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Shapes of subcortical structures in adolescents with and without familial history of substance use disorder

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Abstract

It has been suggested that intergenerational transmission of risk for substance use disorder (SUD) manifests in the brain anatomy of substance naïve adolescents. While volume and shapes of subcortical structures (SSS) have been shown to be heritable, these structures, especially the pallidum, putamen, nucleus accumbens, and hippocampus, have also been associated with substance use disorders. However, it is not clear if those anatomical differences precede substance use or are the result of that use. Therefore, we examined if volume and SSS of adolescents with a family history (FH+) of SUD differed from adolescents without such a history (FH−). Because risk for SUD is associated with anxiety and impulsivity, we also examined correlations between these psychological characteristics and volume/SSS. Using structural MRI and FSL software, we segmented subcortical structures and obtained indices of SSS and volumes of 64 FH+ and 58 FH− adolescents. We examined group differences in volume and SSS, and the correlations between volume/SSS and trait anxiety and impulsivity. FH+ adolescents had a significant inward deformation in the shape of the right anterior hippocampus compared to FH− adolescents, while the volume of this structure did not differ between groups. Neither shape nor volume of the other subcortical structures differed between groups. In the FH+ adolescents, the left hippocampus shape was positively correlated with both trait anxiety and impulsivity, while in FH− adolescents a negative correlation pattern of SSS was seen in the hippocampus. SSS appears to capture local anatomical features that traditional volumetric analysis does not. The inward shape deformation in the right anterior hippocampus in FH+ adolescents may be related to the known increased risk for behavioral dysregulation leading to SUD in FH+ offspring. Hippocampus shape also exhibits opposite patterns of correlation with anxiety and impulsivity scores across the FH+ and FH− adolescents. These novel findings may reveal neural correlates,

not captured by traditional volumetric analysis, of familial transmission of increased vulnerability to SUD.

1 | INTRODUCTION

Substance use disorder (SUD) is prevalent among individuals with a family history (FH) of SUD (FH+), and this increased risk for SUD is most likely transmitted through a complex combination of genetic and environmental/learning mechanisms (Merikangas, et al. 1998). Yet the neural correlates of this transmission remain poorly understood, in part due to the difficulty in distinguishing neural characteristics resulting from familial transmission from those that occur as a result of substance use.

If there are structural brain differences in adolescents from FH+ compared to FH− families, those differences may be important indices of transmitted SUD risk. Differences in subcortical structures, including the nucleus accumbens, pallidum, caudate, putamen, amygdala, and hippocampus, have been implicated in SUD and in behaviors that predispose adolescents to drug use initiation. We, therefore, examined young substance naïve adolescents at high risk for SUD by virtue of a FH of SUD, with the goal of imaging their brains prior to regular substance use. We investigated the shapes and volume of subcortical structures (SSS), two potentially heritable structural features that are also are affected by environmental factors (Hibar, et al. 2015; Roshchupkin, et al. 2016; Satizabal, et al. 2019) to examine the neural correlates of SUD risk. While other anatomical research has investigated familial transmission of SUD risk, to our knowledge, this is the first time that FH+/FH− adolescents have been compared on measures of both SSS and volume. These analyses complement our previous neuroimaging investigations of adolescents at risk of SUD, which used fMRI (Qiao, et al. 2015; Rodriguez-Moreno, et al. 2021) and structural and functional connectivity (He, et al. 2021).

Prior research investigated neural correlates of SUD risk by examining cortical thickness and volume in adolescents with and without FH of drug/alcohol use. For example, thinner cortices were found in the medial orbitofrontal, lateral orbitofrontal, and superior parietal cortices in at risk adolescents with FH of alcohol use disorder (AUD) (Henderson, et al. 2018). In a study of adolescents and young adults with FH+ for AUD, the ratio of orbitofrontal cortex volume to amygdala volume was found to predict time to alcohol dependence across the sample (O'Brien and Hill 2017). In addition, the density of family history of alcoholism was found to be related to the volume of the left nucleus accumbens in adolescent females, but not in adolescent males (Cservenka, et al. 2015). These studies suggest that risk for SUD could be detected in volume of brain structures prior to regular drug or alcohol use.

At the same time, there are numerous studies demonstrating brain changes in individuals with SUD. In a recent study, using the ENIGMA (enhancing neuroimaging genetics through meta-analysis) database, alcohol use dependence (AUD) was found to be associated with abnormalities in the volumes of subcortical brain structures, including hippocampus, thalamus, putamen, and amygdala (Chye, et al. 2019). Moreover, these associations between substance use and brain structure appear to be enduring, with reduced volumes of subcortical structures including hippocampus, pallidum, and thalamus still found in subjects with alcohol dependence after short-term and even long-term abstinence (Fein and Fein 2013). These studies point to a more widespread effect of substance use on subcortical brain structures than previously known.

Prior anatomical studies of the brain have largely been limited by their focus on volumetric analyses. However, aggregate measures, such as subcortical structure volume, do not capture the full complexity of the anatomy subcortical structures. These subcortical structures are composed of multiple nuclei involved in different cortical–subcortical and midbrain-subcortical pathways within specific functional networks (Ji, et al. 2019; Moser and Moser 1998; Sesack and Grace 2010). The heterogeneity of these structures suggests that the detection of localized differences in their shape can provide relevant biological information over and above that of aggregate volumetric measures. Shape analyses involve characterizing local shape deformation by using a mesh vertex index, computed by employing the signed perpendicular distance to a reference surface (Dryden and Mardia 2016; Patenaude, et al. 2011). Shape analyses of brain structures have shown that brain shapes are influenced by heritable contributions beyond the genetic influence on total intracranial volume and the gross volume of each structure (Roshchupkin, et al. 2016). Accumulating evidence indicates that shape analyses of brain structures provide novel and independent information about brain anatomy, not available from conventional volumetric measurements (Gerig, et al. 2001; Roshchupkin, et al. 2016). For example, in a study using the structural MRI data from a mono/dizygotic twin study, the shape analysis captured structural similarities and differences which could not be ascertained by volume analysis (Gerig, et al. 2001).

Because risk for SUD has been shown to be highly associated with impulsivity, a multidimensional construct often defined as a predisposition for immediate reward without adequate regard for the negative consequences (Moeller, et al. 2001), we also assessed impulsivity to understand its relationship to differences in subcortical brain volume and SSS. There are two well-established questionnaire-based

assessments of impulsiveness: the Behavioral Inhibition and Behavioral Activation Scale (BIS/BAS) (Carver and White 1994) and the Barratt Impulsiveness Scale BIS-11 (Patton, et al. 1995). The BIS/BAS assesses avoidance of negative experiences, as well as approach to positive experiences, whereas the BIS-11 assesses attentional, motor, and non-planning impulsivity. A number of studies have found that BIS/BAS scores correlate with drug and alcohol use (Franken and Muris 2006; Rieser, et al. 2019; Simons, et al. 2009). Another important psychological construct association with SUD is anxiety, frequently assessed by the State–Trait Anxiety Inventory (STAI) (Julian 2011). Epidemiologic and treatment studies have found that anxiety disorders and SUD commonly co-occur, but the relationship is complex and variable (Brady, et al. 2013; Smith and Book 2008). We, therefore, also assessed the relationship of anxiety with subcortical brain volume and SSS.

In summary, the aims of this study were, first, to examine the relationship of subcortical volume and SSS measures in substance naïve adolescents with family history (FH+) of drug/alcohol use disorder. The study cohort was comprised of inner-city adolescents who share similar disadvantaged environments. We hypothesized that the subcortical shape analysis would capture relevant morphological features (local inward or outward deformations) associated with FH status. Second, the aim was to explore if the differences in the subcortical volume and SSS across groups were correlated with psychological measures of impulsivity and anxiety.

2 | METHODS

2.1 | Participants

Anatomical MRI scans were acquired from 125 adolescents recruited from a larger study of high-risk minority youth and their parents. Two participants were excluded from analysis due to incidental findings and one participant due to image artifacts, resulting in 64 FH+ adolescents (26 males, age 15.20 ± 1.37) and 58 FH− adolescents (37 males, age 14.93 ± 1.28) (Table 1). The FH+ group was defined as having a parent with a lifetime DSM-IV alcohol ($N = 25$) or drug ($N = 39$) abuse diagnosis based on the Composite International Diagnostic Interview (CIDI) (Robins, et al. 1988). Ninety-seven percent of the adolescents were drug naïve, defined as having consumed less than 6 alcoholic drinks, smoked marijuana less than 6 times, or used any other combination of drugs less than 3 times in their lifetime. Those adolescents who did not match criteria for naïve reported sufficiently rare drug use that was not expected to cause detectable structural brain changes. The New York State Psychiatric Institute's Institutional Review Board approved this study, and informed consent/assent was obtained from every participant and their parent.

2.2 | Psychological measures

Impulsivity and anxiety measures were obtained during a confidential interview of the youth. The BIS/BAS scale examines motivational systems: the BAS (Behavioral Activation System) measures approach to reward using three sub-scales (drive, reward responsiveness, and fun-seeking); the BIS (Behavioral Inhibition System) assesses avoidance of negative outcomes and is composed of a single scale (Carver and White 1994). Previous research with adolescents has shown that higher levels of substance use are associated with high BAS scores and low BIS scores (Genovese and Wallace 2007). The Barratt Impulsiveness Scale (BIS-11) includes three impulsivity scales: attentional, motor, and non-planning (Patton, et al. 1995), with higher scores indicating a higher likelihood of impulsive behaviors. Previous research with adolescents has indicated that higher BIS-11 scores are associated with earlier onset of substance use and a higher likelihood of abuse/dependency issues later in life (von Diemen, et al. 2008). The State–Trait Anxiety Inventory (STAI) consists of a measure of current (state) anxiety and trait (stable personal characteristic) anxiety (Julian 2011). High trait anxiety scores have previously been shown to be associated with adolescent substance use (Ste-Marie, et al. 2006). We included only trait anxiety because the STAI was not necessarily administered during the same day that the MRI scans were acquired for each participant. Subject characteristics and psychological measures were compared between FH+ and FH− groups using chi-square and t-tests.

2.3 | Image acquisition

T1-weighted images were acquired on a GE Discovery MR750 3.0T scanner with a 32-channel, phased array head coil, using a three-dimensional high-resolution BRAVO sequence. The image acquisition parameters: matrix of 256×256, voxel size of $1.0 \times 1.0 \times 1.0$ mm^3, field of view of 256×256 mm, bandwidth of 41.67 kHz, TR:7.2 msec, TE:2.7 msec, Flip angle:12°, 176 slices.

2.4 | Image preprocessing

Each anatomical image was processed using the DARTEL algorithm from the CAT12 toolbox (http://www.neuro.uni-jena.de/cat/) (run under SPM12) to perform bias correction of intensity non-uniformities and skull stripping. A Bayesian model-based segmentation toolbox in FSL (FIRST; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST) (Patenaude, et al. 2011) was used to segment each anatomical image and to create vertex meshes for the following 15 subcortical structures: brainstem and bilateral nucleus accumbens, putamen, caudate, palladium, thalamus, hippocampus, and amygdala. Quality control of the subcortical segmentations was performed based on FSL FIRST guidelines (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide), to ensure that only those error-free and high-quality segmentation outcomes were used in the subsequent analyses (see supporting information for more details).

2.5 | Subcortical shape analyses

For each of the 15 subcortical structures, shape *indices* were calculated using FSL vertex analysis script (*first_utils*), which was based on

Characteristic	FH− (N = 58) N (%)	FH+ (N = 64) N (%)	Chi-square	p-value
Female	29 (50)	29 (45.31)	0.27	0.60
Race/ethnicity			0.78	0.68
Hispanic	38 (65.52)	37 (57.81)		
Black	13 (22.41)	17 (26.56)		
Other/mixed race/unknown	7 (12.07)	10 (15.63)		
Annual household income[a]			0.61	0.74
≤$15,000	21 (36.84)	20 (31.75)		
$15,000–50,000	27 (47.37)	30 (47.62)		
≥$50,000	9 (15.79)	13 (20.63)		
	Mean (SD)	Mean (SD)	t	p-value
Age[b]	14.94 (1.31)	15.11 (1.36)	−0.72	0.47
Tanner average[a]	3.38 (1.00)	3.52 (1.07)	−0.77	0.44
STAI[a]				
Trait score	34.86 (8.88)	37.01 (9.25)	−1.3	0.20
BIS-11[a]				
Attentional impulsiveness	15.51 (2.72)	16.48 (3.22)	−1.78	0.08
Motor impulsiveness	20.95 (3.64)	21.70 (4.32)	−1.02	0.31
Non-planning impulsiveness	27.13 (4.66)	27.94 (5.20)	−0.9	0.37
BIS/BAS[a]				
BAS drive	10.57 (1.89)	10.35 (2.29)	0.57	0.57
BAS fun seeking	11.20 (1.48)	11.16 (1.80)	0.14	0.89
BAS reward responsiveness	15.61 (1.86)	15.70 (2.14)	−0.27	0.79
BIS	17.95 (1.97)	18.04 (2.94)	−0.19	0.85

TABLE 1 Demographic characteristics and psychological measures of FH+ and FH− groups

[a]Statistics reported are based on observations from available data. Information was missing for household income ($n = 2$); Tanner average ($n = 4$); STAI Trait ($n = 2$) scores; BIS-11 attentional ($n = 2$), motor ($n = 3$), and non-planning ($n = 1$) impulsiveness; and BIS/BAS drive ($n = 2$), fun seeking ($n = 3$), reward responsiveness ($n = 1$), and BIS ($n = 2$) scores.

[b]Ages reported are at scan date. For 60% of subjects, the scan and the interview occurred on the same day; for 88.5%, the interview and scan occurred within 1 month of each other. The time difference in days between the date of the scan and the date of the interview did not differ between FH+ and FH− subjects ($p = 0.92$).

the signed perpendicular distance from the surface mesh of the average shape of all participants in the corresponding structure in the MNI space. Positive indices represent *outward deformations* or expansions of the structure surface, and negative indices represent *inward deformations* or shrinkage of the structure surface. These values were then submitted to statistical analysis.

Group (FH+ vs. FH−) differences in subcortical shape were assessed using general linear model (GLM) for each of the 15 subcortical structures using FSL *randomize* procedure and including age and sex as covariates. Our findings were corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) (Smith and Nichols [2009]) with a family wise error (FWE) rate of $p < 0.05$ by running 5000 random permutations. To account for the influence of total intracranial volume (TIV) on the shape analysis, a similar analysis including TIV as a covariate was carried out and reported in the supporting information. The TIV was estimated

for each subject using brain anatomy toolbox, CAT12 (http://www.neuro.uni-jena.de/cat).

2.6 | Subcortical volume analyses

We performed volumetric analyses of all the 15 structures used in the SSS analysis, which were segmented using FSL FIRST. The volume of each subcortical structure for each participant's data was calculated by counting the number of voxels within each segmented structure and multiplying by the voxel size (mm). Similar to the SSS analysis, subcortical volumes for each of the 15 structures were compared between the FH+ and FH− groups using GLM with age, sex, and TIV as covariates. Results for group comparisons were reported with an adjusted p-value that was corrected for multiple comparisons by combining false discovery rate (FDR) and *Bonferroni* correction methods. The rationale for

combining these two methods was to minimize type 2 error caused by either method such that a minimum *t*-score threshold or a maximal *p*-value threshold was adopted to set the final threshold from those which were generated from the two methods (a similar strategy is used in SPM12, see spm_uc.m script). Accordingly, subcortical volume comparisons between FH+ and FH− groups were corrected for multiple comparisons using a combined *p*-value between the FDR correction *p*-value threshold under *q* < 0.05, and *Bonferroni* correction *p* threshold for the 15 structures, which was 0.0033 (0.05/15).

2.7 | Associations of subcortical shapes with psychological measures

We examined associations of SSS with psychological measures using FSL *randomize* with age and sex as covariates. We only report the associations for those subcortical structures that show significant group (FH+ vs. FH−) differences in SSS. Results for main effects and interactions were reported with an adjusted *p*-value corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) with a family wise error (FWE) rate of *p* < 0.05 by running 5000 random permutations. See also supporting information of exploratory analysis of the association of behavioral scores with SSS that did not survive group comparison under FWE *p* < 0.05.

2.8 | Associations of subcortical volumes with psychological measures

Correlations between the volume of subcortical structures and the psychological measures were computed using GLM with age, sex, and TIV as covariates. The linear regression models were estimated using ordinary least squares implemented using MATLAB. We report the association of subcortical volume with psychological measures only for those subcortical structures that show significant group (FH+ vs. FH−) differences in subcortical volume. Results for main effects and interactions were reported with an adjusted *p*-value corrected for multiple comparisons by combining false discovery rate (FDR, *q* < 0.05) and *Bonferroni* correction. Thus, the adjusted *p*-value for the *Bonferroni* correction (120 comparisons) was based on the 15 subcortical structures and 8 psychological measures (1 STAI Trait score, 3 sub-scales for BIS-11, and 4 sub-scales for BIS/BAS) yielding and a *p* threshold of 0.00042 (0.05/120) accordingly. See supporting information for exploratory analysis of the association of behavioral scores with the volumes that did not survive the group comparison.

3 | RESULTS

3.1 | Participants and psychological measures

There were no significant group differences in mean age, sex and other demographic variables, or in any of the psychological measures (Table 1).

3.2 | Volume and SSS of subcortical structures

There was a significant difference between FH+ and FH− groups in the shape of the right anterior hippocampus. For FH+ adolescents the right anterior hippocampus showed significant inward deformation (shrinking) (*p* < 0.05, FWE- & TFCE-corrected, Figure 1, Table 2). There was also inward deformation of the left anterior hippocampus, but it did not reach significance after correction. Furthermore, we did not detect any significant differences between FH+ and FH− adolescents in the volume of the right anterior hippocampus (4989.70 ± 315.52 mm^3 vs. 5004.33 ± 297.77 mm^3).

There were no significant differences that survived multiple comparison corrections between FH+ and FH− groups in shape or volume in any of the other subcortical structures. Therefore, only differences across FH+/FH− groups in the correlations of the shape/volume of the right/left hippocampus with behavioral scores are reported below. Given the changes of other subcortical structures in individual with SUD, we report the association of other subcortical structures' shape/volume with behavioral scores in the supporting information.

3.3 | Associations of volume and shape with psychological measures

Interactions in the correlation of subcortical hippocampal volumes with behavioral scores between FH+ and FH− groups did not survive multiple comparison corrections (*p*-value threshold 0.00042). There were significant interactions in the correlations of the hippocampus shape index with behavioral scores (*p* < 0.05, FWE- & TFCE-corrected) that differed between the FH+ and FH− groups, but surprisingly not in the same hippocampus subregion where we saw shape differences per se. Specifically, the left hippocampus shape showed an interaction with STAI Trait score, BIS-11–Attentional Impulsiveness score, and BAS fun seeking score (Table 2, Figure 2). Post hoc analyses indicate a positive correlation of shape index and behavioral scores for the FH+ group and a negative correlation for FH− group (Figures 3 and 4, respectively). Similar findings were observed in the right hippocampus, but none reached significance after multiple comparison corrections.

Given the changes of other subcortical structures in individual with SUD, we report the association of other subcortical structures' shape/volume with behavioral scores in the supporting information.

4 | DISCUSSION

We examined subcortical brain structures of substance naïve adolescents with and without family history of SUD. Using subcortical volume and shape analysis, we found, for the first time, that FH+ adolescents had significantly greater inward shape deformation in the right anterior hippocampus, even though the total hippocampus volume did not differ across groups. This finding supports our hypothesis
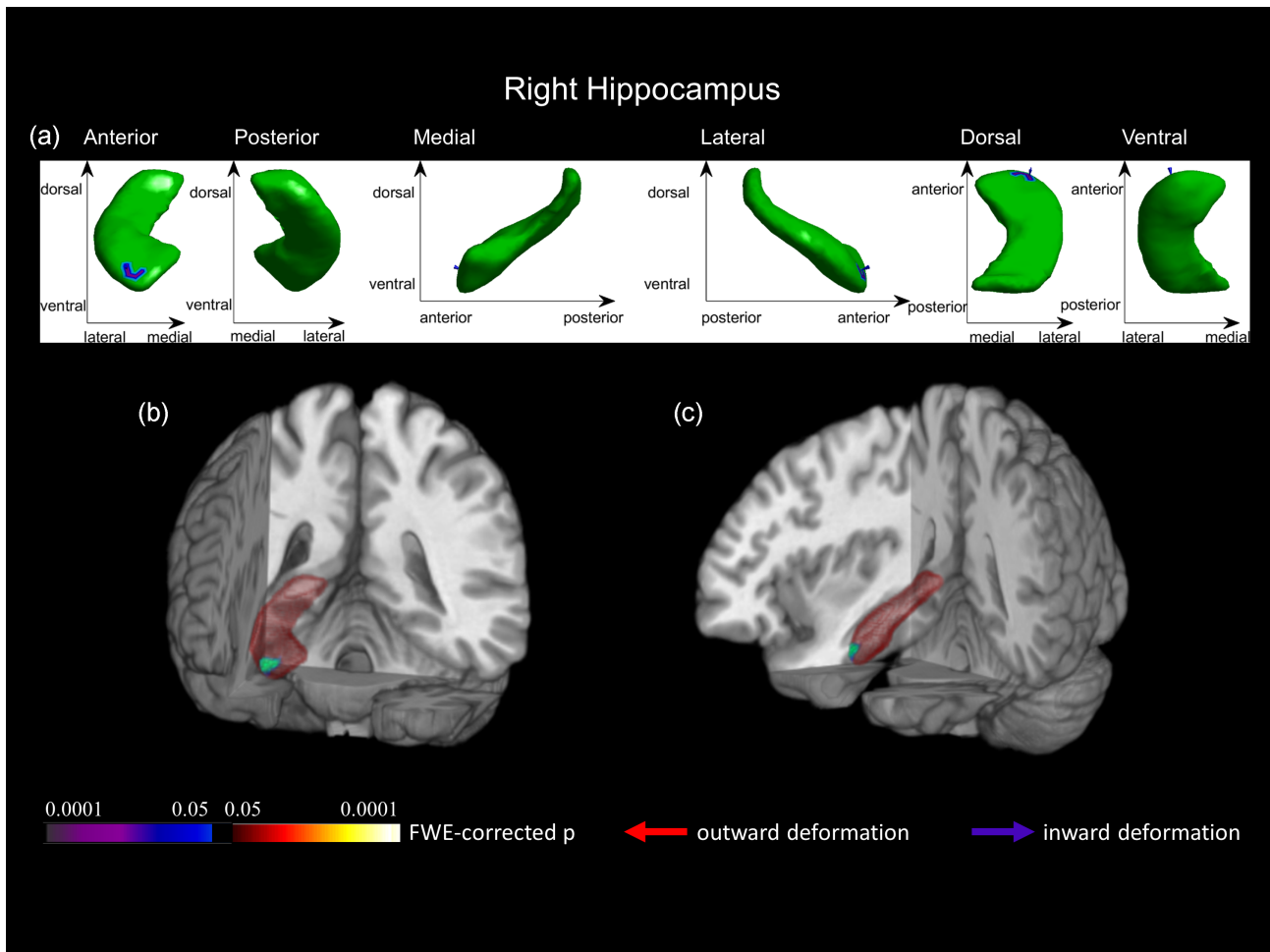
FIGURE 1 Vertex-based shape analysis results for the comparison between FH+ and FH− groups (FWE and TFCE-corrected $p < 0.05$) controlling for age and sex. Blue arrows correspond to inward deformations and red arrows correspond to outward deformations. The x and y axes indicate the anatomical directions. (a) Mesh views, (b) 3D anterior view, and (c) 3D medial view

TABLE 2 Summary of statistical shape analysis results of within different hippocampus regions

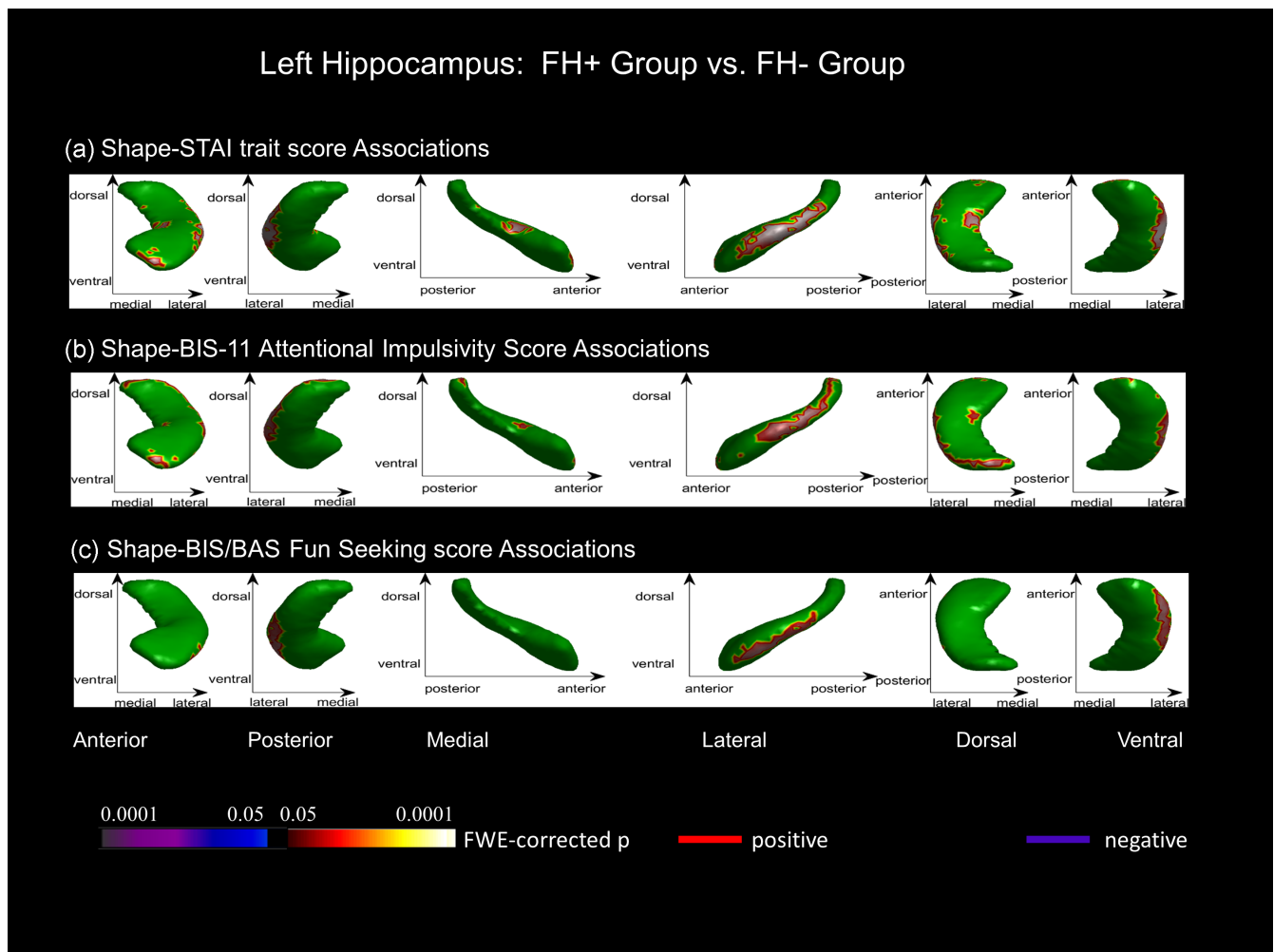| Hippocampus hemisphere | Peak MNI coordinates | | | Number of significant vertices | T statistic |
	x	y	z		
Shape comparison for FH+ versus FH− group					
Left	−25	−7	−23	130	−2.57
Right	28	−7	−24	16	−3.65*
Correlation of shape-psychological measures with group interaction					
STAI trait scores					
Left	−33	−30	−8	698	3.80*
Right	25	−16	−26	1103	2.84
BIS-11 attentional impulsivity					
Left	−23	−42	−3	364	3.05*
Right	13	−11	−20	107	2.22
BIS/BAS fun seeking					
Left	−32	−21	−22	65	3.13*
Right	19	−39	4	431	1.62

*$p < 0.05$, FWE- and TFCE-corrected.

FIGURE 2 Differences between FH+ and FH− groups in the shape associations with psychological measures in the left hippocampus covarying for age and sex (FWE and TFCE-corrected $p < 0.05$). Color bars: red to yellow colors indicate a positive difference of the correlations between the FH+ and FH− groups, whereas blue to purple colors indicate a negative difference of the correlations between the FH+ and FH− groups. This figure shows the differences of comparing FH+ to FH− groups of the correlations between the left hippocampus shape and (a) STAI trait score, (b) BIS-11 attentional impulsivity score, and (c) BAS fun seeking score

that shape index may be a more sensitive neural representation of risk for familial transmission of SUD than volume, which has been the focus of prior neuroanatomical research (Gerig, et al. 2001; Roshchupkin, et al. 2016). Variations in subcortical brain structures are known to be affected by both environmental and genetic factors that may influence familial transmission of SUD risk (Roshchupkin, et al. 2016). Our findings support these notions by showing that the FH+ group differs in the shape of the right anterior hippocampus (inward deformations) compared to the FH− group, indicating familial transmission.

Previous studies have found a correlation between SUD or chronic substance use and hippocampal volume (Fein and Fein 2013), and a few have even reported on the relation of hippocampal shape and active SUD. For example, Chye and colleagues recently found that cannabis use disorder, but not cannabis use, altered both the volume and shape of the hippocampus (Chye, et al. 2019). However, to the best of our knowledge, this is the first report of a difference in

hippocampal shape, based purely on family history of SUD in substance naïve adolescents. Because this study examined the effects of familial SUD on the volume and shape of the hippocampus in the next generation, the findings may implicate hippocampus structure in the mechanism of transmission of SUD risk. Additional supportive research is needed to confirm that this shape anomaly is a neural indicator of familial transmission of risk for SUD.

As noted, much of the relevant literature has focused on the effect of SUD on brain structure and has almost exclusively measured cortical thickness and subcortical volume (Boulos, et al. 2016; Chumachenko, et al. 2015; Chye, et al. 2019; Cservenka, et al. 2015; Fein and Fein 2013; Henderson, et al. 2018; Meier, et al. 2019; Moreno-Alcazar, et al. 2018; O'Brien and Hill 2017; Seifert, et al. 2015). However, there is substantial structural variation in brain morphology, both within a range of normal variability and in the context of various neuropsychiatric disorders. Aggregate measures, such as volume, therefore, do not capture the complexity of the
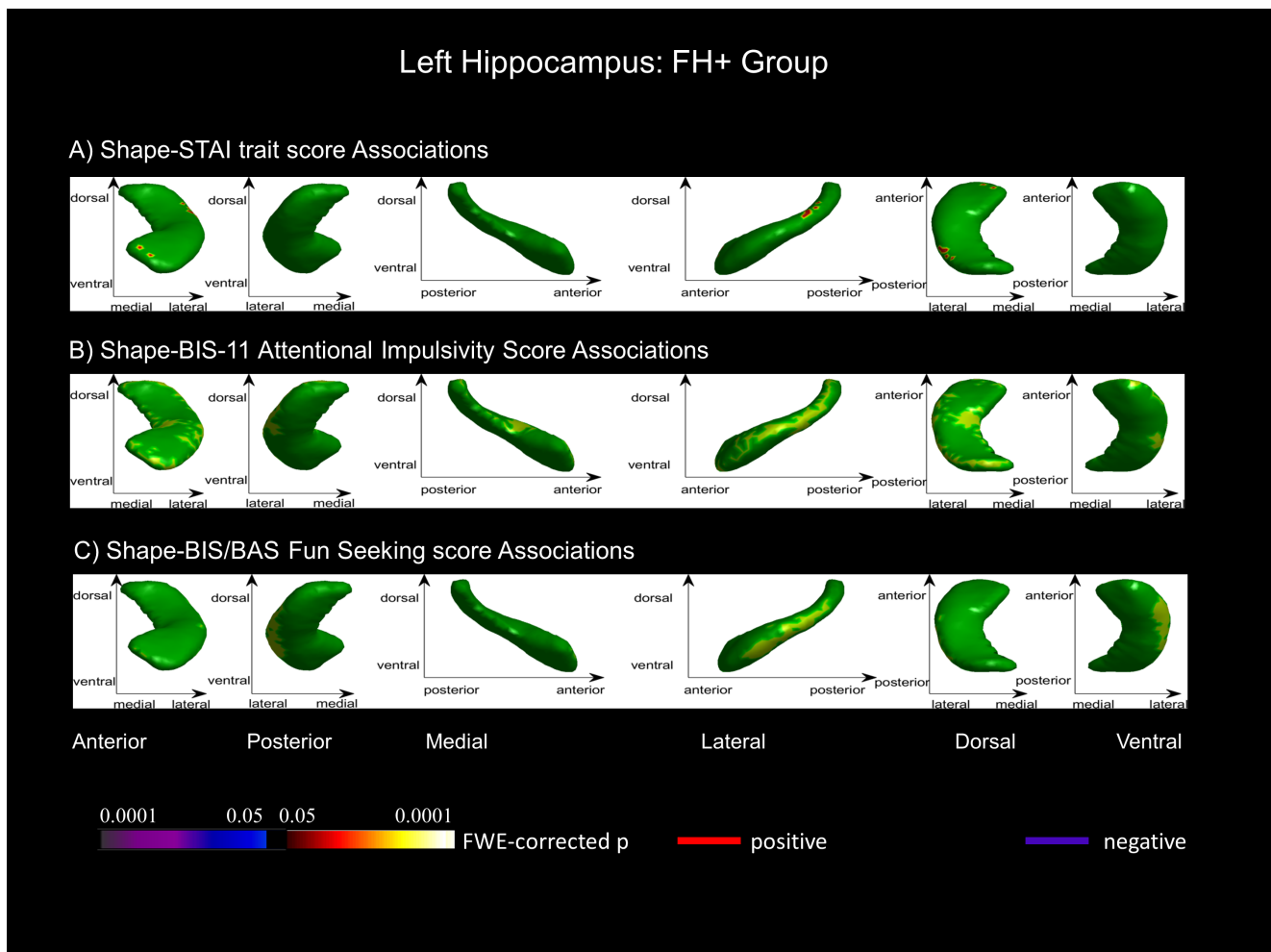
FIGURE 3 Shape-behavioral score correlations for FH+ group covarying for age and sex (FWE and TFCE-corrected *p* < 0.05) in the left hippocampus. Color bars: red to yellow colors indicate a positive correlation, whereas blue to purple colors indicate a negative correlation. This figure shows the correlations in the FH+ group between the left hippocampus shape and (a) STAI trait score, (b) BIS-11 attentional impulsivity score, and (c) BAS fun seeking score

morphology of these subcortical structures (Gerig, et al. 2001; Roshchupkin, et al. 2016). Instead, the high dimensionality of brain morphological features allows for the detection of more localized differences in structure. In particular, shape can provide relevant biological information in addition to the size of a brain structure (Roshchupkin, et al. 2016). An overall change in shape without an overall change in volume is possible. Although at the individual level an inward deformation in shape would be expected to result in the contra-posit outward deformation at another site of the structure, at the group level, such changes need to be consistent in both sites to be detected. Our results showed inward deformation in the anterior region of the right hippocampus across the majority of the subjects, indicating that subjects had this deformation at the same site, thus an anatomical significant change. But there was no corresponding spatially consistent outward deformation found, indicating that the compensatory outward deformations occurred at multiple sites across subjects and were, therefore, statistically undetectable. Thus, the inward deformation was anatomically important, while the compensatory deformations were distributed and undetectable, probably not of biological significance. However, these data could not provide a definative explanation.

While variation in subcortical brain structures' volume and shape are partially genetically determined, they are quite possibly affected by environmental factors, such as education, diet, parental modeling of behaviors, and stress (Roshchupkin, et al. 2016; Satizabal, et al. 2019). Roshchupkin (Roshchupkin, et al. 2016) examined 3686 unrelated individuals between the ages of 45 and 98 and found that the maximal variability of subcortical shape explained by heritability was between 32.7% and 53.3%. This held true across seven bilateral subcortical structures (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus). The level of heritability of SSS is, therefore, higher than the heritability of intracranial volumes. Recognizing that SSS transmission is a gene-by-environment interaction (GxE) phenomenon makes it both scientifically important and clinically relevant to examine SSS as potential neural correlates of familial transmission of SUD risk. Here, we focused on familial transmission of
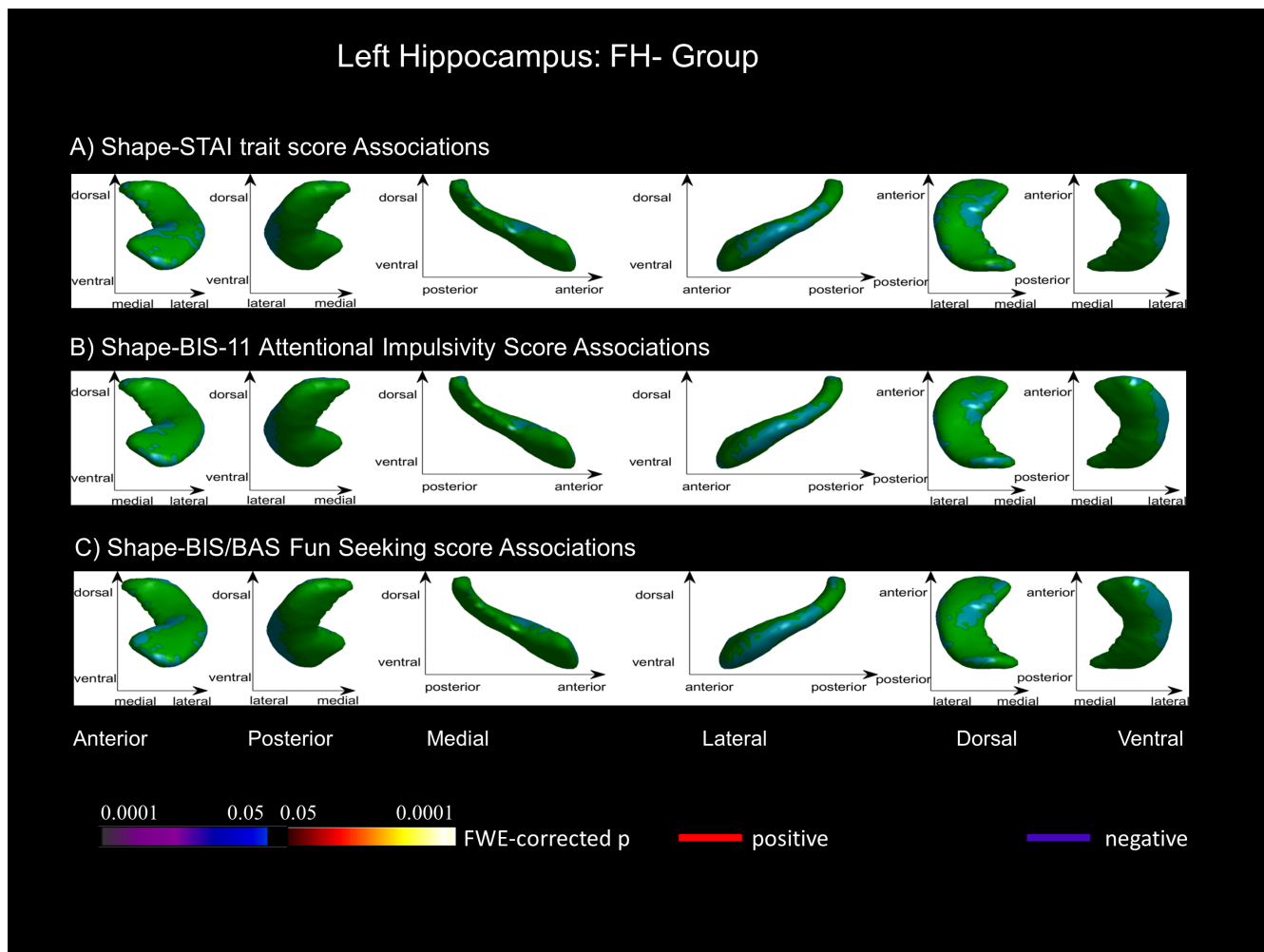
FIGURE 4 Shape-behavioral score correlations for FH− group covarying for age and sex (FWE and TFCE-corrected $p < 0.05$) in the left hippocampus. Color bars: red to yellow colors indicate a positive correlation, whereas blue to purple colors indicate a negative correlation. This figure shows the correlations in the FH− group between the left hippocampus shape and (a) STAI trait score, (b) BIS-11 attentional impulsivity score, and (c) BAS fun seeking score

risk for SUD and found a group difference in the right anterior hippocampus shape but not in its volume, demonstrating the greater sensitivity of measuring shape compared to volume when searching for a potentially subtle neuroanatomic signature of the transmission of risk. Importantly, the anterior part of the hippocampus, with its extensive interconnectivity with other brain regions, mediates anxiety-related behaviors which are known to be associated with SUD (Strange, et al. 2014).

While the mechanism of familial transmission of SUD risk is still not well characterized, it does seem to confer the risk for SUD through the transmission of certain psychological and behavioral characteristics. Moreover, it is well established that certain psychological and behavioral measures do indeed predict a risk for SUD. In order to better understand the familial transmission of these risk factors, it is important to examine the relationship between differences in subcortical volume and shape indices and measures of psychological phenomenon that predict SUD. Accordingly, we also examined correlations between volume or SSS and BIS/BAS, BIS-11, and STAI

Trait scores. We found that compared to the FH− group, FH+ adolescents showed an opposite pattern of correlations between the psychological measures and subcortical shape indices in several subregions of the left hippocampus that were distinct from the shape analysis without behavioral correlation, where the difference between FH+ and FH− was seen as inward deformation in the right hippocampus. We interpret the difference in locations as indicating that the inward deformation of the right anterior hippocampus is not associated with a specific behavior captured by the psychological measures we used. Both left and right anterior hippocampus structures, with their heterogeneity in connectivity, have been associated with differential emotion processing (Robinson, et al. 2015). Thus, this heterogeneity gives rise to differential sensitivity to stress within the hippocampal fibers. In particular, decrease in neural fibers due to atrophy-like changes and poor adult neurogenesis can occur in response to stress (Cameron and Schoenfeld 2018). On the other hand, resilience in the face of chronic stress has been associated with increase in fibers and connectivity with other limbic regions and

prefrontal cortex (Moreno-Lopez, et al. 2020). Thus, these opposite effects may happen in distinct subregions of the hippocampus that are associated with different aspects of emotional processing. In our results, the positive correlations of left hippocampus' shape index with trait anxiety scores and impulsivity measures may provide evidence that differences in the hippocampus morphology are potentially involved in familial transmission of risk for these psychological factors that in turn increase the risk for SUD.

Although no shape or volume differences were observed on other subcortical structures, exploratory analysis (see supporting information) did show differences between the FH+ and FH− in the interactions of the psychological scores and the shape index in brain regions implicated in emotion (amygdala), decision-making, reward (nucleus accumbens, pallidum, and brainstem), motivation and habitual learning (putamen). These regions are part of the limbic system that plays an important role in reward processing, have reciprocal connectivity with hippocampal subregions, and have been considered critical in the development and maintenance of drug and alcohol abuse (Bloomer, et al. 2004).

Regarding neural characteristics of cognitive and behavioral processes, there are precedents suggesting that hippocampi shape is associated with, or even predicts, certain clinical outcomes. The anterior hippocampus has been associated with anxiety-related behaviors (Strange, et al. 2014). Hippocampal shape was used to distinguish Alzheimer's disease from normal aging (Gerardin, et al. 2009), and shape was found to predict the onset of dementia (Costafreda, et al. 2011). Similarly, hippocampus shape has also been associated with psychopathy (Boccardi, et al. 2010) and with schizophrenia (Shenton, et al. 2002; Solowij, et al. 2013) and showed similar anomalies in schizophrenics as in their unaffected siblings (Tepest, et al. 2003), a finding relevant to familial transmission of risk. Crucially, anomalies in hippocampal shape have been reported to be confined to the anterior sub-region of the hippocampus in both childhood onset schizophrenia and their siblings (Johnson, et al. 2013). Those findings may indicate that the familial tendency for a phenotype may be associated with hippocampi shape, potentially representing an index of familial risk, in our case, for SUD. These findings support the notion that the SSS is not only sensitive to family phenotype history but also the SSS index may be correlated with the psychological manifestation within that group. For example, in Johnson's study, the severity of "positive symptoms" of schizophrenia (i.e., hallucinations and delusions) were correlated with the degree of inward deformations in the anterior hippocampus, whereas the degree of outward surface displacement was correlated with overall functioning (Johnson, et al. 2013). Association of volume and symptom severity has also been reported in psychiatric disorders, with volume positively correlated with symptom severity in generalized anxiety disorder (Abdallah, et al. 2013) and negatively correlated with symptom severity in depression (Merz, et al. 2018).

In this paper, we report two types of complementary analyses: shape analysis and volumetric analysis. While shape analysis captures local deformation, volumetric analysis provides global differences of subcortical brain structures. Our findings, thus, reinforce the utility

and importance of shape analysis in neuroimaging research related to psychopathology as an important addition to volumetric analysis. Findings, to date, demonstrate that shape is sensitive to heritable endophenotypes but also that within these endophenotypes the shape index may show further sensitivity to behavioral or other clinical symptoms as previously seen in Alzheimer's and schizophrenia, and now, in our work, in the psychological scores related to overall SUD risk. In addition, we performed correlational analysis between shape/volume and psychological measures that differentiate between the groups in a different hippocampus location. The results of this analysis are thus complex and illustrate the strength of shape analysis, which allows for a fine-tuning assessment of local changes within a larger structure such as the hippocampus. Moreover, the fact that the finding of shape difference between groups and correlations with psychological measures was in different parts of the hippocampus points to the potential role of subregions of the hippocampus in either risk or resilience for SUD.

4.1 | Strengths and limitations

Unlike previous MRI studies of SUD risk among adolescents with FH of SUD, our sample is quite homogeneous as the groups did not differ in any of the social-economic variables (Qiao, et al. 2015). This allows us to attribute any differences in SSS to the family history of SUD, as this was the only known difference between the groups. Another strength of this study is our shape analysis approach which is unique with this type of research in adolescents at risk of SUD and provides promise of a new direction for future research.

However, our participants came from families with a history of either or both alcohol use disorder and drug use disorder. This makes comparison of our results to other studies that address a single type of SUD more difficult, such as the study by Baker and colleagues that shows sex-specific patterns of hippocampal volume changes associated with FH of alcohol use disorder (Baker, et al. 2020). While it is clear that alcohol use and drug use disorders differ in their effect on the brain, there is still debate on whether risk of developing alcohol or drug use disorders is manifested differently in the developing brain. Finally, the lack of differences between the groups in any of the psychological measures prevents us from providing a more straightforward interpretation of the correlation findings.

5 | CONCLUSIONS

We have shown, for the first time, that substance naïve adolescents with FH of SUD have a significant inward shape deformation in their right anterior hippocampus compared to FH− adolescents. The inward shape deformation in the right anterior hippocampus in FH+ adolescents may be related to familial environment characterized by stress and anxiety that are known to be associated with increased risk for SUD in FH+ offspring. We also detected opposite patterns of both volume and SSS associations with anxiety and impulsive

behaviors in the hippocampus between the FH+ and FH− adolescents. The SSS, but not the volume, was correlated with behavioral characteristics, suggesting that analysis of subcortical shapes appears to capture anatomical-clinical correlations better that traditional volumetric analysis does. Importantly, since SSS demonstrates a strong heritability but also sensitivity to environmental factors, these imaging findings could represent the neural correlates of familial transmission of SUD risk.

CONFLICT OF INTERESTS

No authors report any financial relationships with commercial interests.

AUTHOR CONTRIBUTIONS

ZW: literature search, study design, data analysis and interpretation, and manuscript writing; DRM: data collection, data analysis and interpretation, and manuscript writing; YMC: data analysis and interpretation, and manuscript writing; LVA: literature search, study design, data interpretation, and manuscript writing; KCP: data analysis and interpretation; XH: data analysis and interpretation; MR: literature search, data analysis and interpretation, manuscript writing; LGA: study design; GJM: study design, data collection and analysis; AB: study design, data interpretation, and critical revision of the manuscript; CWH: study design, data interpretation, and critical revision of the manuscript.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author (ZW), upon reasonable request.

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