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White matter microstructure correlates of general and specific second-order factors of psychopathology

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ABSTRACT

Increasing data indicate that prevalent forms of psychopathology can be organized into second-order dimensions based on their correlations, including a general factor of psychopathology that explains the common variance among all disorders and specific second-order externalizing and internalizing factors. Nevertheless, most existing studies on the neural correlates of psychopathology employ case-control designs that treat diagnoses as independent categories, ignoring the highly correlated nature of psychopathology. Thus, for instance, although perturbations in white matter microstructure have been identified across a range of mental disorders, nearly all such studies used case-control designs, leaving it unclear whether observed relations reflect disorder-specific characteristics or transdiagnostic associations. Using a representative sample of 410 young adult twins oversampled for psychopathology risk, we tested the hypothesis that some previously observed relations between white matter microstructure properties in major tracts and specific disorders are related to second-order factors of psychopathology. We examined fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD). White matter correlates of all second-order factors were identified after controlling for multiple statistical tests, including the general factor (FA in the body of the corpus callosum), specific internalizing (AD in the fornix), and specific externalizing (AD in the splenium of the corpus callosum, sagittal stratum, anterior corona radiata, and internal capsule). These findings suggest that some features of white matter within specific tracts may be transdiagnostically associated multiple forms of psychopathology through second-order factors of psychopathology rather with than individual mental disorders.

1. Introduction

Traditionally, research on psychopathology has focused on specific disorders and employed case-control designs. This approach has proven problematic given the high degree of heterogeneity within and comorbidity across disorders and the dimensional rather than categorical manner in which psychopathology is expressed (Caspi and Moffitt, 2018; Insel et al., 2010; Lahey et al., 2017a). One solution is to characterize psychopathology in terms of latent factors based on the empirically defined organization of symptoms, with second-order factors capturing the transdiagnostic structure of symptoms. Recently, bifactor models have been used as a tool to quantitatively characterize the dimensional structure of psychopathology (Lahey et al., 2008, 2015). These models include a nonspecific general bifactor on which all prevalent psychiatric disorders load as well as a specific internalizing and specific externalizing factor. The key advantage of this model is that it allows one to disentangle the substantial common variance that is shared across disorders or dimensions (and which has been argued to reflect substantial sharing of etiology across different types of psychopathology), from the variance that is specific to internalizing and externalizing disorders or symptoms (Caspi and Moffitt, 2018; Lahey et al., 2017a).

The general factor of psychopathology was initially identified in an adult sample (ages 18–65), but has since been replicated in both

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children and adolescents (Hankin et al., 2017; Laceulle et al., 2015; Lahey et al., 2015). Caspi and colleagues used data from the Dunedin study to identify a similar model, which includes a general "p-factor" that is defined by shared variance among all disorders (Caspi et al., 2014). When considered at the level of individuals, persons with a broad range of symptoms that cut across second-order dimensions of psychopathology will have a high general factor score, which distinguishes them from persons whose symptoms are limited to just one second-order dimension, such as specific externalizing or specific internalizing symptoms. The extent to which this model of psychopathology proves useful rests on its ability to reveal meaningful features and correlates of psychopathology. In support of this, the general factor predicts both current and future adaptive functioning and demonstrates stability across development (Greene and Eaton, 2017; Lahey et al., 2012; Tackett et al., 2013). Fewer data exist regarding the neural correlates of these dimensions. Such data would be particularly informative because it is difficult to interpret existing case-control studies that cannot discriminate between neural correlates that reflect broad shared etiological features or narrower dimensional features of psychopathology. Identifying the neural correlates of shared features of psychopathology will help provide insight into their etiology and may thus yield novel therapeutic targets.

White matter tracts facilitate communication among brain regions, and perturbations in white matter microstructure been consistently identified as a correlate of psychopathology at the disorder level (Bracht et al., 2015; Chen et al., 2016; Koch et al., 2014; Siehl et al., 2018; Thomason and Thompson, 2011; Waller et al., 2017). A range of tracts have been implicated, and several have been associated with multiple disorders. Commonly identified tracts include the uncinate fasciculus, cingulum, and corpus callosum. These studies most commonly implicate the white matter microstructure property of Fractional Anisotropy (FA), though changes in Axial Diffusivity (AD) and Radial Diffusivity (RD) have also been observed. Each of these measures is sensitive to different properties of white matter microstructure. FA measures diffusion broadly, with increased FA potentially indicative of more efficient white matter microstructure. AD is more sensitive to properties of axons, with decreased AD potentially representative of axon damage (Pierpaoli et al., 1996). Finally RD is more indicative of myelin properties, with increased RD representing possible myelin injury. The heterogeneity of past findings on psychopathology and white matter may reflect in part that studies have not parsed out the extent to which implicated tracts and metrics are relevant for shared features of psychopathology versus specific to a given disorder. When studies test associations between psychopathology and white matter microstructure at the level of individual disorders they fail to account for aspects of the association that may reflect features shared across all disorders.

To our knowledge, only one study to date has reported white matter correlates of second-order factors psychopathology defined in a bifactor model, which found a relation between white matter microstructure in the cerebellum and the general factor of psychopathology (Romer et al., 2018). While this initial result is promising, there are some notable limitations. For one, using a college sample at an elite university may yield findings that would not generalize to either a community sample or one with a wider range of functional impairment. Second, the use of a whole brain voxel-wise approach rather than a tract specific approach may miss relations at the tract level due to the statistical constraints required for voxel-wise analyses. Finally, investigating correlates of only the general factor leaves unclear if white matter microstructure in specific tracts possesses correlates at the level of either the general factor or the specific internalizing or externalizing factors.

The present study sought to examine whether there are relations between white matter microstructure and second-order factors of psychopathology. We used a community twin sample with a wide range of psychopathology, examined relations with all factors of psychopathology from the bifactor model, and used a tract specific approach. We hypothesized that given that a number of white matter tracts have been implicated in multiple categorically defined disorders, we would identify relations between a range of white matter tracts and second-order latent factors of psychopathology (Thomason and Thompson, 2011). Given the dearth of studies on this topic to date, we did not formulate hypotheses about specific tracts, and instead examined relations with major white matter tracts of the brain and used false discovery rate corrections to account for the number of tests.

2. Material and methods

2.1. Participants

Participants were recruited from the Tennessee Twin Study (TTS), which has been conducted in two waves. In the first wave, a representative sample was taken of all live twin births in Tennessee between 1984 and 1995 and consisted of over 3990 twins in 1995 complete pairs (Lahey et al., 2008). During this first wave, participants were children and adolescents (ages 6–17) and completed a structured clinical interview along with several other personality measures. During the second wave of the study, the twin pairs were young adults (ages 23–31). These subjects were selected in 4 replicates (strata) based on age during wave 1 of the study (10–11, 12–13, 14–15, and 16–17 years old). Replicates were recruited starting with the oldest replicate over a period of 3.5 years in order to minimize age differences within wave 2. Twin pairs were eligible if the last known address of both twins was within 300 miles of Vanderbilt University (95.2% of twins).

Wave 2 participants were selected by oversampling on wave 1 psychopathology scores based on the greater rating of each symptom from the parent or youth. High-risk pairs were selected with certainty if either twin had symptom ratings on the total number of internalizing, ADHD, or the combination of ODD and CD symptoms in the top 10% of that age range. In addition, 19–23% of the remainder of each replicate was randomly selected with two constraints: (1) monozygotic pairs were oversampled by randomly excluding 40% of the randomly selected dizygotic pairs, and (2) the number selected from the remainder of the sample varied slightly to equate replicate sizes (100–105 pairs).

Individuals for wave 2 were pre-screened and excluded if they had multiple concussions with loss of consciousness or other head injuries, neurological diseases other than headaches, contraindications for MRI scanning, a diagnosis of schizophrenia, or a major developmental disorder. Three pairs of twins could not be located and 37 pairs refused screening. Eighteen selected pairs of twins across replicates were declared out of scope due to previous participation in a pilot study, mental or physical incapacity, residence outside the U.S., imprisonment, or death. A total of 114 screened individual twins were ineligible for neuroimaging for feasibility (e.g., body weight) and safety reasons, but were eligible for assessment of psychopathology. Vanderbilt University's Institutional Review Board (IRB) approved the study, and the study was conducted in accordance with the guidelines of the IRB including participants providing written informed consent. During wave 2 of the study individuals completed a clinical interview, behavioral tasks, self-report measures, and neuroimaging scans.

Interviews regarding psychopathology were completed for 72% of the screened sample during 2013–2016, including 499 subjects (248 complete twin pairs (49.6% monozygotic; 66.9% high risk) and 3 individuals without their twin). Consistent with oversampling participants based on Wave 1 psychopathology, 50.3% met criteria for at least one Wave 2 mental disorder (46.2% of females; 54.8% of males) in the past year and 26.8% met criteria for ≥ 2 diagnoses. A total of 430 of the subjects who completed the clinical interview also completed a diffusion weighted imaging (DWI) scan. Twenty participants were excluded for poor DWI data quality (excessive movement, missing data, etc.). The final sample available for analysis consisted of 410 subjects. This included 187 participating twin pairs and 36 individuals whose twin did not provide valid data. There were 92 monozygotic pairs (49 female pairs and 43 male pairs), 95 dizygotic pairs (50 same-sex pairs (27

Table 1|
Participant demographics.

Variable	Mean (standard deviation)
Age (Years)	26.05 (1.78)
Family income[a]	18.79 (4.97)
Mother's education (Years)	13.64 (2.72)

Variable	N (Percentage)
Sex	
Male	196 (47.80)
Female	214 (52.19)
Ethnicity	
White	295 (71.95)
African American	102 (24.88)
Other	13 (3.17)
Handedness	
Right	371 (90.49)
Left	39 (9.51)
Scanner[b]	
3TA	214 (52.20)
3TB	196 (47.80)

[a] Family income from wave 1 reported in brackets ranging from 0 (no income) to 24 ($100,000 and over). 18 = $35,000 - $44,999.

[b] Imaging data were acquired on two identical 3T Intera-Achieva Phillips MRI scanners.

female pairs and 23 male pairs) and 25 different-sex pairs), and 36 individuals whose twin pair did not have useable data (17 females and 19 males). See Table 1 for demographic characteristics of the sample.

2.2. Measures

All measures used in the current analyses other than family income and mother's education were obtained during wave 2 of the study when participants were young adults.

2.2.1. Young adult diagnostic interview for children (YA-DISC)

A trained interviewer administered the computer-assisted implementation of the Young Adult Diagnostic Interview for Children (YA-DISC) to all participants in wave 2 of this study (Shaffer et al., 2000). The YA-DISC has the primary advantage that it has few skip-outs, and thus queries symptoms even when the participant cannot reach criteria for a diagnosis, which is critical when measuring dimensional psychopathology. This differs from most structured diagnostic interviews that insert multiple skip-outs to save time. The YA-DISC has been primarily developed for 18–24 year olds (Hart et al., 1995; Shaffer et al., 1996), whereas the present sample included subjects from 23 to 31. However, questions are worded in a manner that appears equally appropriate for individuals throughout their early adulthood. The present analyses are based on dimensional scores based on YA-DISC assessed symptoms of generalized anxiety disorder (GAD), major depressive disorder (MDD), posttraumatic stress disorder (PTSD), agoraphobia, obsessive-compulsive disorder (OCD), manic episodes, panic attacks, social phobia, specific phobia, antisocial personality disorder, attention deficit and hyperactivity disorder (ADHD), as well as nicotine, alcohol, marijuana, and other drug use disorders during the last 12 months.

2.2.2. DWI acquisition

Imaging data were acquired on two identical 3T Intera-Achieva Phillips MRI scanners (3TA and 3TB) using a 32-channel head coil. T1-weighted images were acquired with a 3-D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (TE/TR/TI = 4.6/9.0/644(shortest) ms; SENSE = 2.0; echo train = 131; scan time = 4 min 32 s; FOV: 256x256x170 mm, 1 mm isotropic resolution). For DWI, we used a 5 min 2 s multi-slice Stejskal-Tanner spin echo sequence with an echo planar imaging readout (TE/TR = 52/7750 ms, SENSE = 2.2, FOV: 240 × 240 mm, 2.5 mm isotropic, 50 slices, 2.5 mm slice thickness). This was acquired with one image without diffusion weighting ("b_0") and 32 diffusion-weighted images equally distributed over a hemisphere (b = 1000 s/mm^2).

2.3. Data analysis

2.3.1. DWI data processing

The DWI data were preprocessed based on methods detailed by Lauzon et al. (2013). The fMRIB's Linear Image Registration Tool (FLIRT) from the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL;www.fmrib.ox.ac.uk/fsl) was used to register DWI images to the B_0 volume, and then the Brain Extraction Tool (BET) was used to mask the B_0 volume (Jenkinson et al., 2002; Smith, 2002). Next FSL was used to perform eddy current and motion corrections. Then the CAMINO software package was used to implement RESTORE robust tensor fitting (Chang et al., 2005; Cook et al., 2006).

After preprocessing the data was quality checked for motion, FA bias and standard deviation, and goodness of fit of the data to the diffusion model (Lauzon et al., 2013). Subjects were excluded if they were an outlier on any quality assurance metric. Next Tract Based Spatial Statistics (TBSS) were run using FSL, which produced skeletonized white matter images based on the procedures detailed in Smith et al. (2006). Subjects' FA images were first moved to standard space based on a non-linear transformation to the FMRIB58_FA template. Images were then averaged to create a mean FA image, thinned in order to derive a skeletonized mean image, and thresholded at FA > 0.2. Next, each subject's FA image was projected onto the mean skeleton, which produced a 4D file that was used for statistical analyses. Finally, both AD and RD skeletonized images were created. This was done by applying the non-linear warp that had been used to bring each FA image to the template, and then applying each subject's projection vectors onto the mean skeleton.

We then used the JHU ICBM-DTI white matter labels atlas (Mori et al., 2005) to create masks of the following major white matter tracts: corpus callosum (body, genu, and splenium), corona radiata (anterior, superior, and posterior), internal capsule, external capsule, cingulum, posterior thalamic radiation, uncinate fasciculus, fornix, superior fronto-occipital fasciculus, superior longitudinal fasciculus, and sagittal stratum. Tract masks were overlaid with the white matter skeleton mask generated from the present sample, and only overlapping voxels were included in the final masks. FA, RD, and AD values were averaged from bilateral tracts across all subjects. Values were z-transformed to achieve a mean of 0 and a standard deviation of 1.

2.4. Statistical analyses

All factor analyses and structural equation modeling were performed using Mplus 8.1 (Muthén and Muthén, 2018). These analyses accounted for stratification and clustering within twin pairs and used weights that both (a) accounted for the inverse of the probability of selection into wave 2 based on the selection strategy (taking into account wave 1 psychopathology, zygosity, and number of twin pairs in each stratum), and (b) adjusted for any biases due to nonresponse or missing data after quality control using lasso logistic regression relative to the participant's age in wave 2, sex, family income, maternal education, and wave 1 measures of psychopathology, dispositions, and working memory. These joint weights allow valid parameter estimates when weighted back to the full wave 1 TTS sample (Korn and Graubard, 1999). Robust maximum likelihood (MLR) estimation was used to account for non-normality in first-order symptom dimensions and adjust standard errors to reflect the clustering of twins within twin pairs.

In the first step of these analyses, general, internalizing, and externalizing factors were estimated using a bifactor measurement model. This model was estimated with fixed nonstandardized factor loadings for symptom dimension on externalizing, internalizing, and general factors

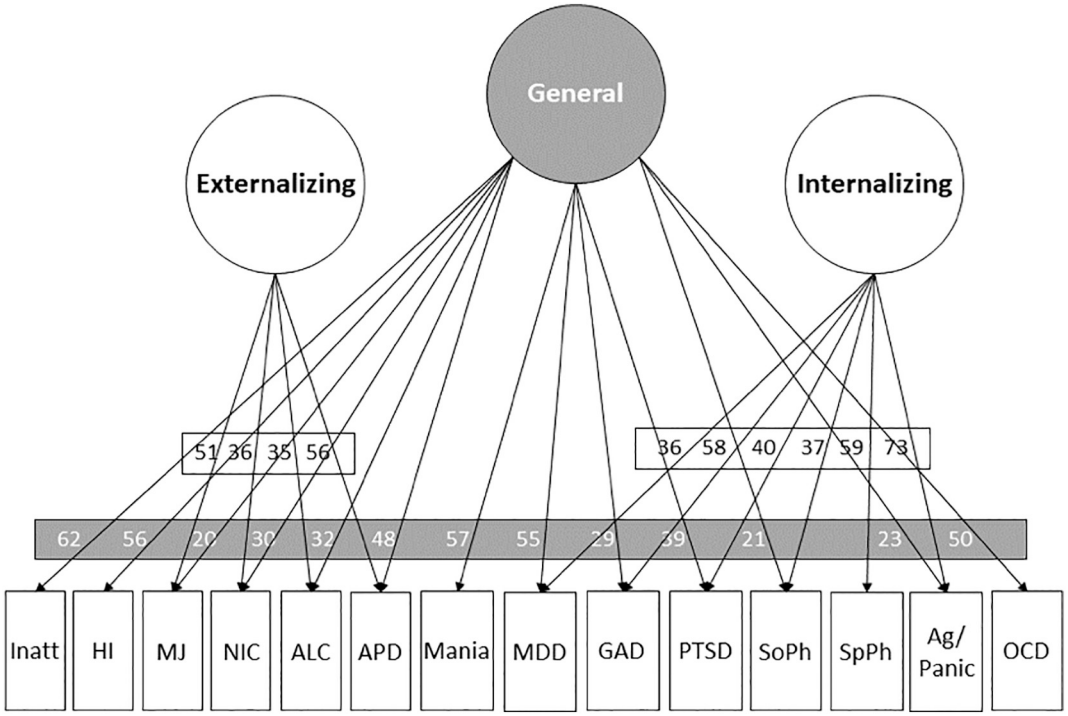

Fig. 1. Standardized factor loadings for the bifactor psychopathology measurement model used in the present tests of associations between measures of white matter microstructure in structural equation models. Loadings not significant at $p < .05$ uncorrected are omitted. Abbreviations are as follows: inattention (Inatt), hyperactivity/impulsivity (HI), marijuana use (MJ), nicotine use (NIC), alcohol use (ALC), antisocial personality disorder (APD), major depressive disorder (MDD), generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), social phobia (SoPh), specific phobia (SpPh), agoraphobia/panic (Ag/Panic), and obsessive compulsive disorder (OCD).

based on a previously published study but using slightly updated weights (Lahey et al., 2017c). In this prior study, a bifactor model was fitted using a latent factor analysis with the full wave 2 TTS dataset ($n = 499$) to produce the best fitting model. First-order symptom scores were allowed to load on a general factor. First order symptom counts of antisocial personality disorder and maladaptive nicotine, alcohol, and marijuana misuse all loaded significantly onto the specific externalizing factor and MDD, GAD, PTSD, agoraphobia/panic, social phobia, and specific phobia loaded significantly onto the specific internalizing factor. Because common variance is accounted for by the general factor, the specific internalizing and specific externalizing factors were set to be orthogonal. This differs from more traditional correlated factor models in which internalizing and externalizing factor loadings do not distinguish between common and specific sources of variance, and are therefore correlated. Standardized factor loadings in the bifactor measurement model of second-order factors used in these analyses are shown in Fig. 1.

In the second step, to look at relations between white matter microstructure and latent factors of psychopathology we conducted multiple regressions within structural equation models. Latent factor scores were entered as independent variables, and white matter tract measures (average FA, AD, and RD) across bilateral tracts were dependent variables in separate models. In each model the other latent factors were entered as covariates (e.g. for general factor the specific internalizing and specific externalizing served as covariates). We included the following covariates of no interest: age, sex, ethnicity, scanner and handedness. In order to minimize bias, these analyses applied weights to account for potential differences in the rates of subjects lacking useable DWI data, and also accounted for clustering due to the non-independence of twin pairs and stratification based on the age of subjects during the original wave 1 data collection. Significance thresholds were set at $p < .05$ using false discovery rate (FDR) within families of tests (FA, AD, and RD) in order to account for the large number of tests (45 per family). All raw and processed data are available by request through the RDoC-DB https://data-archive.nimh.nih.gov/rdocdb/.

2.4.1. Sensitivity analyses

We conducted a series of planned sensitivity analyses to verify the robustness of significant relations. As in the primary analyses, multiple regressions included covariates of no interest, used sampling weights, and accounted for clustering and stratification. We first tested relations separately in males and females given known sex differences in latent factors of psychopathology and in properties of white matter microstructure (Caspi et al., 2014; Hsu et al., 2008). Secondly, we included total intracranial volume (TICV) as a covariate in a set of sensitivity analyses, since some white matter microstructure properties may be impacted by head size (Takao et al., 2011, 2014). TICV was calculated using FreeSurfer segmentations of T1 images (Fischl, 2012). FreeSurfer segmentations were visually inspected and edits were made according to the standardized protocols on the software's website. We excluded data for a total of 8 subjects whose segmentations failed quality assurance checks (excessive movement, processing errors, etc.), and thus analyses with TICV were conducted in a subset of the sample ($n = 402$).

In the third sensitivity analyses, we tested if findings remained significant with inclusion of the additional demographic covariates of family income and mother's education from wave 1. In the fourth sensitivity analysis, we looked only at the tracts that showed a significant relation with the specific second-order externalizing factor, and included a covariate of current drug use (absent or present) as measured on the day of the study visit in a urine screen in order to determine if findings were driven solely by substance use. Current substance use was determined based on a urine drug test conducted on the day of testing that included cotinine, amphetamines, methamphetamines, cannabis, methadone, opioids, phencyclidine, barbiturates, benzodiazepines, oxycontin, ecstasy, and propoxyphene. For sensitivity analyses, the significance threshold was set to $p < .05$ with FDR corrections within families of tests (sex stratified analyses, demographic covariates, TICV, and drug use).

2.4.2. Secondary analyses

Based on the results of the primary regression analyses, we completed secondary analyses in order to test whether microstructure in tracts showing associations with the second-order psychopathology factors also showed significant associations with each individual first-order psychopathology dimension symptom score considered separately. These analyses allowed us to contrast the utility of using second-order latent factors to detect associations with microstructure relative to the traditional approach of testing associations between microstructure and each specific symptom dimension one at a time. Note that these secondary analyses at the level of single first-order dimensions of psychopathology conflate associations between microstructure and both the unique characteristics of each first-order dimension and the unmodeled characteristics they share in common with all other first-order dimensions of psychopathology with which they are correlated. In contrast, the primarily analyses of second-order factors assess associations between microstructure and only characteristics that are *common* to all first-order dimensions that load on that second-order. It must be noted, that the analyses of latent factors versus disorder symptom scores should not be considered completely parallel in that there are differences in both distributions of the data and the number of statistical tests.

3. Results

Participant demographics are presented in Table 1. Multiple regression results are presented in Table 2 including standardized betas, standard errors, and *p*-values. White matter tracts showing significant associations with second-order factors of psychopathology are depicted in Fig. 2. After correction for multiple testing, the general factor had a significant positive relationship with FA in the body of the corpus callosum (CC), such that higher general factor scores are associated with higher FA ($\beta = 0.25$, $p = .001$). FA in other tracts did not showed a significant association with the general factor. AD, which scales in the same direction as FA, showed a number of significant negative associations with specific high order factors. The specific externalizing factor was significantly related to AD in the splenium of the corpus callosum ($\beta = -0.22$, $p = .002$), anterior corona radiata ($\beta = -0.28$, $p = .001$), internal capsule ($\beta = -0.23$, $p = .003$), and sagittal stratum ($\beta = -0.33$, $p < .001$). The specific internalizing factor showed a significant association with AD in the fornix ($\beta = -0.18$, $p = .003$).

3.1. Sensitivity analyses

Sensitivity analyses results are presented in Table 3 including standardized betas and standard errors. These analyses confirmed that findings were largely robust to inclusion of additional demographic covariates (mother's education and family income in wave 1) and were not driven by head size or current substance use (all *p*s remained $<$ 0.01 after inclusion of these control variables). In order to test for the presence of interactions with sex, for each of the tracts that showed a significant association in at least one sex, we ran a model in which regression coefficients were allowed to vary by sex for the significant latent factor (e.g. specific internalizing for fornix) and a model in which they were constrained to be equal in the two sexes. We then ran the Satorra-Bentler X^2 difference test to compare models. These analyses revealed no interactions between sex and psychopathology in their associations with white matter metrics that were significant at even nominal levels (*p*s $>$ 0.10).

3.2. Secondary analyses of individual first-order symptom dimensions

Given the observed significant relations between white matter tract properties and latent factors of psychopathology, we sought to assess if the individual disorder-specific symptoms dimensions that were the basis of the second-order factor scores were predictive of microstructure in the same tracts when considered one first-order dimension at a time. Consistent with other analyses, the significance threshold was set to $p < .05$ with FDR corrections within families of tests (within each white matter tract), but fewer tests were conducted than in the primary analyses across all tracts. These regressions included the same covariates as the primary analyses. As shown in Table 4, FA in the CC body was positively associated with both the first-order hyperactivity-impulsivity and alcohol use disorder dimensions in separate analyses after FDR correction. In addition, AD in each of the tracts found to be inversely associated with the specific second-order externalizing factor (corpus callosum splenium, anterior corona radiata, internal capsule, and sagittal stratum) was significantly associated with at least one specific externalizing disorder. In three of these cases, the significant associations included antisocial personality disorder. Similarly, AD in the fornix, which was significantly associated with the specific second-order internalizing factor, was found to be inversely associated with both depression and agoraphobia/panic in separate analyses.

4. Discussion

Applying a bifactor model to characterize second-order dimensions of psychopathology defined by the patterned correlations among first-order dimensions, we observed relations between second-order factors of psychopathology and several features of white matter microstructure. These findings extend a small but growing literature on the neural correlates of latent factor dimensions of psychopathology and demonstrate the potential utility of the general factor model in elucidating biological features that reflect broad nonspecific aspects of psychopathology (Zald and Lahey, 2017). Each second-order latent factor had some distinct white matter correlates, providing evidence that they are separable at a biological level. These findings join an increasing body of literature indicating associations between transdiagnostic dimensions of psychopathology and other neural measures (reviewed by Zald and Lahey, 2017). To facilitate interpretation of associations between second-order factors of psychopathology and microstructure, we also conducted analyses of associations between each white matter tract that was significantly associated with a second-order factor and each of the individual first-order dimensions of psychopathology one at a time.

4.1. Microstructural correlates of the specific second-order externalizing factor

The specific externalizing factor defined in the bifactor model demonstrated the most widespread pattern of correlations, with significant negative associations between this factor and AD in the splenium of the CC, anterior corona radiata (ACR), sagittal stratum (SS), and internal capsule (IC). In the bifactor model the disorders that load significantly onto externalizing include antisocial personality disorder and substance use disorders. The tracts identified in this study have all been identified in antisocial personality disorder (Waller et al., 2017). The ACR, splenium of the CC, and IC, have been identified previously in case-control design studies on substance use disorders (Baker et al., 2013; Bava et al., 2009; Berns et al., 2009; Paul et al., 2008). Thus, the present results show some consistency with prior findings, while also providing greater specificity on the tracts that are associated with specific externalizing once overlap across disorders has been removed. The broader nature of the associations identified with the externalizing factor also shows some concordance with the work of Muetzel and colleagues who observed reduced development in global white matter integrity in relation to externalizing symptoms in childhood as measured by the Child Behavior Checklist (Muetzel et al., 2017).

Given that problematic substance use is a component of the specific externalizing factor, an important question is the extent to which present findings may represent a consequence of substance use rather than reflecting etiology. To address this question, we conducted a sensitivity

Table 2|
Multiple regressions of skeletonized white matter tract indices on latent general and specific internalizing and externalizing factors based on the fixed-loadings bifactor model, controlling demographic covariates of no interest[a] (all models n = 410).

		Fractional anisotropy		Radial diffusivity		Axial diffusivity	
Outcome	Predictor	Regression coeff (SE)	p	Regression coeff (SE)	p	Regression coeff (SE)	p
Corpus callosum (body)	**General**	**0.25 (0.08)**	**0.001**	−0.25 (0.08)	0.002	−0.05 (0.09)	0.581
	Internalizing	−0.06 (0.07)	0.347	0.06 (0.07)	0.424	−0.03 (0.07)	0.688
	Externalizing	0.08 (0.09)	0.378	−0.10 (0.09)	0.274	−0.11 (0.10)	0.238
Corpus callosum (genu)	General	−0.01 (0.06)	0.823	−0.04 (0.06)	0.566	−0.19 (0.10)	0.049
	Internalizing	0.18 (0.06)	0.004	−0.16 (0.07)	0.014	0.04 (0.09)	0.636
	Externalizing	0.01 (0.07)	0.865	−0.03 (0.07)	0.626	−0.05 (0.10)	0.581
Corpus callosum (splenium)	General	−0.09 (0.08)	0.230	0.05 (0.08)	0.480	−0.11 (0.07)	0.132
	Internalizing	0.04 (0.07)	0.627	−0.03 (0.08)	0.708	0.00 (0.07)	0.949
	Externalizing	0.06 (0.08)	0.437	−0.15 (0.08)	0.071	**−0.22 (0.07)**	**0.002**
Anterior corona radiata	General	−0.05 (0.08)	0.516	0.03 (0.08)	0.742	−0.09 (0.07)	0.237
	Internalizing	0.12 (0.08)	0.138	−0.11 (0.09)	0.209	0.06 (0.08)	0.435
	Externalizing	−0.20 (0.09)	0.019	0.04 (0.08)	0.666	**−0.28 (0.08)**	**0.001**
Superior corona radiata	General	0.10 (0.10)	0.293	−0.08 (0.10)	0.409	0.02 (0.07)	0.751
	Internalizing	0.10 (0.07)	0.139	−0.08 (0.07)	0.213	0.05 (0.07)	0.474
	Externalizing	0.03 (0.09)	0.729	−0.11 (0.08)	0.149	−0.17 (0.09)	0.055
Posterior corona radiata	General	0.03 (0.07)	0.697	0.00 (0.06)	0.974	0.02 (0.08)	0.775
	Internalizing	0.12 (0.07)	0.071	−0.10 (0.09)	0.222	0.02 (0.09)	0.839
	Externalizing	0.04 (0.10)	0.674	−0.11 (0.08)	0.165	−0.16 (0.08)	0.043
Internal capsule	General	−0.02 (0.09)	0.793	−0.01 (0.09)	0.945	−0.11 (0.08)	0.132
	Internalizing	0.08 (0.07)	0.283	−0.10 (0.07)	0.127	−0.03 (0.07)	0.672
	Externalizing	−0.09 (0.09)	0.339	−0.03 (0.10)	0.727	**−0.23 (0.08)**	**0.003**
External capsule	General	0.11 (0.10)	0.253	−0.11 (0.10)	0.267	−0.03 (0.07)	0.672
	Internalizing	−0.09 (0.08)	0.231	0.07 (0.10)	0.488	−0.07 (0.05)	0.174
	Externalizing	−0.04 (0.09)	0.681	−0.09 (0.09)	0.353	−0.17 (0.07)	0.016
Cingulum	General	0.03 (0.10)	0.750	−0.02 (0.08)	0.789	0.05 (0.09)	0.602
	Internalizing	0.11 (0.07)	0.126	−0.11 (0.07)	0.077	−0.02 (0.06)	0.788
	Externalizing	−0.12 (0.10)	0.227	0.02 (0.10)	0.813	−0.15 (0.09)	0.095
Posterior thalamic radiation	General	−0.07 (0.08)	0.388	0.07 (0.07)	0.368	0.00 (0.06)	0.965
	Internalizing	0.14 (0.08)	0.086	−0.15 (0.08)	0.072	−0.02 (0.05)	0.725
	Externalizing	−0.03 (0.08)	0.710	−0.09 (0.08)	0.272	−0.19 (0.07)	0.010
Uncinate fasciculus	General	0.05 (0.08)	0.553	−0.08 (0.07)	0.307	−0.04 (0.08)	0.673
	Internalizing	−0.05 (0.06)	0.388	0.06 (0.07)	0.336	0.01 (0.06)	0.848
	Externalizing	0.04 (0.09)	0.644	−0.12 (0.09)	0.185	−0.09 (0.09)	0.312
Fornix	General	0.14 (0.07)	0.051	−0.12 (0.07)	0.069	−0.07 (0.08)	0.396
	Internalizing	0.12 (0.05)	0.022	−0.14 (0.05)	0.005	**−0.18 (0.06)**	**0.003**
	Externalizing	−0.08 (0.07)	0.264	−0.02 (0.07)	0.815	−0.08 (0.07)	0.249
Superior fronto-occipital fasciculus	General	−0.07 (0.11)	0.517	0.11 (0.09)	0.200	0.03 (0.10)	0.751
	Internalizing	−0.02 (0.07)	0.836	−0.10 (0.09)	0.261	−0.16 (0.08)	0.046
	Externalizing	−0.05 (0.12)	0.697	−0.04 (0.09)	0.636	−0.11 (0.11)	0.330
Superior longitudinal fasciculus	General	0.01 (0.08)	0.867	−0.02 (0.08)	0.796	0.01 (0.07)	0.871
	Internalizing	0.21 (0.08)	0.006	−0.17 (0.07)	0.024	0.12 (0.06)	0.031
	Externalizing	−0.02 (0.07)	0.754	−0.08 (0.07)	0.250	−0.18 (0.09)	0.034
Sagittal stratum	General	−0.02 (0.09)	0.777	0.03 (0.09)	0.708	0.00 (0.06)	0.959
	Internalizing	0.03 (0.07)	0.656	0.01 (0.08)	0.949	0.03 (0.05)	0.514
	Externalizing	−0.14 (0.08)	0.057	−0.05 (0.08)	0.545	**−0.33 (0.08)**	**0.000**

Regressions that were significant after FDR correction are displayed in bold.

[a] Covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1). Coefficients in bold were significant after FDR correction within families of 45 tests of significance for each index.

analysis in which drug use detected in a urine screen at the time of scanning was included as a covariate. All significant relations remained significant, suggesting that findings were not exclusively driven by recent substance use. As we note below, however, concerns remain regarding the possible effects of substance use on microstructure.

4.2. Microstructural correlates of the specific second-order internalizing factor

In the present study, we found a significant negative relation between AD in fornix and the second-order specific internalizing factor. These findings appear generally consistent with prior studies finding decreased integrity in the fornix in categorically defined internalizing disorder (MDD, PTSD, and panic disorder) using case-control designs (Geng et al., 2016; Kennis et al., 2015; Kim et al., 2017; Korgaonkar et al., 2011). These prior studies have more frequently implicated FA rather than AD, however. This may be in part because earlier clinical studies simply more commonly examined FA than AD and other properties of white matter microstructure (Thomason and Thompson, 2011). Given that both the second-order specific internalizing and externalizing factors were related to AD rather than FA in the present study, it may be that properties of axons rather than broad diffusion are most relevant for these specific second-order factors. The present results are somewhat inconsistent with a recent meta-analysis that examined shared white matter microstructure correlates of emotional disorders (MDD, bipolar, PTSD, OCD, and social anxiety). This study identified a number of shared tracts across disorders including the uncinate fasciculus, inferior fronto-occipital fasciculus, forceps minor, anterior thalamic radiation, superior corona radiata, superior longitudinal fasciculus, and cerebellum (Jenkins et al., 2016). The inconsistency with the present findings may be due primarily to methodological difference, for the meta-analysis analyzed case-control designs, and thus didn't account for shared variance across disorders. The present results suggest that while the specific internalizing factor may be linked to white matter microstructure, other neural features may be more central to its etiology.

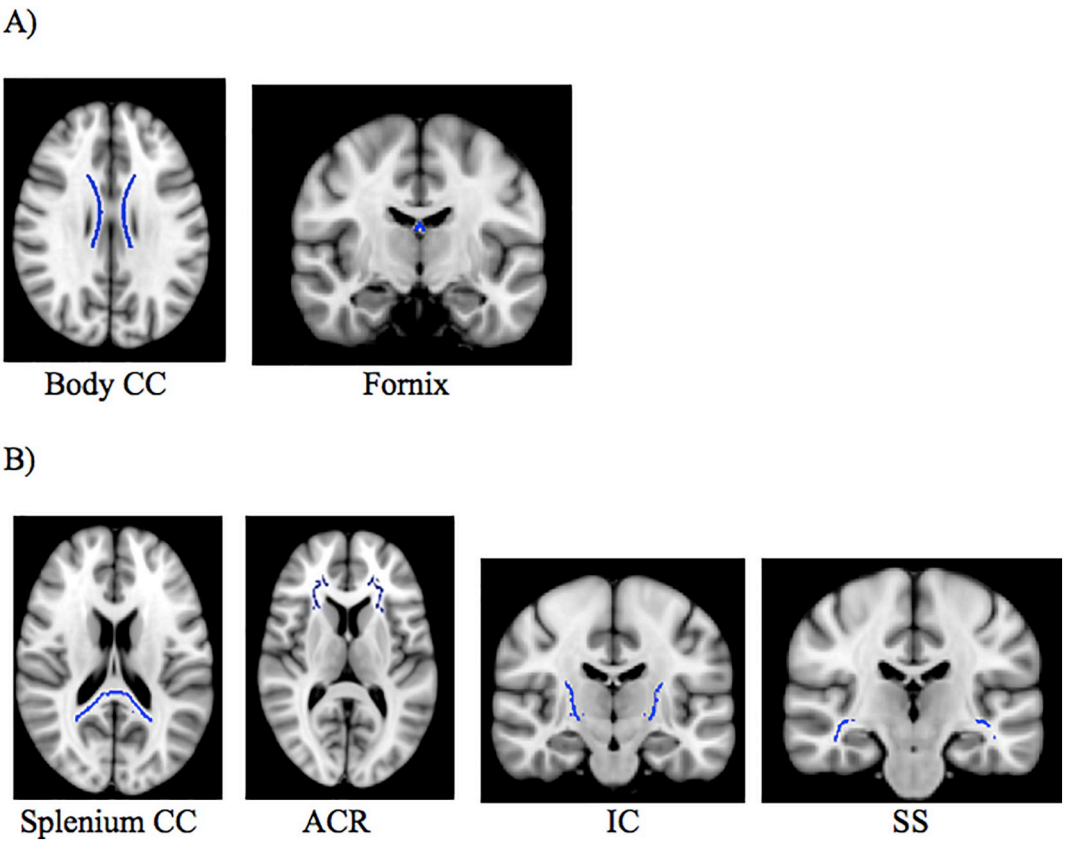

Fig. 2. Tracts which showed significant relations with latent factors of psychopathology. A) Left: tract showing significant relation with general factor (body of corpus callosum). Right: tract showing significant relation with specific internalizing (fornix) B) Tracts showing significant relations with the specific externalizing. From left to right: splenium of the corpus callosum, anterior corona radiata, internal capsule, and sagittal stratum.

4.3. Microstructural correlates of the general factor

In the present study, we found a significant positive relation between the general factor and FA in the body of the CC. This finding at the level of the general factor converges with recent neuroimaging and genetics studies that demonstrate that some of the neural correlates of psychopathology reflect broad transdiagnostic aspects rather than being limited to narrower phenotypic features (Goodkind et al., 2015; Kaczkurkin et al., 2017). However, when considered in the context of most previous studies of the association of variations in CC white matter to mental disorders, the present finding of a positive association of the general factor with CC FA is perhaps surprising. Most studies in adult

Table 3|
Sensitivity analyses to test robustness of significant relations between white matter tracts and second-order factors of psychopathology. Analyses consist of testing significant relations separately in males and females and inclusion of additional covariates[a].

Outcome	Predictor	Sex stratified analyses[c]		Additional covariates analyses		
		Males (n = 196)	Females (n = 214)	Total intracranial volume (n = 402)	Family income and mother's education [b] (n = 410)	Drug use[d] (n = 410)
		Regression coeff (SE)	Regression coeff (SE)	Regression coeff (SE)	Regression coeff (SE)	Regression coeff (SE)
Body CC FA[e]	General	0.21 (0.11)	**0.30 (0.12)**	**0.25 (0.09)**	**0.26 (0.07)**	**0.25 (0.08)**
Fornix AD	Internalizing	−0.20 (0.12)	**−0.18 (0.06)**	**−0.19 (0.07)**	**−0.18 (0.07)**	–[f]
Splenium CC AD	Externalizing	**−0.22 (0.09)**	−0.19 (0.15)	**−0.21 (0.07)**	**−0.21 (0.07)**	**−0.23 (0.07)**
ACR AD	Externalizing	**−0.39 (0.10)**	−0.20 (0.12)	**−0.20 (0.08)**	**−0.28 (0.08)**	**−0.28 (0.08)**
IC AD	Externalizing	**−0.30 (0.10)**	−0.16 (0.11)	−0.13 (0.07)	**−0.22 (0.08)**	**−0.26 (0.08)**
SS AD	Externalizing	**−0.31 (0.11)**	**−0.35 (0.13)**	**−0.31 (0.07)**	**−0.32 (0.07)**	**−0.35 (0.08)**

Regressions that were significant after FDR correction are displayed in bold.

[a] All multiple regressions contain the following covariates of no interest: age in wave 2, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner. Additional covariates analyses also included sex as a covariate. Regression coefficients are fully standardized (M = 0, SD = 1). Coefficients in bold are significant after FDR correction within families of 6 tests for each sensitivity analysis.

[b] Mother's education and log transform of family income from wave 1.

[c] There were no significant interactions (ps > 0.10).

[d] Positive drug screen on day of study visit. Analyses only conducted for tracts that showed significant relations with factors that substance misuse loads onto (externalizing and general).

[e] Abbreviations are as follows: corpus callosum (CC), anterior corona radiata (ACR), internal capsule (IC), sagittal stratum (SS), fractional anisotropy (FA), and axial diffusivity (AD).

[f] Drug use sensitivity analyses were only conducted for latent factors which substance misuse loaded significantly onto (general and externalizing).

Table 4|
Multiple regressions of individual symptom dimensions with tracts that showed significant relations with latent factors of psychopathology.

Symptom Dimension	Body CC FA[a]		Fornix AD		Splenium CC AD		ACR AD		IC AD		SS AD	
	Reg Coeff (SE)	p	Reg Coeff (SE)	p	Reg Coeff (SE)	p	Reg Coeff (SE)	p	Reg Coeff (SE)	p	Reg Coeff (SE)	p
Mania	0.13 (0.07)	0.042	−0.09 (0.07)	0.237	−0.07 (0.07)	0.298	−0.05 (0.05)	0.305	−0.10 (0.06)	0.114	−0.02 (0.06)	0.798
Inattention	0.12 (0.08)	0.121	0.05 (0.06)	0.380	−0.02 (0.07)	0.720	−0.01 (0.07)	0.873	0.01 (0.07)	0.880	0.10 (0.05)	0.052
Hyperactivity/ impulsivity	**0.14 (0.05)**	**0.006**	−0.11 (0.07)	0.082	−0.08 (0.07)	0.290	−0.04 (0.05)	0.505	−0.11 (0.06)	0.052	−0.04 (0.06)	0.495
Depression	0.12 (0.07)	0.077	**−0.16 (0.05)**	**0.003**	−0.14 (0.06)	0.011	−0.03 (0.05)	0.534	−0.12 (0.07)	0.072	−0.07 (0.05)	0.216
GAD	0.03 (0.06)	0.608	−0.12 (0.05)	0.020	−0.04 (0.05)	0.472	−0.01 (0.04)	0.845	0.02 (0.07)	0.820	0.00 (0.06)	0.989
PTSD	0.08 (0.04)	0.034	−0.06 (0.05)	0.280	0.05 (0.05)	0.367	−0.03 (0.05)	0.562	−0.01 (0.03)	0.702	0.04 (0.06)	0.572
Social Phobia	−0.14 (0.07)	0.072	−0.04 (0.06)	0.468	−0.10 (0.05)	0.024	0.04 (0.07)	0.548	−0.04 (0.06)	0.472	−0.13 (0.08)	0.086
Agoraphobia/panic	0.03 (0.05)	0.547	**−0.13 (0.05)**	**0.007**	−0.06 (0.05)	0.276	−0.00 (0.05)	0.988	−0.07 (0.06)	0.224	0.02 (0.05)	0.718
Specific Phobia	−0.01 (0.08)	0.911	−0.17 (0.07)	0.011	0.00 (0.06)	0.965	0.03 (0.08)	0.741	−0.09 (0.08)	0.230	0.07 (0.05)	0.148
OCD	0.10 (0.05)	0.049	−0.06 (0.06)	0.332	0.06 (0.06)	0.314	0.00 (0.06)	0.964	−0.01 (0.06)	0.854	0.03 (0.06)	0.631
APD	0.08 (0.06)	0.185	−0.00 (0.08)	0.978	**−0.22 (0.07)**	**0.002**	**−0.21 (0.07)**	**0.004**	**−0.21 (0.05)**	**0.000**	−0.16 (0.07)	0.014
Alcohol use	**0.24 (0.05)**	**0.000**	−0.08 (0.06)	0.190	−0.06 (0.06)	0.262	**−0.15 (0.05)**	**0.004**	−0.12 (0.06)	0.050	−0.09 (0.06)	0.144
Marijuana	0.09 (0.05)	0.056	−0.09 (0.05)	0.065	−0.07 (0.05)	0.150	−0.09 (0.05)	0.079	−0.06 (0.05)	0.260	−0.13 (0.05)	0.012
Nicotine	0.08 (0.06)	0.226	−0.13 (0.06)	0.025	−0.13 (0.06)	0.027	−0.12 (0.06)	0.026	−0.11 (0.06)	0.066	**−0.17 (0.05)**	**0.000**

Regressions that were significant after FWE correction are displayed in bold.

[a] Abbreviations are as follows: corpus callosum (CC), anterior corona radiata (ACR), internal capsule (IC), sagittal stratum (SS), fractional anisotropy (FA), and axial diffusivity (AD).

samples that have identified the CC as a correlate of psychopathology have identified decreased integrity in patient populations as compared with healthy controls (Arnone et al., 2008; Jiang et al., 2017; Lindner et al., 2016). Nonetheless, some case-control studies of persons given the diagnosis of schizophrenia have found hyperconnectivity between hemispheres (David, 1993; Schmidt et al., 2015). This is important because, in other studies, schizophrenia loads strongly on the general factor of psychopathology (Carragher et al., 2016; Caspi et al., 2014).

Notably, some studies of children and adolescents with a broad range of disorders including ADHD, CD, alcohol use disorder, and OCD have also shown a trend consistent to the present results with increased white matter integrity in patient populations in the CC, although these results were observed in the context of specific case-control type designs rather than reflecting transdiagnostic characteristics (De Bellis et al., 2008; Decety et al., 2015; Jayarajan et al., 2012; Lawrence et al., 2013; Menks et al., 2017; Pape et al., 2015; Zarei et al., 2011; Zhang et al., 2014). It is notable that in the context of such studies it has been hypothesized that individuals with psychopathology may have an accelerated trajectory of white matter development with an earlier peak and subsequent earlier and steeper decline, thus explaining increased integrity relative to controls during childhood but decreased integrity during adulthood (Menks et al., 2017). The body of the CC is one of the last tracts to complete myelination, not reaching its peak until around age 35 (Lebel et al., 2012). Given that the present sample consists of young adults ages 23–31, it is likely that there is some heterogeneity in the state of development of white matter tracts. Whereas most subjects in this sample have likely reached peak development in all earlier developing tracts, the majority of individuals may not have reached the peak for the body of CC. If the present results reflect a prolonged developmental trajectory in the CC, this might help explain why white matter microstructure properties of the CC body demonstrate findings more in line with pediatric studies. However, the literature on developmental trajectories of white matter and psychopathology shows substantial inconsistencies across studies. For instance, Muetzel and colleagues found that higher early childhood internalizing and externalizing symptoms predicted smaller increases in global FA development later in childhood (Muetzel et al., 2017). By contrast, a more recent study by the same group found there was not a significant association between childhood externalizing symptoms and global FA (Bolhuis et al., 2018). Longitudinal imaging studies will be critical in understanding the complex interplay between white matter tract development trajectories and second-order factors of psychopathology.

4.4. Implications of tests of associations with individual first-order dimensions of psychopathology

The primary analyses of associations of measures of white matter microstructure with second-order factors of psychopathology addressed the extent to which it is possible to identify individual differences in brain that are correlated nonspecifically with all first-order dimensions of psychopathology through the general factor, and with all internalizing and all externalizing dimensions after correlations among every dimension of psychopathology are captured by the general factor. It is useful to ask, therefore, if any microstructural correlate of the general factor is associated with *every* first-order dimension of psychopathology considered one at a time. Similarly, it is important to ask if each microstructural correlate of the specific internalizing and specific externalizing factor is associated with every first-order dimension of internalizing and externalizing psychopathology, respectively. If that were the case, there would be no need to use second-order latent factors to identify microstructural correlates associated with every form of psychopathology. The reason that such findings are unlikely, however, is that individual tests of each first-order dimension of psychopathology one at a time are fundamentally different from testes of associations with second-order factors. Individual tests of a single first-order dimension conflate both variance that is unique to that dimension and some degree of the variance that it shares with every other correlated first-order dimension both within and across the internalizing and externalizing spectra. In contrast, tests of microstructural correlates of second-order factors address only the transdiagnostic variance that is shared in common by all of the first-order dimensions that load on the second-order factor.

In tests of associations with individual first-order dimensions of psychopathology conducted one at time, FA in the CC body was positively associated with two first-order dimensions, hyperactivity-impulsivity and alcohol use disorder dimensions after FDR correction. Other first-order dimensions were positively associated with FA in the CC body, but were not significant after FDR correction. This suggests that the nonspecific association of these first-order dimensions with greater FA in the CC body was not efficiently captured in analyses of individual dimensions, perhaps because first-order dimension scores combine dimension-specific and a degree of shared variance.

AD in the fornix, which was inversely associated with the specific second-order internalizing factor, was associated with none of the first-order externalizing dimensions, but was inversely associated with depression and agoraphobia/panic after FDR correction, both of which

loaded significantly on the specific internalizing factor (Fig. 1). Similarly, AD in each the four tracts found to be inversely associated with the specific second-order externalizing factor was significantly associated with none of the first-order internalizing dimensions, but was significantly associated with at least one first-order externalizing dimensions (antisocial personality disorder in three cases). This is sensible since antisocial personality has the highest loading on the specific externalizing factor in this study (Fig. 1). Overall, the magnitudes of association for second-order factors were in the same range as for the first-order factors, suggesting that use of the second-order factors was unlikely to be masking significant relations that would have been seen at a more specific level. While these results suggest that none of the significant associations with higher factors were driven exclusively by individual symptom dimensions, these symptom dimensions may be contributing to the associations.

It is important to note the significant associations of individual first-order dimension of maladaptive alcohol use (positive for FA in the body of the CC; negative for AD in the ACR) and nicotine (negative for AD in the SS). Although the inclusion of current drug use as measured by urine screening as a covariate did not alter findings of associations of microstructure with second-order psychopathology factors, the findings of significant associations with self-reported maladaptive use of alcohol and nicotine mean that future longitudinal study is needed to disentangle the extent to which the observed white matter correlates of the externalizing factor in these specific tracts (as well as the general factor and the body of the CC) are a consequence versus a causative correlate of substance use.

4.5. Limitations

Based on our scanning parameters we had limited coverage of the cerebellum, and thus we were unable to test for a previously reported association between the general factor and white matter microstructure in the cerebellum (Romer et al., 2018). Another limitation is that we excluded individuals who reported psychotic disorders on screening, and therefore more extreme forms of psychopathology were not included in the present sample. Moreover, we did not probe for psychotic symptoms outside of mood congruent symptoms in the context of mood disorders questions. As such, we could not test for correlates of a second-order thought disorder factor, or include thought disorder dimensions in the extraction of the general factor. Studies employing a more comprehensive interview should examine if this putative thought disorder factor has unique white matter microstructure correlates.

In secondary analyses, we contrasted the results of analyzing disorder specific symptom counts with the results of latent factor scores. It must be noted, that such comparisons are not equivalent statistically since the analysis of multiple disorder dimensions greatly expands multiple comparison issues, and do not attempt to control for other non-target symptoms. Indeed, we felt compelled to not test for associations at the disorder specific level when there were no associations for a given tract metric at the second-order factor level in order to avoid an explosion of comparisons. In this sense, the latent factor approach may have an advantage over assessments of multiple disorders in the same data set. However, the restriction of tracts and metrics to only those that already shown associations at the latent factor level means that disorder specific associations may well exist that were not tested for because the initial broad phenotypes were masking the narrower relationships.

5. Conclusions

The majority of prior studies on white matter microstructure and psychopathology have used case-control designs that obscure the extent to which identified associations reflect nonspecific versus specific aspects of psychopathology. By contrast, the present study applied a bifactor model that allows for a transdiagnostic quantitative approach to distinguish between different second-order dimensions of psychopathology. While there are methodological limitations when using fit statistics to adjudicate between bifactor and traditional correlated factor models of psychopathology, increasing data indicate the ability of this approach to differentiate meaningful nonspecific and dimension-specific correlates of psychopathology including etiological, concurrent and predictive correlates (Caspi and Moffitt, 2018; Lahey et al., 2017b; Wade et al., 2018). Importantly, in the present study, we identified both broad nonspecific (FA in the body of the CC) and second-order externalizing or internalizing level dimensions (AD in the fornix, sagittal stratum, anterior corona radiata, and splenium of the CC) white matter correlates of psychopathology. Although requiring replication, these results highlight the utility of this quantitative latent factor approach for revealing the neural correlates of psychopathology.

Disclosures

The authors have nothing to disclose.

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References

Arnone, D., Barrick, T.R., Chengappa, S., Mackay, C., Clark, C.A., Abou-Saleh, M., 2008. Corpus callosum damage in heavy marijuana use: preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. NeuroImage 41, 1067–1074.

Baker, S.T., Yücel, M., Fornito, A., Allen, N.B., Lubman, D.I., 2013. A systematic review of diffusion weighted MRI studies of white matter microstructure in adolescent substance users. Neurosci. Biobehav. Rev. 37, 1713–1723.

Bava, S., Frank, L.R., McQueeny, T., Schweinsburg, B.C., Schweinsburg, A.D., Tapert, S.F., 2009. Altered white matter microstructure in adolescent substance users. Psychiatry Res. Neuroimaging 173, 228–237.

Berns, G.S., Moore, S., Capra, C.M., 2009. Adolescent engagement in dangerous behaviors is associated with increased white matter maturity of frontal cortex. PLoS One 4, e6773.

Bolhuis, K., Muetzel, R.L., Stringaris, A., Hudziak, J.J., Jaddoe, V.W., Hillegers, M.H., White, T., Kushner, S.A., Tiemeier, H., 2018. Structural brain connectivity in childhood disruptive behavior problems: a multidimensional approach. Biol. Psychiatry 85 (4), 336–344.

Bracht, T., Linden, D., Keedwell, P., 2015. A review of white matter microstructure alterations of pathways of the reward circuit in depression. J. Affect. Disord. 187, 45–53.

Carragher, N., Teesson, M., Sunderland, M., Newton, N., Krueger, R., Conrod, P., Barrett, E., Champion, K., Nair, N., Slade, T., 2016. The structure of adolescent psychopathology: a symptom-level analysis. Psychol. Med. 46, 981–994.

Caspi, A., Moffitt, T.E., 2018. All for one and one for all: mental disorders in one dimension. Am. J. Psychiatr. 175 (9), 831–844 (appi. ajp. 2018.17121383).

Caspi, A., Houts, R.M., Belsky, D.W., Goldman-Mellor, S.J., Harrington, H., Israel, S., Meier, M.H., Ramrakha, S., Shalev, I., Poulton, R., 2014. The p factor one general psychopathology factor in the structure of psychiatric disorders? Clin. Psychol. Sci. 2, 119–137.

Chang, L.Ä., Jones, D.K., Pierpaoli, C., 2005. RESTORE: robust estimation of tensors by outlier rejection. Magn. Reson. Med. 53, 1088–1095.

Chen, G., Hu, X., Li, L., Huang, X., Lui, S., Kuang, W., Ai, H., Bi, F., Gu, Z., Gong, Q., 2016. Disorganization of white matter architecture in major depressive disorder: a meta-analysis of diffusion tensor imaging with tract-based spatial statistics. Sci. Rep. 6, 21825.

Cook, P., Bai, Y., Nedjati-Gilani, S., Seunarine, K., Hall, M., Parker, G., Alexander, D., 2006. Camino: Open-Source Diffusion-MRI Reconstruction and Processing. 14th Scientific Meeting of the International Society for Magnetic Resonance in Medicine.

David, A.S., 1993. Callosal transfer in schizophrenia: too much or too little? J. Abnorm. Psychol. 102, 573.

De Bellis, M.D., Van Voorhees, E., Hooper, S.R., Gibler, N., Nelson, L., Hege, S.G., Payne, M.E., MacFall, J., 2008. Diffusion tensor measures of the corpus callosum in

adolescents with adolescent onset alcohol use disorders. Alcohol. Clin. Exp. Res. 32, 395–404.
Decety, J., Yoder, K.J., Lahey, B.B., 2015. Sex differences in abnormal white matter development associated with conduct disorder in children. Psychiatry Res. Neuroimaging 233, 269–277.
Fischl, B., 2012. FreeSurfer. NeuroImage 62, 774–781.
Geng, H., Wu, F., Kong, L., Tang, Y., Zhou, Q., Chang, M., Zhou, Y., Jiang, X., Li, S., Wang, F., 2016. Disrupted structural and functional connectivity in prefrontal-hippocampus circuitry in first-episode medication-naive adolescent depression. PLoS One 11, e0148345.
Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., 2015. Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 72, 305–315.
Greene, A.L., Eaton, N.R., 2017. The temporal stability of the bifactor model of comorbidity: an examination of moderated continuity pathways. Compr. Psychiatry 72, 74–82.
Hankin, B.L., Davis, E.P., Snyder, H., Young, J.F., Glynn, L.M., Sandman, C.A., 2017. Temperament factors and dimensional, latent bifactor models of child psychopathology: transdiagnostic and specific associations in two youth samples. Psychiatry Res. 252, 139–146.
Hart, E.L., Lahey, B.B., Loeber, R., Applegate, B., Frick, P.J., 1995. Developmental change in attention-deficit hyperactivity disorder in boys: a four-year longitudinal study. J. Abnorm. Child Psychol. 23, 729–749.
Hsu, J.-L., Leemans, A., Bai, C.-H., Lee, C.-H., Tsai, Y.-F., Chiu, H.-C., Chen, W.-H., 2008. Gender differences and age-related white matter changes of the human brain: a diffusion tensor imaging study. NeuroImage 39, 566–577.
Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatr. 167, 748–751.
Jayarajan, R.N., Venkatasubramanian, G., Viswanath, B., Reddy, Y.J., Srinath, S., Vasudev, M.K., Chandrashekar, C.R., 2012. White matter abnormalities in children and adolescents with obsessive-compulsive disorder: a diffusion tensor imaging study. Depression Anxiety 29, 780–788.
Jenkins, L.M., Barba, A., Campbell, M., Lamar, M., Shankman, S.A., Leow, A.D., Ajilore, O., Langenecker, S.A., 2016. Shared white matter alterations across emotional disorders: a voxel-based meta-analysis of fractional anisotropy. NeuroImage Clin. 12, 1022–1034.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17, 825–841.
Jiang, W., Shi, F., Liu, H., Li, G., Ding, Z., Shen, H., Shen, C., Lee, S.-W., Hu, D., Wang, W., 2017. Reduced white matter integrity in antisocial personality disorder: a diffusion tensor imaging study. Sci. Rep. 7, 43002.
Kaczkurkin, A., Moore, T., Calkins, M., Ciric, R., Detre, J., Elliott, M., Foa, E., de la Garza, A.G., Roalf, D., Rosen, A., 2017. Common and dissociable regional cerebral blood flow differences associate with dimensions of psychopathology across categorical diagnoses. Mol. Psychiatry 23 (10), 1981–1989.
Kennis, M., Van Rooij, S.J., Tromp, D.P., Fox, A.S., Rademaker, A.R., Kahn, R.S., Kalin, N.H., Geuze, E., 2015. Treatment outcome-related white matter differences in veterans with posttraumatic stress disorder. Neuropsychopharmacology 40, 2434.
Kim, M.-K., Kim, B., Choi, T.K., Lee, S.-H., 2017. White matter correlates of anxiety sensitivity in panic disorder. J. Affect. Disord. 207, 148–156.
Koch, K., Reeß, T.J., Rus, O.G., Zimmer, C., Zaudig, M., 2014. Diffusion tensor imaging (DTI) studies in patients with obsessive-compulsive disorder (OCD): a review. J. Psychiatr. Res. 54, 26–35.
Korgaonkar, M.S., Grieve, S.M., Koslow, S.H., Gabrieli, J.D., Gordon, E., Williams, L.M., 2011. Loss of white matter integrity in major depressive disorder: evidence using tract-based spatial statistical analysis of diffusion tensor imaging. Hum. Brain Mapp. 32, 2161–2171.
Korn, E., Graubard, B., 1999. Analysis of Health SurveysWiley. (New York).
Laceulle, O.M., Vollebergh, W.A., Ormel, J., 2015. The structure of psychopathology in adolescence: replication of a general psychopathology factor in the TRAILS study. Clin. Psychol. Sci. 3, 850–860.
Lahey, B.B., Rathouz, P.J., Van Hulle, C., Urbano, R.C., Krueger, R.F., Applegate, B., Garriock, H.A., Chapman, D.A., Waldman, I.D., 2008. Testing structural models of DSM-IV symptoms of common forms of child and adolescent psychopathology. J. Abnorm. Child Psychol. 36, 187–206.
Lahey, B.B., Applegate, B., Hakes, J.K., Zald, D.H., Hariri, A.R., Rathouz, P.J., 2012. Is there a general factor of prevalent psychopathology during adulthood? J. Abnorm. Psychol. 121, 971.
Lahey, B.B., Rathouz, P.J., Keenan, K., Stepp, S.D., Loeber, R., Hipwell, A.E., 2015. Criterion validity of the general factor of psychopathology in a prospective study of girls. J. Child Psychol. Psychiatry 56, 415–422.
Lahey, B.B., Krueger, R.F., Rathouz, P.J., Waldman, I., Zald, D.H., 2017a. A hierarchical causal taxonomy of psychopathology across the life span. Psychol. Bull. 143, 142–186.
Lahey, B.B., Krueger, R.F., Rathouz, P.J., Waldman, I.D., Zald, D.H., 2017b. Validity and utility of the general factor of psychopathology. World Psychiatry 16, 142–144.
Lahey, B.B., Zald, D.H., Perkins, S.F., Villalta-Gil, V., Werts, K.B., Van Hulle, C.A., Rathouz, P.J., Applegate, B., Class, Q.A., Poore, H.E., 2017c. Measuring the hierarchical general factor model of psychopathology in young adults. Int. J. Methods Psychiatr. Res. 27, e1593.
Lauzon, C.B., Asman, A.J., Esparza, M.L., Burns, S.S., Fan, Q., Gao, Y., Anderson, A.W., Davis, N., Cutting, L.E., Landman, B.A., 2013. Simultaneous analysis and quality assurance for diffusion tensor imaging. PLoS One 8, e61737.
Lawrence, K.E., Levitt, J.G., Loo, S.K., Ly, R., Yee, V., O'Neill, J., Alger, J., Narr, K.L., 2013. White matter microstructure in subjects with attention-deficit/hyperactivity disorder and their siblings. J. Am. Acad. Child Adolesc. Psychiatry 52, 431–440 (e434).
Lebel, C., Gee, M., Camicioli, R., Wieler, M., Martin, W., Beaulieu, C., 2012. Diffusion tensor imaging of white matter tract evolution over the lifespan. NeuroImage 60, 340–352.
Lindner, P., Savic, I., Sitnikov, R., Budhiraja, M., Liu, Y., Jokinen, J., Tiihonen, J., Hodgins, S., 2016. Conduct disorder in females is associated with reduced corpus callosum structural integrity independent of comorbid disorders and exposure to maltreatment. Transl. Psychiatry 6, e714.
Menks, W.M., Furger, R., Lenz, C., Fehlbaum, L.V., Stadler, C., Raschle, N.M., 2017. Microstructural white matter alterations in the corpus callosum of girls with conduct disorder. J. Am. Acad. Child Adolesc. Psychiatry 56, 258–265 (e251).
Mori, S., Wakana, S., Van Zijl, P.C., Nagae-Poetscher, L., 2005. MRI Atlas of Human White Matter. Elsevier.
Muetzel, R.L., Blanken, L.M., van der Ende, J., El Marroun, H., Shaw, P., Sudre, G., van der Lugt, A., Jaddoe, V.W., Verhulst, F.C., Tiemeier, H., 2017. Tracking brain development and dimensional psychiatric symptoms in children: a longitudinal population-based neuroimaging study. Am. J. Psychiatr. 175, 54–62.
Muthén, B., Muthén, L., 2018. Mplus 8.1. Muthén & Muthén, Los Angeles.
Pape, L.E., Cohn, M.D., Caan, M.W., van Wingen, G., van den Brink, W., Veltman, D.J., Popma, A., 2015. Psychopathic traits in adolescents are associated with higher structural connectivity. Psychiatry Res. Neuroimaging 233, 474–480.
Paul, R.H., Grieve, S.M., Niaura, R., David, S.P., Laidlaw, D.H., Cohen, R., Sweet, L., Taylor, G., Clark, C.R., Pogun, S., 2008. Chronic cigarette smoking and the microstructural integrity of white matter in healthy adults: a diffusion tensor imaging study. Nicotine Tob. Res. 10, 137–147.
Pierpaoli, C., Jezzard, P., Basser, P.J., Barnett, A., Di Chiro, G., 1996. Diffusion tensor MR imaging of the human brain. Radiology 201, 637–648.
Romer, A.L., Knodt, A.R., Houts, R., Brigidi, B.D., Moffitt, T.E., Caspi, A., Hariri, A.R., 2018. Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders. Mol. Psychiatry 23, 1084.
Schmidt, A., Lenz, C., Smieskova, R., Harrisberger, F., Walter, A., Riecher-Rössler, A., Simon, A., Lang, U.E., McGuire, P., Fusar-Poli, P., 2015. Brain diffusion changes in emerging psychosis and the impact of state-dependent psychopathology. Neurosignals 23, 71–83.
Shaffer, D., Fisher, P., Dulcan, M.K., Davies, M., Piacentini, J., Schwab-Stone, M.E., Lahey, B.B., Bourdon, K., Jensen, P.S., Bird, H.R., 1996. The NIMH diagnostic interview schedule for children version 2.3 (DISC-2.3): description, acceptability, prevalence rates, and performance in the MECA study. J. Am. Acad. Child Adolesc. Psychiatry 35, 865–877.
Shaffer, D., Fisher, P., Lucas, C.P., Dulcan, M.K., Schwab-Stone, M.E., 2000. NIMH diagnostic interview schedule for children version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. J. Am. Acad. Child Adolesc. Psychiatry 39, 28–38.
Siehl, S., King, J., Burgess, N., Flor, H., Nees, F., 2018. Structural white matter changes in adults and children with posttraumatic stress disorder: a systematic review and meta-analysis. NeuroImage Clin. 19, 581–598.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17, 143–155.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage 31, 1487–1505.
Tackett, J.L., Lahey, B.B., Van Hulle, C., Waldman, I., Krueger, R.F., Rathouz, P.J., 2013. Common genetic influences on negative emotionality and a general psychopathology factor in childhood and adolescence. J. Abnorm. Psychol. 122, 1142.
Takao, H., Hayashi, N., Inano, S., Ohtomo, K., 2011. Effect of head size on diffusion tensor imaging. NeuroImage 57, 958–967.
Takao, H., Hayashi, N., Ohtomo, K., 2014. Sex dimorphism in the white matter: fractional anisotropy and brain size. J. Magn. Reson. Imaging 39, 917–923.
Thomason, M.E., Thompson, P.M., 2011. Diffusion imaging, white matter, and psychopathology. Annu. Rev. Clin. Psychol. 7.
Wade, M., Fox, N.A., Zeanah, C.H., Nelson, C.A., 2018. Effect of foster care intervention on trajectories of general and specific psychopathology among children with histories of institutional rearing: a randomized clinical trial. JAMA Psychiatry. 75 (11), 1137–1145.
Waller, R., Dotterer, H.L., Murray, L., Maxwell, A.M., Hyde, L.W., 2017. White-matter tract abnormalities and antisocial behavior: a systematic review of diffusion tensor imaging studies across development. NeuroImage Clin. 14, 201–215.
Zald, D.H., Lahey, B.B., 2017. Implications of the hierarchical structure of psychopathology for psychiatric neuroimaging. Biol. Psychiatry Cogn. Neurosci. Neuroimaging. 2 (4), 310–317.
Zarei, M., Mataix-Cols, D., Heyman, I., Hough, M., Doherty, J., Burge, L., Winmill, L., Nijhawan, S., Matthews, P.M., James, A., 2011. Changes in gray matter volume and white matter microstructure in adolescents with obsessive-compulsive disorder. Biol. Psychiatry 70, 1083–1090.
Zhang, J., Zhu, X., Wang, X., Gao, J., Shi, H., Huang, B., Situ, W., Yi, J., Zhu, X., Yao, S., 2014. Increased structural connectivity in corpus callosum in adolescent males with conduct disorder. J. Am. Acad. Child Adolesc. Psychiatry 53, 466–475 (e461).