside from lower educational attainment in signature 1 and an association of signature strength with longer illness duration only in signature 1) (5).

Signature 2 captures at least two aspects of brain structure: one is intact or mildly enlarged cortical volume, and the other is a marked enlargement of the striatum and internal capsule. While it seems certain that a substantial subset of individuals with clinical risk for psychosis express a signature 2-like phenotype, the specificity of this phenotype as defined here is not sufficient to identify a group with elevated psychosis spectrum symptoms in the general population. Signature 1 may thus be more strongly associated with primary neurostructural abnormalities, and we speculate that clinical deficits in the signature 2 group, with its largely intact structure, are associated with primary functional abnormalities, perhaps in dopaminergic systems, leading secondarily to basal ganglia enlargement. As noted above, a greater degree of signature 2 expression or combined occurrence with other factors may be needed to confer substantial schizophrenia risk. Broadly, the results here as well as the previous findings in schizophrenia are consistent with signature 1 reflecting an early developmental vulnerability to schizophrenia, while signature 2 reflects a signature devoid of substantial premorbid deficits.

The present study also identified increased polygenic risk for schizophrenia in individuals expressing signature 1 relative to those with neither signature; however, polygenic risk did not differ between the two schizophrenia signatures. These results are consistent with heterogeneity in the neurostructural phenotypes linked to the broad genetic risk profile captured by the schizophrenia PRS. The more robust genetic relationship with signature 1 is consistent with higher prevalence of this signature in schizophrenia; with prior evidence that polygenic risk is particularly associated with schizophrenia following early neurodevelopmental insults (22) and with cognitive impairment (23); and with findings in the general population linking schizophrenia polygenic risk to lower cortical volume (14).

Limitations

Several important limitations of this study should be acknowledged. The data are cross-sectional, and future studies will need to assess change in signature expression over time, as well as whether signatures predict treatment response or other outcomes. The sample size for genetic analyses was relatively small; studies in larger samples will be important. While the PNC had a rich data set of clinical and cognitive measures in youths and the UK Biobank had a rich data set of genetics in adults, examination of large samples including comprehensive measures will be critical. Our clinical focus is on psychosis, as these signatures were identified in schizophrenia; however, a detailed understanding of the extent to which they are truly psychosis specific will require further work across multiple psychiatric populations. Furthermore, this work only investigates neurostructural signatures; such volumetric measures are highly reliable, but an important future direction will be to examine noisier functional neuroimaging phenotypes (38) and to evaluate multimodal biotypes. Lastly, we note that the relationships we identified have small effect sizes, as is typical for brain-behavior relationships when accurately assessed in large samples (39). While this requires caution regarding expectations of clinical applications, small effects can still provide critical clues to underlying pathophysiology (40).

CONCLUSIONS

We identified two replicable schizophrenia signatures and showed that they are also detectable in a majority of individuals with psychosis spectrum symptoms even in the subclinical range, as well as a substantial minority of individuals without significant psychopathology. In these population-based cohorts, only the more neuroanatomically abnormal signature 1 was associated with cognitive impairment, and the elevation in polygenic risk for schizophrenia was somewhat higher in signature 1. These results may enhance future efforts to parse neurobiological heterogeneity and develop personalized approaches to identifying risk and preventing illness progression.

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Code availability: HYDRA (https://github.com/evarol/HYDRA) and MIDAS (https://github.com/evarol/MIDAS) codes used in this study are publicly available. The custom codes used in this study are also publicly available at https://github.com/ganchand/AJP_Codes.

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Examination Questions for Schizophrenia Imaging Signatures and Their Associations With Cognition, Psychopathology, and Genetics in the General Population

1. **Which one of the followings is generally known as a semi-supervised machine learning method?**
   - A. Control and patient labels are provided as input in machine learning method
   - B. Control and patient labels are provided as input in machine learning method, but patient clusters are unknown and needed to identify
   - C. Control and patient labels are not provided as input in machine learning method
   - D. None of above
2. **Which of the following relationships are reported between two schizophrenia imaging signatures and cognition?**
   - A. Schizophrenia signature 1 was associated negatively with cognitive performance while signature 2 associated positively
   - B. Only schizophrenia signature 1 was associated with cognitive performance
   - C. Both schizophrenia signatures were associated negatively with cognitive performance
   - D. Both schizophrenia signatures did not associate with cognitive performance
3. **What are the reported relationships of gray matter volumetric patterns in the two schizophrenia imaging signatures compared to the none of signature group?**
   - A. Gray matter volume is lower in both schizophrenia signature 1 and signature 2
   - B. Gray matter volume is lower in schizophrenia signature 1 while it is higher in signature 2
   - C. Gray matter volumes were not associated with two schizophrenia signatures
   - D. None of above