

Neurostructural Heterogeneity in Youths With Internalizing Symptoms

Antonia N. Kaczkurkin, Aristeidis Sotiras, Erica B. Baller, Ran Barzilay, Monica E. Calkins, Ganesh B. Chand, Zaixu Cui, Guray Erus, Yong Fan, Raquel E. Gur, Ruben C. Gur, Tyler M. Moore, David R. Roalf, Adon F.G. Rosen, Kosha Ruparel, Russell T. Shinohara, Erdem Varol, Daniel H. Wolf, Christos Davatzikos, and Theodore D. Satterthwaite

ABSTRACT

BACKGROUND: Internalizing disorders such as anxiety and depression are common psychiatric disorders that frequently begin in youth and exhibit marked heterogeneity in treatment response and clinical course. Given that symptom-based classification approaches do not align with underlying neurobiology, an alternative approach is to identify neurobiologically informed subtypes based on brain imaging data.

METHODS: We used a recently developed semisupervised machine learning method (HYDRA [heterogeneity through discriminative analysis]) to delineate patterns of neurobiological heterogeneity within youths with internalizing symptoms using structural data collected at 3T from a sample of 1141 youths.

RESULTS: Using volume and cortical thickness, cross-validation methods indicated 2 highly stable subtypes of internalizing youths (adjusted Rand index = 0.66; permutation-based false discovery rate $p < .001$). Subtype 1, defined by smaller brain volumes and reduced cortical thickness, was marked by impaired cognitive performance and higher levels of psychopathology than both subtype 2 and typically developing youths. Using resting-state functional magnetic resonance imaging and diffusion images not considered during clustering, we found that subtype 1 also showed reduced amplitudes of low-frequency fluctuations in frontolimbic regions at rest and reduced fractional anisotropy in several white matter tracts. In contrast, subtype 2 showed intact cognitive performance and greater volume, cortical thickness, and amplitudes during rest compared with subtype 1 and typically developing youths, despite still showing clinically significant levels of psychopathology.

CONCLUSIONS: We identified 2 subtypes of internalizing youths differentiated by abnormalities in brain structure, function, and white matter integrity, with one of the subtypes showing poorer functioning across multiple domains. Identification of biologically grounded internalizing subtypes may assist in targeting early interventions and assessing longitudinal prognosis.

Keywords: Cortical thickness, Heterogeneity, Internalizing, Structure, Volume, Youth

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Internalizing disorders, including depression and anxiety disorders, are the most common psychiatric conditions (1) and result in an enormous worldwide burden of illness (2). In contrast to cardiovascular or neurodegenerative disorders, internalizing disorders often begin in youth, leading to a lifetime of morbidity (1,3). At the present time, the diagnosis of internalizing disorders is driven by presenting symptoms, as codified in DSM-5. However, such diagnoses often lack specificity, as evinced by the high degree of comorbidity with other psychiatric disorders (4,5) and marked heterogeneity in both treatment response and longitudinal outcome (6).

Emerging evidence from epidemiology, genetics, and clinical neuroimaging often does not support the current diagnoses codified in the DSM-5 (7–9). One alternative is to evaluate dimensions of symptoms that cross diagnostic boundaries (10). However, dimensional models based on

symptoms do not account for the neurobiological mechanisms underlying psychiatric symptoms. A classification approach that parses heterogeneous clinical syndromes based on neurobiological data would be a significant advancement for the field (11). Intensifying efforts are being made to identify neurobiologically informed subtypes using machine learning techniques. Using such an approach, patients are clustered into disease subgroups according to shared patterns in imaging or other data types to reveal the heterogeneous biological mechanisms that underlie comorbid disorders. Recent work has delineated neurobiological subtypes in Alzheimer's disease (12–14), depression (15,16), and psychosis (17–19) in adults as well as in attention-deficit/hyperactivity disorder in youths (20,21).

To our knowledge, as of yet there have been no efforts to parse neurobiological heterogeneity in youths with internalizing

symptoms. Accordingly, the aim of the current study was to delineate patterns of neurostructural heterogeneity in internalizing symptoms in relation to typically developing control youths among 1141 youths using data-driven machine learning techniques. Both volume and cortical thickness were included, as genetic studies suggest that these two measures can provide complementary but distinct information (22). These subtypes were then evaluated using independent clinical, cognitive, and neuroimaging data that were not used in the clustering process.

METHODS AND MATERIALS

Participants

As part of the Philadelphia Neurodevelopmental Cohort, a large community-based sample of youths, 1601 participants 8 to 23 years of age received multimodal neuroimaging, clinical phenotyping, and cognitive assessment (23,24). After standard exclusion criteria (including medical disorders and structural image quality) (Supplement), 715 participants met screening criteria for an anxiety and/or depressive disorder, and 426 were typically developing youths with no psychiatric diagnoses (total $N = 1141$). As expected, the internalizing group had a greater percentage of female participants than the control group of typically developing youths. Furthermore, modality-specific quality assurance was performed and resulted in a sample of 840 youths with resting-state functional magnetic resonance imaging (rsfMRI) and 923 youths with diffusion imaging data (Supplement). Finally, a subsample with data on gestational age at birth ($n = 282$) was used to examine birth history (25). The institutional review boards of the University of Pennsylvania and the Children's Hospital of Philadelphia approved the study procedures. All participants provided written informed consent after receiving a complete description of the study.

Clinical Assessment

As described in detail in our previous work (23,24,26) and in the Supplement, assessment of lifetime psychopathology was conducted using GOASSESS, a structured screening interview based on a modified version of the Kiddie Schedule for Affective Disorders and Schizophrenia (27). We included participants in the internalizing group if they met criteria for any anxiety and/or depressive disorder, including agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, separation anxiety disorder, social anxiety disorder, specific phobia, or major depressive disorder (Table 1).

Clinical and Cognitive Factor Analyses

As in prior work (28,29), to provide a dimensional summary of the diverse psychopathology data, we used a confirmatory bifactor analysis (30,31) to model 4 orthogonal factors (anxious-misery, psychosis, behavioral, and fear) plus a general factor, overall psychopathology, which represents symptoms common across all psychiatric disorders (Supplement). Cognition was assessed using the University of Pennsylvania Computerized Neurocognitive Battery, which has been described in detail elsewhere (32). Fourteen cognitive tests

Table 1. Summary of Demographic Data

	TD ($n = 426$)	S1 ($n = 403$)	S2 ($n = 312$)
Age, Years, Mean (\pm SD)	14.68 (\pm 4.05)	15.35 (\pm 3.35)	15.10 (\pm 3.66)
Sex, n (%)			
Female	208 (49)	240 (60)	179 (57)
Male	218 (51)	163 (40)	133 (43)
Trauma Exposure, n (%)			
No trauma	295 (69)	146 (36)	142 (46)
1 trauma	86 (20)	113 (28)	92 (29)
\geq 2 traumas	45 (11)	144 (36)	78 (25)
Internalizing Disorders ($n = 715$), n (%)			
Agoraphobia	–	51 (4)	27 (2)
Generalized anxiety disorder	–	13 (1)	14 (1)
Major depression	–	109 (10)	82 (7)
Obsessive-compulsive disorder	–	26 (2)	17 (1)
Panic	–	10 (0.9)	4 (0.4)
PTSD	–	112 (10)	56 (5)
Separation anxiety	–	29 (3)	34 (3)
Social anxiety	–	193 (17)	125 (11)
Specific phobia	–	230 (20)	184 (16)
Comorbid Disorders, n (%)			
ADHD	–	77 (7)	70 (6)
Anorexia	–	10 (0.8)	5 (0.4)
Bulimia	–	2 (0.2)	3 (0.3)
Conduct disorder	–	65 (6)	19 (2)
Mania	–	7 (0.6)	5 (0.4)
Oppositional defiant disorder	–	200 (18)	106 (9)
Psychosis spectrum	–	169 (15)	106 (9)

Owing to comorbidity, individual participants may be present in more than 1 category of lifetime prevalence.

ADHD, attention-deficit/hyperactivity disorder; PTSD, posttraumatic stress disorder; S1, subtype 1; S2, subtype 2; TD, typically developing youths.

evaluating aspects of cognition were summarized with exploratory factor analysis into 3 domains: 1) executive function and complex reasoning, 2) social cognition, and 3) episodic memory (Supplement). Reading skills were measured with the Wide Range Achievement Test–4th Edition reading subscale (33).

Image Acquisition, Quality Assurance, and Image Processing

Image acquisition, processing, and quality assurance procedures for volume, cortical thickness, rsfMRI, and diffusion tensor imaging (DTI) measures have been previously described (24,34,35) and are detailed in the Supplement. Structural images were processed using the top-performing tools included in Advanced Normalization Tools (36). Functional connectivity among brain regions is primarily attributable to correlations between low-frequency fluctuations in regional activation patterns (37). Therefore, we computed the voxelwise amplitude of low-frequency fluctuations (ALFF) as the sum over frequency bins in the low-frequency (0.01–0.08 Hz) band of the power spectrum (37). Although there are many different resting-state functional connectivity measures, here we used

ALFF based on prior work showing abnormal-resting state fluctuations in subjects with psychopathology (37–43). ALFF also allowed us to compare our structural measures with a resting-state measure using the same atlas, allowing for correspondence of brain regions across modalities. Cortical thickness, volume, and ALFF were summarized in anatomic regions within gray matter defined on an individual basis using a top-performing multi-atlas labeling procedure with joint label fusion (44). Fractional anisotropy maps were calculated from DTI using FSL (45) and summarized in tracts defined by the Johns Hopkins University white matter tractography atlas (46).

Parsing Heterogeneity With Semisupervised Machine Learning

To identify neurostructural subtypes within youths with internalizing symptoms, we used a recently developed semisupervised machine learning tool, HYDRA (heterogeneity through discriminative analysis) (12). In contrast to fully supervised learning techniques (i.e., support vector machines or random forests), which cannot distinguish between subtypes of cases (Figure 1A), HYDRA clusters cases based on their differences from controls by finding multiple linear hyperplanes, which together form a convex polytope (Figure 1B). In contrast to unsupervised clustering techniques (i.e., k means or community detection), HYDRA does not cluster patients based on their similarity, which is a process that is vulnerable to confounding interindividual variations that are irrelevant to disease (e.g., owing to age or sex).

HYDRA defined neurostructural subtypes using the volume of 112 cortical and subcortical regions as well as the cortical

thickness of 98 regions, adjusted for age and sex. Consistent with studies using this technique (12), we derived multiple clustering solutions requesting 2 to 10 clusters to obtain a range of possible solutions. The adjusted Rand index (ARI) was calculated using 10-fold cross-validation to evaluate the stability of each solution; the solution with the highest ARI value was selected for subsequent analyses. If instead a 1-cluster solution exists, the reproducibility of the solutions will be poor. Permutation testing was used to statistically evaluate the stability of observed ARI values compared with a null distribution (Supplement).

Group-Level Statistical Analyses

After parsing subtypes of internalizing youths based on structural data, we sought to 1) define how the subtypes differed on demographics, psychopathology, and cognition; 2) understand what structural features (thickness, volume) drove the subtypes discovered; and 3) investigate differences between the subtypes in 2 independent neuroimaging sequences not used in clustering (ALFF from rsfMRI and fractional anisotropy from DTI). Both linear and nonlinear age effects were modeled using penalized splines within a generalized additive model, which assesses a penalty on nonlinearity using restricted maximum likelihood to avoid overfitting (47,48). Age, sex, and image quality (see Supplement for details) were modeled as follows:

$$\text{Region} = \text{spline}(\text{age}) + \text{sex} + \text{image quality rating} + \text{group}$$

Omnibus analyses of variance and pairwise post hoc tests were corrected for multiple comparisons by controlling the

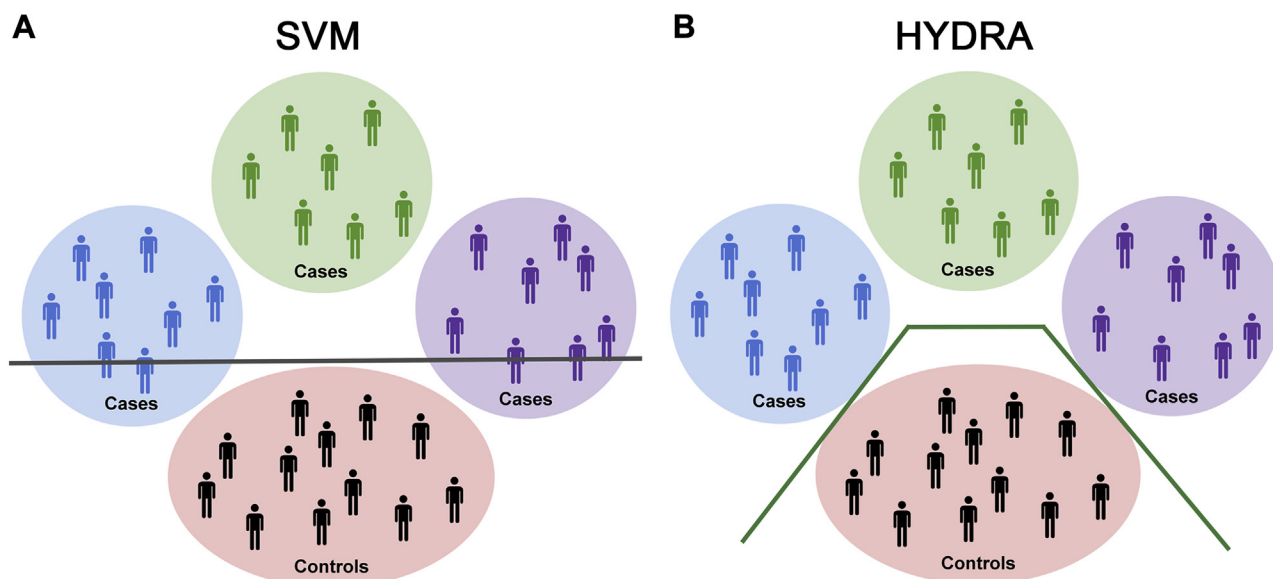


Figure 1. Schematic representing the utility of the semisupervised machine learning tool HYDRA (heterogeneity through discriminative analysis) over support vector machines (SVMs) for parsing heterogeneity. **(A)** Schematic illustrating the use of a linear support vector machine to separate cases from controls with a separating hyperplane, shown here as a gray line. Heterogeneity within cases is represented by blue, green, and purple circles. As can be seen in this schematic, linear support vector machines do not capture the heterogeneity that exists in the cases. **(B)** Conversely, HYDRA is able to classify each cluster of cases separately from controls. This is accomplished by using multiple classifiers that form linear hyperplanes (green lines) whose segments separate the clusters of cases from controls. The goal is to estimate k hyperplanes that distinguish controls and cases with the largest margin, thus allowing HYDRA to identify heterogeneous groups within the cases.

false discovery rate ($q < .05$). Interactions between group and age as well as group and sex were also evaluated. Finally, sensitivity analyses that excluded subjects on psychiatric medications and included race as an additional covariate were conducted.

Data and Code Availability

See <https://github.com/PennBBL/KaczurkinHeterogenInternalizing> for all data analysis codes used in this article and a wiki detailing what each script does and the order the scripts were run. Data from the Philadelphia Neurodevelopmental Cohort can be accessed at https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000607.v3.p2. The HYDRA code can be found at <https://github.com/evanol/HYDRA>.

RESULTS

HYDRA Identifies Subtypes of Internalizing Youths With a High Degree of Stability

HYDRA identified k neurostructural subtypes from 210 regional brain features (volume and cortical thickness) after adjusting for age and sex. Evaluation of cluster stability using 10-fold cross-validation exhibited a well-defined peak at $k = 2$ (Figure 2), suggesting the existence of 2 highly reproducible subtypes (ARI = 0.66) within internalizing youths. Finding a

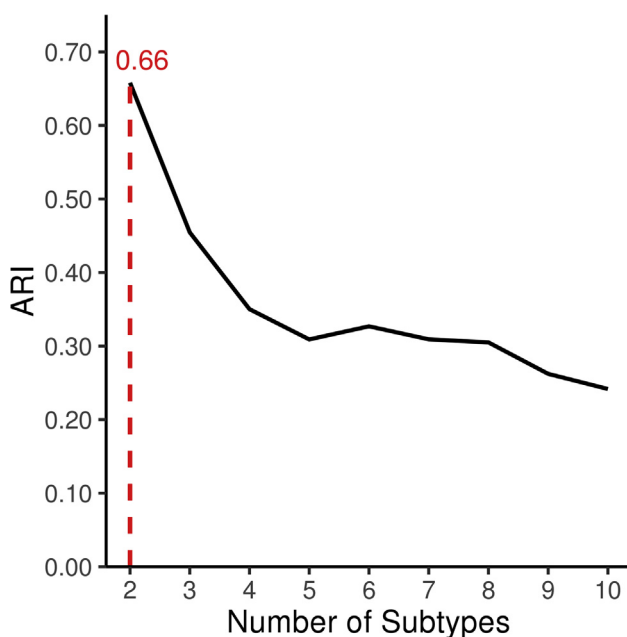


Figure 2. The semisupervised machine learning tool HYDRA (heterogeneity through discriminative analysis) identifies 2 subtypes of internalizing youths with a high level of stability. Cross-validated adjusted Rand index (ARI) for 2–10 cluster solutions was obtained with HYDRA. ARI was computed with 10-fold cross-validation to quantify the similarity between different clustering results while controlling for grouping by chance, resulting in a more conservative estimation of the overlap between clustering solutions. The figure shows a clear peak at the 2-cluster solution (shown with a dotted line), suggesting our data have 2 subtypes of internalizing youths that show a high degree of stability (ARI = 0.66).

reproducible solution for $k > 1$ suggests that there is structure in the data (in other words, the data are not homogeneous), as the reproducibility of the solution would be poor if the data were instead characterized by a 1-cluster solution. Permutation results further demonstrated a significantly higher ARI for the 2-subtype solution compared with a null distribution (false discovery rate $p < .001$).

Subtype Demographics

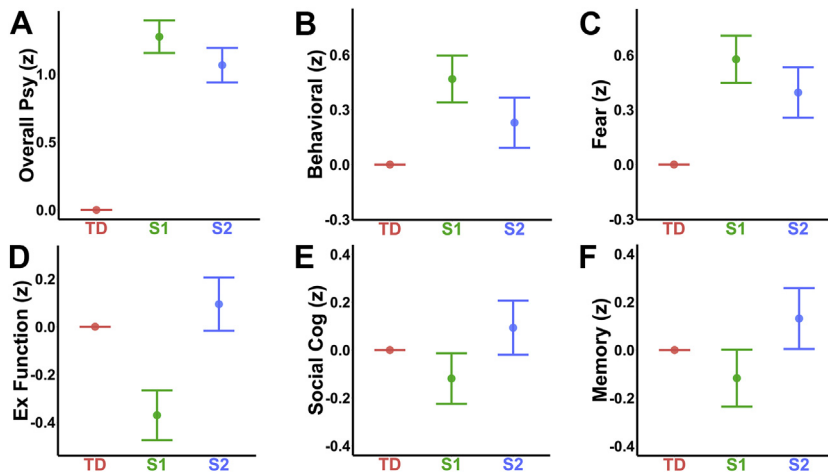
As an initial step, we evaluated the demographics of our neurostructural subtypes (Supplemental Table S1). Groups differed in age, with subtype 1 being slightly older than typically developing youths; no other age effects were significant. All subsequent analyses controlled for age and sex. Subtype 1 also had lower maternal education than subtype 2 or typically developing youths, whereas subtype 2 did not differ from typically developing youths in this regard. In addition, both subtype 1 and subtype 2 showed higher levels of trauma exposure than typically developing youths; moreover, subtype 1 had higher levels of trauma exposure compared with subtype 2. In a subsample of subjects with data on gestational age at birth ($n = 282$), subtype 1 had a lower gestational age on average than typically developing youths but did not significantly differ from subtype 2.

Elevated Psychopathology Is Present in Subtype 1

Next, we evaluated whether the internalizing neurostructural subtypes differed in terms of psychopathology. Psychopathology symptoms were summarized as factors that reflect anxious-misery, psychosis, behavioral, fear, and overall psychopathology. As expected based on the inclusion criteria (all patients met criteria for an internalizing disorder), both subtype 1 and subtype 2 showed elevated psychopathology symptoms compared with typically developing youths in all domains (Supplemental Table S1). Accordingly, we focused on differences between the subtypes. Subtype 1 showed greater overall psychopathology symptoms (Figure 3A), behavioral symptoms (Figure 3B), and fear symptoms (Figure 3C) compared with subtype 2. No significant differences were found between the subtypes for anxious-misery or psychosis. These results demonstrate that subtype 1 shows a higher burden of psychiatric symptoms than both subtype 2 and typically developing youths across multiple domains.

Subtype 1 Is Marked by Impaired Cognition

We then evaluated whether the subtypes differed in cognitive performance and reading skills. Notably, these independent data were not used in clustering. Subtype 1 showed significantly reduced overall accuracy relative to subtype 2 and typically developing youths, with no difference found between typically developing youths and subtype 2 (Supplemental Table S1). Analyses of the specific accuracy factors revealed that subtype 1 showed reduced performance relative to subtype 2 on all factors, including executive function/complex reasoning (Figure 3D), social cognition (Figure 3E), and episodic memory (Figure 3F; Supplemental Table S1). Compared with typically developing youths, subtype 1 had lower performance for executive function/complex reasoning and social cognition, but not for episodic memory. Subtype 2



were no significant differences between S1 and S2 for the anxious-misery or psychosis factors. In terms of cognition, S1 showed significantly lower performance on (D) executive (Ex) functioning tasks than both TD and S2; S2 did not differ from TD. S1 also performed more poorly relative to the other 2 groups in terms of (E) social cognition (Cog), whereas S2 again did not differ from TD. Additionally, S1 performed significantly below S2 on (F) episodic memory; however, neither S1 nor S2 significantly differed from TD.

did not significantly differ from typically developing youths on any of these measures. In terms of academic skills, subtype 1 demonstrated lower reading skills than both subtype 2 and typically developing youths, who did not differ from each other (Supplemental Table S1).

Subtypes Display Markedly Divergent Patterns of Brain Structure

Having identified 2 subtypes of internalizing youths based on total gray matter volume and cortical thickness data, we examined the structural features that drove this clustering. The results demonstrated that subtype 1 showed smaller regional volumes than either subtype 2 or typically developing youths for all 112 regions (Figure 4A; Supplemental Figure S1A; Supplemental Table S2). Likewise, subtype 1 had thinner cortex in 96 of 98 regions compared with subtype 2 (Figure 4B; Supplemental Table S2) and in 95 regions compared with typically developing youths (Supplemental Figure S1B; Supplemental Table S2). Compared with typically developing youths, subtype 2 demonstrated greater volume in 111 regions (Supplemental Figure S2A; Supplemental Table S2) and greater cortical thickness in 81 regions (Supplemental Figure S2B; Supplemental Table S2). Interactions between group and age as well as group and sex were evaluated but found to be nonsignificant except for volume of occipital fusiform gyrus. The results were similar when examining total brain volume (TBV) or intracranial volume (ICV) (Supplemental Table S2), as TBV and ICV are highly correlated in this developmental sample (Supplemental Figure S3).

Subtype 1 Shows Abnormalities in Resting-State and Diffusion Measures

Finally, to further understand differences in these neurostructural subtypes, we examined 2 independent imaging modalities that were not used in clustering: ALFF from rsfMRI and fractional anisotropy from DTI. ALFF was reduced in subtype 1 compared with subtype 2 in 40 frontal cortex and

Figure 3. Comparing subtype 1 (S1) and subtype 2 (S2), S1 shows greater psychopathology and poorer cognitive performance. (A–F) Estimates are shown on the y-axis from the fitted model testing for group differences in each domain. Each vertical line represents the 95% confidence interval, with the comparison group (typically developing youths [TD]) represented by its mean line. The subtype is significantly different from TD if its corresponding confidence interval does not contain 0 (the mean of TD). To examine differences in psychopathology, symptoms were summarized into anxious-misery, psychosis, behavioral, fear, and overall psychopathology factors (28,29,57). As expected, both S1 and S2 showed greater levels of psychopathology compared with TD across all psychopathology factors; thus, we focus on the differences between S1 and S2. S1 showed higher levels of (A) overall psychopathology (Psy), (B) behavioral symptoms, and (C) fear symptoms than S2. There

limbic regions, including bilateral middle/superior frontal gyrus, right amygdala, and right hippocampus (Figure 4C; Supplemental Table S3). Subtype 1 also showed reduced amplitudes in 25 of these regions compared with typically developing youths (Supplemental Figure S1C; Supplemental Table S3). Conversely, subtype 2 demonstrated greater ALFF in 13 regions compared with typically developing youths (Supplemental Figure S2C; Supplemental Table S3). These results suggest that subtype 1 shows abnormalities in the resting-state power spectrum in regions associated with executive functioning and affective processing.

Differences between subtype 1 and subtype 2 were also apparent in fractional anisotropy. Subtype 1 showed reduced fractional anisotropy compared with subtype 2 in 10 of 18 white matter tracts, including the inferior longitudinal fasciculus, uncinate fasciculus, anterior thalamic radiation, corticospinal tracts, parahippocampal cingulum bundle, superior longitudinal fasciculi, and forceps minor (Figure 4D; Supplemental Table S4). Subtype 1 also showed reduced fractional anisotropy in 8 tracts compared with typically developing youths (Supplemental Figure S1D; Supplemental Table S4). Subtype 2 showed relatively similar fractional anisotropy to typically developing youths, with only the left and right anterior thalamic radiations demonstrating higher levels in subtype 2 (Supplemental Figure S2D; Supplemental Table S4). These results emphasize that subtype 1 has reduced white matter integrity in several key tracts that link frontal cortex and limbic brain regions. The interrelationships between structure, ALFF, fractional anisotropy, and cognition are shown in Supplemental Figure S4.

Sensitivity Analyses Provide Convergent Results

Sensitivity analyses were conducted after excluding the minority of participants who were taking psychotropic medications at the time of imaging ($n = 1037$). In this subsample, the pattern of results for demographics, psychopathology, and cognition/academic skills remained highly similar

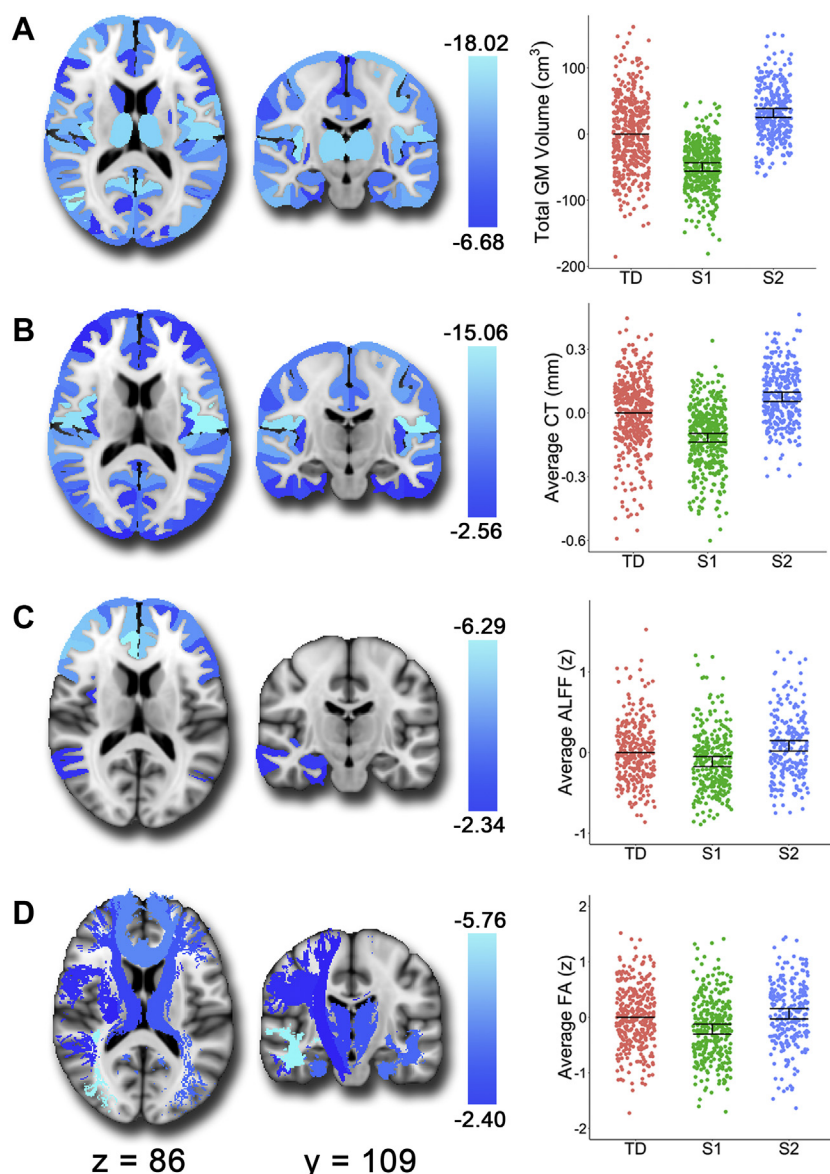


Figure 4. Subtype 1 (S1) shows smaller volume, thinner cortex, lower resting-state amplitude of low-frequency fluctuations (ALFF), and reduced white matter integrity relative to subtype 2 (S2). **(A–D)** Brain images show the t values for S1 > S2 contrast, and scatterplots show the estimates from the fitted generalized additive model with all 3 groups for comparison. Each vertical line represents the 95% confidence interval, with the comparison group (typically developing youths [TD]) represented by its mean line. The subtype is significantly different from TD if its corresponding confidence interval does not contain 0 (the mean of TD). **(A)** S1 showed smaller gray matter (GM) volumes than S2 consistently across the brain. **(B)** S1 showed reduced cortical thickness (CT) compared with S2 in all regions except the left and right entorhinal cortices. **(C)** S1 also demonstrated reduced resting-state ALFF in frontal regions, the right amygdala, and the right hippocampus compared with S2. **(D)** Finally, relative to S2, S1 showed reduced fractional anisotropy (FA) in white matter tracts, including the inferior longitudinal fasciculi, uncinate fasciculus, anterior thalamic radiation, corticospinal tract, parahippocampal cingulum bundle, superior longitudinal fasciculus, and forceps minor.

(Supplemental Table S5). For the structural results, sensitivity analyses yielded nearly identical results (Supplemental Table S6). In addition, 27 of 41 resting-state ALFF regions remained significant between the subtypes (Supplemental Table S7). The fractional anisotropy results were quite similar, with 9 of 10 tracts remaining significant between subtype 1 and subtype 2 (Supplemental Table S8). We also conducted sensitivity analyses while including race as an additional covariate. The results remained similar for structure (Supplemental Table S9), ALFF (Supplemental Table S10), and fractional anisotropy (Supplemental Table S11). Additionally, as a supplemental analysis to the bifactor model, we examined subtype group differences in each categorical diagnosis separately (Supplemental Table S12). The results were consistent with the bifactor model, with subtype 1 and subtype

2 showing greater symptoms than typically developing youths for all diagnostic categories. Furthermore, subtype 1 showed greater symptoms than subtype 2 on disorders related to fear (social anxiety disorder, agoraphobia, and posttraumatic stress disorder) and behavioral problems (oppositional defiant disorder and conduct disorder). Lastly, controlling for TBV and average cortical thickness before clustering with HYDRA produces clusters with a very low ARI (ARI < 0.20), a measure of out-of-sample reproducibility.

DISCUSSION

Capitalizing on a large sample of youths and recent advances in semisupervised machine learning, we identified 2 reliable neurostructural subtypes of internalizing disorders. Subtype 1

was marked by elevated levels of psychopathology, impaired cognition, and multiple deficits apparent on multimodal imaging. These deficits included smaller gray matter volumes and thinner cortices, reduced ALFF in frontolimbic cortex, and reduced integrity of white matter tracts. In contrast, subtype 2 had preserved cognitive functioning and brain integrity despite clinically significant levels of psychopathology. These results provide a new account of the heterogeneity in brain structure and function present in youths with internalizing disorders.

Heterogeneous Neurostructural Abnormalities in Internalizing Disorders

The pattern of deficits revealed between the subtypes of internalizing youths illustrates the detrimental effects associated with abnormal structural development. Reduced volume and cortical thickness are associated with numerous detrimental effects, including deficits in cognitive functioning (49,50), impaired academic skills (50–52), and greater psychopathology (53–58). Our results show widespread effects for both volume and cortical thickness, with subtype 1 showing deficits across the entire brain compared with subtype 2 and typically developing youths. Group differences were apparent when examining total gray matter volume, TBV, or ICV, consistent with the high interrelationships between these variables in developmental samples (59). When TBV is controlled for along with age and sex before clustering, no reliable clustering solution emerges. There are 2 possible explanations for these results. One possibility is that the distributed pattern found may mediate the separation of the groups. A second hypothesis is that this distributed pattern directly occurs as a result of smaller ICV, as smaller heads have smaller volumes and are associated with lower IQ and greater psychopathology in studies of prematurity (60,61). However, the very high correlation between ICV and TBV in this sample does not allow us to disentangle these competing hypotheses.

These structural abnormalities are likely the result of a combination of genetic and environmental effects (62). Environmental factors, such as low socioeconomic status (SES) and childhood adversity, are associated with chronic exposure to stress hormones (63,64), which have been shown to impact the development of structures related to psychopathology (65,66) and cognition (67,68). In line with this prior research, our subtypes show an association between neurostructural deficits and lower SES, greater trauma exposure, greater levels of psychopathology, and impaired cognition. This is consistent with prior work from our group and others showing a robust relationship between psychopathology and structural brain deficits (53–58). Additionally, it is possible that these differences were established in utero. Whereas we found that subtype 1 had a lower gestational age than typically developing youths in a subset of the data, subtype 1 did not differ from subtype 2, suggesting that preterm birth may not account for the differences between the subtypes. However, we had gestational age data for only a relatively small number of subjects; thus, our analyses may have been underpowered to detect a significant effect. Therefore, we cannot rule out the possibility that our results are related to birth complications.

We expand on previous work by showing related deficits in 2 independent modalities, with neurostructural deficits

associated with reduced resting-state ALFF and fractional anisotropy in white matter tracts. Reduced resting-state ALFF in frontolimbic regions may reflect dysregulated regional spontaneous neural activity (37) in executive functioning regions, consistent with poorer cognitive performance. Our results are also consistent with prior studies showing reduced resting-state ALFF in frontal regions in children with attention-deficit/hyperactivity disorder (37). Additionally, reduced white matter integrity in tracts such as the inferior longitudinal fasciculus, uncinata fasciculus, and forceps minor is consistent with previous studies implicating these tracts in depression (69,70), attention-deficit/hyperactivity disorder (71,72), and poorer cognitive functioning (73).

In contrast to the deficits seen in subtype 1, subtype 2 was characterized by preserved brain structure and cognitive functioning, but still showed high levels of psychopathology. This may suggest compensatory mechanisms, whereby individuals with greater brain reserve can compensate for deficits typically associated with psychopathology, allowing for preserved cognition (74). These results demonstrate the impact of abnormal structural development on cognitive and affective functioning, with greater neural resources potentially mitigating detrimental effects on cognition. However, this does not explain why preserved brain structure, function, and cognition does not also protect against psychiatric symptoms, suggesting disparate pathways to apparently similar manifestations of psychopathology (75).

Advances in Parsing Neurobiological Heterogeneity in Youths

The results of the current study provide both conceptual and methodological advances in the classification of internalizing disorders in youths. Prior studies have primarily used symptom-based diagnostic categories to explore associated neurobiological mechanisms in a case-control design or examined associations between dimensional clinical phenotypes and imaging measures across diagnostic categories. More recent efforts have used clustering techniques to identify subtypes in Alzheimer's disease using structural data (12–14), in depression using resting-state connectivity data (15,16), and in psychosis using multimodal data (17–19,76–78). However, several of these studies defined subtypes using symptoms or cognitive performance rather than imaging measures. Functional connectivity data have been used in youths to reveal neurobiological subtypes of attention-deficit/hyperactivity disorder using community detection (20,21). Whereas clustering methods have also been used previously to identify subtypes of internalizing adults (79), these methods have clustered on symptoms only and then related symptom subtypes to physiological measures. The current study extends this research by using structural data to delineate neuroanatomical subtypes of internalizing symptoms, which were then evaluated using independent cognitive and neuroimaging measures. Additionally, whereas the majority of prior studies on heterogeneity have considered adults, our results build on this work by parsing neurostructural heterogeneity in a community-based sample of youths.

In addition, this study is distinctive from prior efforts in its methodological approach. Until relatively recently, the majority

of approaches for understanding the neurobiological differences underlying psychiatric symptoms (case-control, linear support vector machines) have assumed that a single discriminative pattern differentiates subjects with psychiatric symptoms from healthy control subjects. However, as noted above, there has been a movement toward using methods that parse neurobiological heterogeneity within patient groups (12–21). Whereas unsupervised methods cluster patients based on how similar they are to each other, one advantage of the approach taken here is that the semisupervised learning procedure implemented in HYDRA allows us to cluster patients by how different they are from typically developing youths, yielding subtype-specific neurobiological signatures that differ from control subjects. In contrast, traditional clustering techniques are susceptible to splitting the data on nonspecific factors such as age or sex, producing clusters that may not be aligned well on psychopathology. In the current study, HYDRA allowed us to identify 2 subtypes of internalizing youths that differed from control youths on multiple clinical, cognitive, and imaging measures of interest.

Several limitations of the current study should be noted. First, longitudinal designs are needed to determine the trajectory of these neurostructural differences over time in youths. A second limitation is the lack of data collected on household income as a measure of SES. However, we used maternal education as a proxy for SES, as prior work shows that maternal level of education is more strongly associated with several developmental outcomes than other measures of SES (80–82). Third, the current study had gestational age data from only a subsample of the cohort (25); thus, future work would benefit from replicating these results in a sample with data on gestational age as well as information on pregnancy and birth complications. Fourth, future work would benefit from performing similar clustering in an older sample with internalizing symptoms, as ICV and TBV are highly correlated in this developmental sample, making it difficult to disentangle the relative contributions of each to these clustering patterns. Fifth, the putative mechanisms (e.g., environmental vs. genetic) driving the differences between the subtypes could be tested by integrating genetic data into future work. Sixth and finally, whereas machine learning can find reliable and distinct subtypes, this does not rule out the possibility that dimensional approaches can also provide useful and important information.

Taken together, this study provides important data regarding neurostructural heterogeneity in youths with internalizing disorders. Given the early age of onset of anxiety and depressive symptoms during development (3), biomarkers that dissect heterogeneous neural patterns in a developmental sample may aid in identifying youths at risk for these symptoms. A greater understanding of how abnormalities in the brain give rise to these symptoms in youths is critical for the development of earlier and more effective treatments that may reduce the negative long-term outcomes associated with internalizing symptoms.

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From the Departments of Psychiatry (ANK, EBB, RB, MEC, ZC, REG, RCG, TMM, DRR, AFGR, KR, DHW, TDS) and Radiology (AS, GBC, GE, YF, REG, RCG, EV, CD), Perelman School of Medicine, University of Pennsylvania; Center for Biomedical Image Computing and Analytics (AS, GBC, GE, YF, RTS, EV, DHW, CD, TDS) and Department of Biostatistics, Epidemiology, and Informatics (RTS), University of Pennsylvania; Philadelphia Veterans Administration Medical Center (RCG), Philadelphia, Pennsylvania; Department of Psychology (ANK), Vanderbilt University, Nashville, Tennessee; Department of Radiology (AS), Washington University, St. Louis, Missouri; and Grossman Center for the Statistics of Mind (EV), Center for Theoretical Neuroscience, Department of Statistics, Columbia University, New York, New York.

Address correspondence to Antonia N. Kaczkurkin, Ph.D., Richards Building, 5th Floor, Suite 5A, 3700 Hamilton Walk, Philadelphia, PA 19104-6085; E-mail: antoniak@pennmedicine.upenn.edu.

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