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Brain cortical thickness in male adolescents with serious substance use and conduct problems

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Abstract

Background—Adolescents with substance use disorder (SUD) and conduct problems exhibit high levels of impulsivity and poor self-control. Limited work to date tests for brain cortical thickness differences in these youths.

Objectives—To investigate differences in cortical thickness between adolescents with substance use and conduct problems and controls.

Methods—We recruited 25 male adolescents with SUD, and 19 male adolescent controls, and completed structural 3T magnetic resonance brain imaging. Using the surface-based morphometry software FreeSurfer, we completed region-of-interest (ROI) analyses for group cortical thickness differences in left, and separately right, inferior frontal gyrus (IFG), orbitofrontal cortex (OFC) and insula. Using FreeSurfer, we completed whole-cerebrum analyses of group differences in cortical thickness.

Results—Versus controls, the SUD group showed no cortical thickness differences in ROI analyses. Controlling for age and IQ, no regions with cortical thickness differences were found using whole-cerebrum analyses (though secondary analyses co-varying IQ and whole-cerebrum cortical thickness yielded a between-group cortical thickness difference in the left posterior

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DECLARATION OF INTEREST

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cingulate/precuneus). Secondary findings showed that the SUD group, relative to controls, demonstrated significantly less right>left asymmetry in IFG, had weaker insular-to-whole-cerebrum cortical thickness correlations, and showed a positive association between conduct disorder symptom count and cortical thickness in a superior temporal gyrus cluster.

Conclusion—Functional group differences may reflect a more nuanced cortical morphometric difference than ROI cortical thickness. Further investigation of morphometric differences is needed. If replicable findings can be established, they may aid in developing improved diagnostic or more targeted treatment approaches.

Keywords

substance use; adolescents; cortical thickness

INTRODUCTION

Youths with serious substance use and conduct problems

Substance use disorders (SUD) commonly have their onset in adolescence (1, 2) and different substance use disorder diagnoses tend to cluster within individuals especially in younger males (3), or in youths whose problem behaviors are severe enough to merit referral for treatment (4, 5). For example, about three quarters of those admitted to adolescent-substance-use-disorder-treatment facilities require services for both alcohol *and* other drug issues (6). Substance use disorder carries with it great morbidity and risk for mortality, underscoring the importance of better understanding neural contributions to these disorders.

Adolescents affected by SUD are also very likely to meet criteria for conduct disorder (7, 8), which is characterized by aggression to people and animals, destruction of property, deceitfulness or theft, and serious rule violations (9, 10). These two disorders, conduct disorder and SUD, cluster together so often in our clinical populations, that we have termed such youth as having “antisocial substance dependence” in our previous publications (11, 12). Numerous longitudinal studies now support that an early predisposition toward behavioral under-control or disinhibition predicts a broad number of externalizing behaviors (13, 14, 15, 16). In part because of such observations, researchers have explored the covariance across externalizing behavior problems and have shown that a single factor, sometimes called “behavioral disinhibition”, may predispose individuals to externalizing psychopathology generally (17) and this single factor is highly heritable (18, 19).

Given this conceptualization, study designs typically choose a narrow or broad focus. On the one hand, selecting samples with a single externalizing disorder (i.e. cannabis use but not conduct disorder, other substance use disorder or antisocial personality disorder) allows researchers to importantly reduce some confounds (e.g. brain changes induced by substances other than cannabis), but this approach also necessitates recruiting subjects with relatively low “behavioral disinhibition”. Studying those individuals with a strong inherited general vulnerability to externalizing disorders requires recruitment of youths with high levels of diagnostic comorbidity. Here we focus on youths with severe antisocial behavior problems, multiple substance use disorder diagnoses and high impulsiveness, i.e. youths with serious substance use and conduct problems and high “behavioral disinhibition.”

Cortical Thickness

We have previously utilized this sample of adolescent males to examine SUD group-vs-control differences in grey matter volume using voxel-based morphometry (VBM) (12). Although grey matter volume is determined by the product of cortical thickness and surface area, examination of cortical thickness provides meaningful information beyond that obtained from grey-matter volume (as obtained in VBM analyses). First, the cortex is organized into ontogenic columns perpendicular to the brain surface (20), and the radial unit hypothesis supports that cells within such columns share a common origin (21, 22, 23). Thus, cortical thickness is related to the number of cells within a column, while surface area is related to the number of columns. Surface area and cortical thickness are both highly heritable, but are essentially determined by independent genetic effects (24, 25), and grey matter volume is more closely related to surface area (24, 26). Thus measuring both grey matter volume (12) and cortical thickness, as we have done here, provides complementary information.

Cortical thickness in frontal regions has been associated with impulsiveness in healthy adults (27) and differences in cortical thickness have been demonstrated among adult alcoholics in regions relevant to the brain reward circuit (28). Therefore, cortical thickness represents one logical brain phenotype in the search for brain structural differences in youths with serious substance use and conduct problems. Several studies have examined this phenotype, finding differences in cortical thickness between heavy marijuana using adolescents (29) or binge-drinking adolescents (30) and controls. Conduct disorder (31) and disruptive behavior disorders (32) have also been shown to be linked to cortical thickness differences in several regions. In more recent investigations, when controlling for (among other variables) intracranial volume (ICV) and age, cortical thickness differences were found between youths with documented externalizing behavior (33) or conduct disorder specifically (34) and controls.

Accordingly, we used brain magnetic resonance imaging (MRI) to study male youths with serious substance use and conduct problems, and controls, to search for inter-group differences in cortical thickness. Utilizing a male sample of 25 adolescents with SUD and conduct problems and 19 male adolescent controls, we tested for inter-group differences in cortical thickness. We hypothesized that youths with serious substance use and conduct problems would demonstrate thinner cortices in regions important for response inhibition and reward-related processing, namely in inferior frontal gyrus, OFC, and insula (35, 36, 37, 38). In addition, given the limited information on cortical thickness in this population of adolescents with serious substance use and conduct problems, we also completed whole–cerebrum analyses for group differences in cortical thickness.

METHODS

Sample selection and exclusion criteria

All subjects were right-handed males, between the ages of 14 and 18, and were required to score a minimum of 80 on a test of IQ. Participants were excluded if they had a history of head injury with loss of consciousness for more than 15 minutes, or history of significant

neurological illness or neurosurgery. All adolescent subjects and their parent/guardian had adequate English proficiency to understand the study procedures and provide informed assent/consent to research participation. By protocol, all subjects submitted a urine and saliva sample for on-site testing (AccuTest™ for THC, cocaine, methamphetamine, amphetamine, barbiturates, benzodiazepines, MDMA, methadone, other opioids, PCP and saliva AlcoScreen™ for alcohol) about 7 days and immediately prior to scanning. Positive results excluded controls from the study and the experimental group adolescents from participating at that time. A set of MRI-related exclusion criteria (such as the presence if implanted ferromagnetic objects) were also enforced for subject safety. Functional brain activation (11) and grey matter volume (12) of these subjects, or a subset of them, have been reported previously. Procedures and a complete explanation of inclusion and exclusion criteria are described in our previous publication (12).

Adolescent SUD sample—Adolescents with serious substance use and conduct problems (n=25; the experimental group) were recruited from a university-based treatment program that serves such youths. These experimental group adolescents were commonly referred from probation and social service agencies. Subjects were required to meet at least one non-nicotine substance use disorder (by the Diagnostic Statistical Manual, or DSM-IV criteria; 9) and to have been referred to treatment for serious conduct problems.

Control sample—Control adolescents (n=19) were recruited through a research marketing company and local advertisements. Recruitment ensured that controls resided in the same zip codes that experimental group adolescents commonly come from, and that our control sample was similar to these experimental group adolescents in age and race/ethnicity. Controls were excluded if they met criteria for conduct disorder, any non-nicotine substance use disorder (according to DSM-IV criteria) or if they had a prior court conviction or substance use-related sequelae (e.g., arrest, treatment, or school expulsion).

Assessments

All youths completed:

(1) *Youth Self Report* which produces dimensional ratings of conduct, attention, and affective problems, with excellent reliability and validity (39);

(2) *National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Children-Version IV* (DISC-IV; 40), a fully-structured computer-assisted diagnostic interview for youths. Youth-only reports of conduct-disorder symptoms from this instrument have excellent discriminative validity (7);

(3) *Composite International Diagnostic Interview-Substance Abuse Module* (41) a structured, computerized interview which provides valid (42) diagnoses of adolescent (7) DSM-IV-defined substance abuse and dependence diagnoses;

(4) *Wechsler Abbreviated Scale of Intelligence* (WASI; Psychological Corporation) (43). We estimated full scale IQ from the Vocabulary and Matrix Reasoning subtests. Subjects with estimated IQ < 80 were excluded.

(5) *Eysenck Junior Impulsiveness Scale* (44); and

(6) a measure of *Peak Aggressive Behavior* (45).

Parents/guardians completed:

(7) a self-reported race/ethnicity questionnaire; and

(8) *Child Behavior Checklist* (46); this parent-report assessment (CBCL) is standardized for ages 4–18 and provides dimensional ratings of conduct, attention, and affective problems in children.

Magnetic Resonance Imaging

High-resolution 3D T1-weighted coronal slices were acquired in a research-dedicated 3 Tesla MR scanner (General Electric) using a standard quadrature head coil, an SPGR-IR sequence and the following parameters: TR/TE/T1/flip angle = 9 ms/1.9 ms/500 ms/10°, FOV = 220 mm^2 in plane, slice thickness = 1.7 mm, 256^2 matrix, and number of slices = 124. Structural acquisition took 9 minutes and 12 seconds.

Measuring Cortical Thickness

We utilized FreeSurfer v4.5, an automated morphometric program (47, 48, 49). Steps included normalization for intensity, resampling into isotropic voxels, skull stripping, and segmentation. Pial and grey-white matter surfaces were tessellated. The distance between these two surfaces estimates cortical thickness. Images were then normalized to a standard spherical space. Skull stripping and segmentation were verified through visual inspection by a study investigator blinded to group status. Errors due to topological defects, or skull-stripping were corrected using methods available in the FreeSurfer toolbox such as introducing controls points for white-matter mis-registration, pial editing for obviously erroneous inclusion of skull or dura or the use of the water-shed algorithm to improve skull-stripping. Individual subject data was registered into standard space using the FreeSurfer tool “FSAverage brain.”

Data Analyses

We evaluated the distributions of variables for outliers and for normality, when appropriate. Descriptive characteristics, including age, race, IQ, years of schooling completed, nicotine dependence diagnosis, SUMDEP (the sum of DSM-IV dependence symptoms across drug categories), lifetime conduct disorder symptom count, and impulsivity, peak aggression, and aggressive behavior scores, were compared between groups with independent t-tests (or Mann Whitney U test when appropriate) and chi-square tests. We employed two approaches: region of interest (ROI) and whole-cerebrum analyses to test for group differences in cortical thickness. The two approaches are complementary in that the ROI approach tests for group differences in a priori predicted regions and is sensitive to small magnitude differences over

larger well-defined areas. In contrast, whole-cerebrum analyses can identify large-magnitude group differences in small regions anywhere in the cerebrum.

Region of Interest Analyses and Covariate Selection—We used FreeSurfer automatically-generated parcellation-units (50) for ROI analyses. The FreeSurfer output divides the inferior frontal gyrus into three regions (pars orbitalis, triangularis and opercularis) and OFC into two regions (medial and lateral). Mean cortical thickness for each parcellation-unit (or ROI as a whole if it contained only a single parcellation unit) were obtained using FreeSurfer's built in cortical thickness tools. Average cortical thicknesses for ROIs with multiple parcellation units were then calculated by the average of said parcellation units, weighted by the surface area as follows:

$$\text{L OFC CT}=\frac{[(\text{L med OFC CT})\,(\text{L med OFC SA})]}{[(\text{L med OFC SA})+(\text{L lat OFC SA})]}+\frac{[(\text{L lat OFC CT})\,(\text{L lat OFC SA})]}{[(\text{L med OFC SA})+(\text{L lat OFC SA})]}$$

Eq. 1

where CT=cortical thickness; L=left; med=medial, lat=lateral, OFC=orbitofrontal cortex; SA=surface area.

Given that IQ is related to cortical thickness (51), as well as the very strong data supporting the importance of age on cortical thickness in adolescence (52), we included IQ and exact age (date of assessment minus date of birth) as covariates in all of our regression analyses. In preparation for completing multiple regression analyses, we investigated, across-all subjects and within-group, the relationship (Pearson correlations) between these two regression covariates, as well as whole-cerebrum average cortical thickness and ICV, and our six regions of interest (bilateral inferior frontal gyrus, OFC and insula). To evaluate potential group differences in correlations between whole-cerebrum cortical thickness and the 6 regions of interest, the Pearson correlations estimates (r's) for each group were converted via Fisher's Z-transformation and then compared with a z test using a standard error based on the square root of their summed variances.

Separate multiple regression analyses were completed for each of our six regions of interest (dependent variables) with group as our independent variable of interest, covarying age and IQ. Because several other reports covary whole-cerebrum average cortical thickness (53) or ICV (33, 34), these covariates were separately added to a subsequent set of exploratory models. These QDEC ("Query, Design, Estimate, Contrast;" the Free Surfer tool used for these analyses) analyses failed, likely due to multi-collinearity, possibly due to inclusion of age. Because groups did not differ significantly on age, and because we assumed that developmental differences in the small age window (14–18 years) would be captured by average cortical thickness to a limited extent, we conducted a subsequent set of exploratory models that covaried for IQ and whole-brain cortical thickness but not age.

Also, because some prior work has suggested that the link between antisocial behavior problems and low IQ is explained by shared genetic influences (54), controlling for IQ could limit our ability to find inter-group differences. Therefore, we completed exploratory analyses without including IQ as a covariate in the model.

Whole-cerebrum analyses—Between-group, whole-cerebrum, vertex-by-vertex analyses were completed using the FreeSurfer tool QDEC while, again, controlling for age and IQ. Family-wise error correction at cluster level ($p<0.05$, 2-tailed) was applied to correct for multiple comparisons, and the corresponding threshold cluster size was determined by Monte Carlo simulation (10,000 iterations) with a cluster-forming threshold vertex-level p-value of 0.005 (55).

Exploratory analyses—We completed exploratory regression analyses within the experimental group, testing for associations between (1) impulsivity measured by the Eysenck Junior Impulsiveness Scale, (2) lifetime conduct disorder symptom count and (3) across-drug substance use disorder symptom count and cortical thickness, enforcing the same threshold as in our whole-cerebrum analyses.

RESULTS

Sample description

Adolescents with serious substance use and conduct problems, as well as control group adolescents, did not significantly differ in age (experimental group mean 16.64 years; control mean 16.59 years) but groups differed significantly in estimated IQ (experimental group mean 98.1; control mean 105.2; $p=0.01$; see Table 1). Adolescents with serious substance use and conduct problems also had significantly higher lifetime cross-drug substance dependence symptom counts and conduct disorder symptom counts, and scored significantly higher on measures of impulsivity and aggression. Although not shown in Table 1, 84% of experimental group adolescents met criteria for cannabis abuse or dependence, 84% for alcohol abuse or dependence, 36% for club drug abuse or dependence, 32% for cocaine abuse or dependence, and 20% for hallucinogen abuse or dependence. Across 10 drug categories, excluding nicotine, the experimental group adolescents averaged 2.7 lifetime substance use disorder diagnoses (standard deviation = 1.4). As this was an exclusion criterion, no control individuals met lifetime criteria for a substance use disorders for these 10 categories.

Initial Cortical Thickness analyses

Tables 2a and 2b show initial analyses completed in preparation for regression analyses. Table 2a shows mean cortical thickness for left and right hemisphere and for our six regions of interest (left and right inferior frontal gyrus (IFG), OFC, and insula), as well as the computed left-right asymmetry. Asymmetry was computed as described by Shaw et al. (56), where asymmetry = (LCT-RCT)/[0.5*(LCT+RCT)], where LCT and RCT denote cortical thicknesses of left or right ROI sides, respectively. The asymmetry calculation results suggested right>left cortical thickness asymmetry in the IFG of control adolescents, which has been demonstrated in several samples of normally developing adolescents (see Figure 2

in Shaw et al. (56) and Table 2 in (57)) and young adults (58). However, this IFG asymmetry was not noted in adolescents with serious substance use and conduct problems, which is in line with the literature that finds disruption of frontal cortical thickness differences in adolescents with psychiatric disorders including ADHD (56) or PTSD (59). We compared the calculated IFG asymmetry values between experimental group adolescents and controls, which yielded a significant difference (t_{42}=−2.1; p=0.04). Although not part of our planned analyses, these results suggest that adolescent normative (right>left) cortical thickness asymmetry in IFG may not be present in male adolescents with serious substance use and conduct problems and high behavioral disinhibition. No significant inter-group asymmetry differences were found in the OFC (t_{42}=−0.6; p=0.58) or insula (t_{42}=0.3; p=0.74).

Pearson correlations across and within groups

Table 2b presents Pearson correlations between the cortical thickness of our six regions of interest and covariates in our regression analyses (age and IQ), as well as average whole-cerebrum cortical thickness and ICV (covariates used only in exploratory analyses). In this sample's small age window (14–18 years), age was not significantly associated with cortical thickness in any of our regions of interest within-experimental group, within-controls or across-both-groups. IQ and ICV also did not significantly correlate with any of our regions of interest across groups. Also, when considering all subjects (i.e., the adolescents with serious substance use and conduct problems and controls), average cortical thickness across the entire brain was modestly and negatively correlated with age, positively correlated with all six regions of interest but not related to IQ. However, when considering experimental group adolescents and controls separately, group differences in magnitude of correlations between average cortical thickness across the whole cerebrum and our six regions of interest were provocative enough to warrant a further, more concrete investigation.

Significance values from comparing groups' correlations between whole-cerebrum cortical thickness and the 6 regions of interest after Fisher's Z transformation are presented in the last row of Table 2b. Several regions demonstrated between-group correlation differences with whole-cerebrum cortical thickness, including the right IFG, bilateral OFC, and the right insula. Again, although not part of our original hypotheses, these findings suggest that controls have a more cohesive pattern of cortical thickness across the whole-cerebrum, and that adolescents with serious substance use and conduct problems have greater region-to-region variability.

Region of Interest Analyses

No ROI showed significant inter-group cortical thickness difference in our regression analyses when covarying for age and IQ (see Table 3). After separately adding whole-cerebrum cortical thickness and ICV as exploratory covariates in two additional sets of analyses, we demonstrated no significant group difference for our six ROIs. In our exploratory analyses that covaried age but not IQ, no ROI showed significant inter-group differences.

Whole-cerebrum Analyses

QDEC analyses were run covarying age and IQ. At the *a priori* whole-cerebrum threshold a cluster of 1,009 contiguous vertexes (392.64 mm^2), no significant inter-group cortical thickness differences were found.

In subsequent exploratory analyses that repeated the QDEC while covarying IQ, age, and whole-cerebrum cortical thickness, QDEC analyses failed, likely due to mutli-collinearity, possibly from including age. Subsequent analyses covarying IQ and whole-cerebrum cortical thickness, but not age, did not fail, and found thinner cortical thickness in adolescents with serious substance use and conduct problems compared to controls mainly in the left posterior cingulate extending into the precuneus (Figure 1, panel A). Controls showed no significant region with thinner cortex when compared to experimental group adolescents at the set statistical threshold. QDEC analyses covarying age, IQ and ICV failed to demonstrate any significant group differences. Our exploratory analyses that covaried age but not IQ, also failed to demonstrate significant group differences.

Exploratory Analyses

Exploratory regression analyses within experimental group adolescents, testing for associations between (1) impulsivity, (2) conduct disorder symptom count and (3) substance use disorder symptom count and cortical thickness, yielded one significant result, showing a positive association between cortical thickness in the superior temporal gyrus and conduct disorder symptom count (see Figure 1, panel B).

DISCUSSION

Main study findings

Imaging a male adolescent sample of adolescents with serious substance use and conduct problems and controls, with or without controlling for whole-cerebrum cortical thickness or ICV, we found no significant differences in cortical thickness using region of interest analysis. In the whole-cerebrum QDEC analyses, covarying age and IQ (with or without ICV), we also did not find any significant differences. When controlling for whole-cerebrum cortical thickness in the QDEC, we demonstrated significantly greater cortical thickness in controls than experimental group adolescents in a relatively large cluster in the posterior cingulate cortex extending into the precuneus. In exploratory analyses we found one region, superior temporal gyrus, which was positively associated with conduct disorder symptom count.

Even with the positive QDEC result in the posterior cingulate cortex and the association between conduct disorder symptom count and superior temporal gyrus cortical thickness, our findings in this study are certainly weak, and primarily negative. They contrast with the previously cited cortical thickness literature on similar phenotypes (32, 29, 31, 30). Our findings also contrast with past behavioral and functional studies. Strong evidence supports the important role of ventrolateral prefrontal cortex, including the inferior frontal gyrus (IFG), in response inhibition (see Chikazoe (60) for a review), and this region along with anterior insula has been hypothesized to be critically important for guiding behavior in

relation to risks and rewards, especially in situations with low predictability (61) and for generating emotional empathy (62). Although IFG has been implicated generally in response inhibition, there is hemispheric asymmetry with the right ventrolateral prefrontal cortex (including inferior frontal gyrus) appearing to be critical to response inhibition (60). The posterior cingulate cortex has been implicated in past studies of addiction (63), in paradigms involving moral decision-making (64), in self-appraisal and self-reflection (64), theory-of-mind (65), and in reward-related decision-making (66).

There are several explanations for why our findings contrast with this existing functional and behavioral work. First, it is of note that several past studies have covaried ICV (33, 34) or whole-cerebrum average cortical thickness (53). One conclusion that could be drawn from this incongruence of our findings to these studies is that, as opposed to experimental group adolescents having absolutely thinner cortices in the regions of interest, the inter-group difference lies in the ratio of the regional cortical thickness to whole-brain measures. However, we found cortical thickness differences in posterior cingulate when controlling for whole-cerebrum cortical thickness, but found no inter-group differences when controlling for ICV. The second and indeed simplest explanation is that the macroscopic structure of experimental group adolescents versus control ROIs is similar. The difference may be microscopic (at the cellular, synapse, or receptor level), affecting how the regions of interest function on their own, or in a network with other behaviorally important structures. However, this explanation would fail to account for the previously discussed positive cortical thickness findings. Thirdly, although we utilized a sample similarly sized to some past studies (29, 31, 34), we may have lacked adequate power (67). Lastly, between-study differences may explain our negative findings. Between-study differences included: varying phenotypes of focus (e.g. conduct disorder-only, binge drinking, callous-unemotional traits, “externalizing behavior,” or, here, serious substance use and conduct problems), various approaches to threshold selection, and differences in sample age ranges, or inclusion of mixed-sex samples (as opposed to our male-only sample). A male-only sample might be expected to reduce confounds, given that sex-differences have been demonstrated in brain imaging (68, 30) and genetic studies (69) of externalizing youths and in studies of normative brain development (70, 71).

We selected cases for high behavioral disinhibition and controls without such behavioral issues for case-control comparisons on cortical thickness. Because comorbity is so common in these adolescent populations, researchers must choose a “narrow” versus “broad” approaches to sample selection (see Introduction, Section 1.1). Here we employ a “broad” approach, which allowed us to recruit a clinically representative sample with high behavioral disinhibition, but includes co-morbidity and reduces the ease of interpretability of findings (e.g., a broad approach cannot with certainty identify that this cortical thickness finding is related to conduct disorder but not substance use disorders). While this broad approach has yielded differences in brain structure and function in our prior publications (e.g. 11, 12, 72, 73), we did not demonstrate strong cortical thickness differences here. Findings using the broad approach to experimental group member selection may not be specific to one disorder vs. another, but instead may be indicative of non-specific neurodevelopmental problems. There are certainly examples in the literature of such indicators of neurodevelopmental problems (e.g. large cavum septum pellucidum; 74–76). In contrast, narrow approaches

might examine disorder specific brain findings or domain specific brain correlates (e.g. National Institute of Mental Health Research Domain Criteria, or RDoC). Certainly, the successes using this narrow approach have been previously reviewed and specific network-to-disorder models have been proposed (e.g., 77). The disadvantages of the narrow approach include that selecting samples for one disorder but no others (when co-morbidity is commonplace), may result in atypical, less severely affected samples (17). Thus there are advantages and tradeoffs with each design and they might be viewed as complementary, but it is important to recognize that our broad approach may obscure easy interpretation of results and our secondary findings should be viewed through this lens. Future studies should focus on investigating the relationship between "broad" and "narrow" phenotypes and cortical thickness, and might utilize the NIMH Research Domain Criteria such as the "Response Selection, Inhibition or Suppression" subconstruct (domain: "Cognitive Systems," construct: "Cognitive Control").

Secondary findings

Although not part of our hypotheses, our analyses yielded two secondary findings. First, we demonstrate that adolescents with serious substance use and conduct problems have very little left-right asymmetry in inferior frontal gyrus cortical thickness. One relatively large sample of normally developing children suggests that asymmetry of inferior frontal gyrus thickness is normative and that in our sample age range, we would expect right>left cortical thickness with a mean difference of ~0.05–0.10 mm (see Figure 2 in Shaw et al. (56)). Our results in control adolescents are remarkably consistent with this. However, this IFG asymmetry is not present in our experimental group sample. According to Shaw and colleagues, this lack of asymmetry does occur in normal individuals around age ~11 years, but disappears thereafter (56). Meanwhile, others have shown that the effacement of R>L frontal volume differences in psychiatric disorders (56, 59). In addition and more generally, the development of verbal fluency is associated with thinning of the left inferior frontal gyrus (78) and that early measurement of language skills are predictive of the development of concern and disregard for others (79). In rhesus monkeys, too, a link between cortical asymmetry effacement and reactive and aggressive behavior has been demonstrated (80). However, beyond these studies, few exist looking at the effect of patient/control status (in the context of any psychiatric disorder) on frontal asymmetry. Our findings add to this limited pool of data, and suggest an opportunity for further investigation of inferior frontal asymmetry as a marker of the development of empathic concern and self-control/inhibition.

Second, experimental group adolescents and controls differed dramatically in the correlation between insula cortical thickness and average cortical thickness across the whole cerebrum. Structural covariance may signal functional connectivity and "synchronized maturation" between brain regions (81) and our method (region of interest correlation with whole-cerebrum average cortical thickness) approximates the strength of MACACC (Mapping Anatomical Correlations Across Cerebral Cortex), a statistical technique that uses whole-cortical morphometric data to examine the interrelationships between brain structures (82). Some evidence suggests that the correlation of regional cortical thickness provides information about functional connectivity (82), at least for positively correlated areas (83). Among normally developing children insula shows at least moderate MACACC strength

scores (see Figure 3 in Lerch et al. (82)), consistent with our control sample results. Thus, although our approximate MACACC strength estimates were conducted only in preparation for our planned region of interest regression analyses of group differences, they raise the possibility that the near zero insula-to-whole-cerebrum cortical thickness correlations seen in our experimental sample may indicate relatively poor connectivity.

Study limitations

It is important to view this work within the context of the study's limitations. First, as previously discussed, our study may have lacked adequate power to establish significance of inter-group cortical thickness differences. Thus, future studies with larger sample sizes may be required. Second, it should be noted that our experimental and control groups had different mean IQs. While we included IQ as a covariate in an attempt to filter out its effect on our findings, ideally experimental and control groups without IQ differences might also be studied. Such samples would allow the ability to rule out that observed group differences were not driven by IQ differences. As such, it may be fruitful to replicate our investigation in a larger sample that allows for an IQ-matched subsample. Third, it should be noted that while our ROI selection was rational and based on the existing literature, it was by no means absolutely inclusive. ROIs that may have had significant inter-group differences could have been missed. This possibility cannot be discounted by citing the negative QDEC findings, since exploratory analyses covarying whole-cerebrum cortical thickness did in fact find significant differences in the left posterior cingulate and precuneus (neither of which were selected as initial ROIs). Follow-up studies may find it fruitful to include these regions in future ROI analyses.

CONCLUSIONS

We attempted to characterize an empirical, quantifiable difference between control individuals and male youths with serious substance use and conduct problems. If successful, such findings could potentially be used in diagnosis and treatment of this at-risk population, or to further our understanding of the underpinnings of this phenotype. Using both ROI and whole-brain analysis, we failed to demonstrate inter-group differences in brain cortical thickness, or any such differences within the experimental group. The incongruence between our findings and those of previous studies merits further investigation of the nuances in cortical morphometric features of adolescents with substance use and conduct problems. However, our significant exploratory QDEC findings in the posterior cingulate cortex and precuneus (when controlling for whole-brain cortical thickness) and in superior temporal gyrus (exploring associations with conduct disorder symptom count), as well as our significant secondary findings (of limited asymmetry in experimental group adolescents' IFGs, as well as group differences in the correlations of insula cortical thickness vs whole-brain cortical thickness) do hint at potential empirical inter-group differences we sought, and certainly merit further study.

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References

1. Li TK, Hewitt BG, Grant BF. Alcohol use disorders and mood disorders: a National Institute on Alcohol Abuse and Alcoholism perspective. Biol Psychiatry. 2004; 56(10):718–20. [PubMed: 15556112]
2. Stinson FS, Ruan WJ, Pickering R, Grant BF. Cannabis use disorders in the USA: prevalence, correlates and co-morbidity. Psychol Med. 2006; 36(10):1447–60. [PubMed: 16854249]
3. Stinson FS, Grant BF, Dawson DA, Ruan WJ, Huang B, Saha T. Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend. 2005; 80(1):105–16. [PubMed: 16157233]
4. Brown, SA.; Ramo, DE. Clinical course of youth following treatment for alcohol and drug problems. In: Liddle, HA.; Rowe, CL., editors. Adolescent Substance Abuse: Research and Clinical Advances. Cambridge, UK: Cambridge University Press; 2006. p. 79-103.
5. Sakai JT, Hall SK, Mikulich-Gilbertson SK, Crowley TJ. Inhalant use, abuse, and dependence among adolescent patients: commonly comorbid problems. J Am Acad Child Adolesc Psychiatry. 2004; 43:1080–1088. [PubMed: 15322411]
6. DASIS Report. Facilities Primarily Serving Adolescents. 2002. http://www.samhsa.gov/data/2k3/YouthFacilities/YouthFacilities.htm, Accessed on December 30th, 2011
7. Crowley TJ, Mikulich SK, Ehlers KM, Whitmore EA, Macdonald MJ. Validity of structured clinical evaluations in adolescents with conduct and substance problems. J Amer Acad Child Adolesc Psychiatry. 2001; 40:265–273. [PubMed: 11288767]
8. Stallings MC, Corley RP, Dennehey B, Hewitt JK, Krauter KS, Lessem JM, et al. A genome-wide search for quantitative trait Loci that influence antisocial drug dependence in adolescence. Arch Gen Psychiatry. 2005; 62:1042–51. [PubMed: 16143736]
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Washington, DC: 1994.
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition (DSM-5). Arlington, VA: 2013.
11. Crowley TJ, Dalwani MS, Mikulich-Gilbertson SK, Du YP, Lejuez CW, Raymond KM, et al. Risky decisions and their consequences: neural processing by boys with Antisocial Substance Disorder. PLoS One. 2010; 5(9):e12835. [PubMed: 20877644]
12. Dalwani M, Sakai JT, Mikulich-Gilbertson SK, Tanabe J, Raymond K, McWilliams SK, et al. Reduced cortical gray matter volume in male adolescents with substance and conduct problems. Drug Alcohol Depend. 2011; 118:295–305. [PubMed: 21592680]
13. Fergusson DM, Horwood LJ, Ridder EM. Show me the child at seven: the consequences of conduct problems in childhood for psychosocial functioning in adulthood. J Child Psychol Psychiatry. 2005; 46:837–849. [PubMed: 16033632]
14. Krueger RF. Personality traits in late adolescence predict mental disorders in early adulthood: a prospective-epidemiological study. J Pers. 1999; 67:39–65. [PubMed: 10030020]
15. McGue M, Iacono WG. The association of early adolescent problem behavior with adult psychopathology. Am J Psychiatry. 2005; 162:1118–1124. [PubMed: 15930060]
16. Tarter RE, Kirisci L, Mezzich A, Cornelius JR, Pajer K, Vanyukov M, et al. Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. Am J Psychiatry. 2003; 160:1078–1085. [PubMed: 12777265]
17. Krueger RF. The structure of common mental disorders. Arch Gen Psychiatry. 1999; 56:921–926. [PubMed: 10530634]
18. Young SE, Stallings MC, Corley RP, Krauter KS, Hewitt JK. Genetic and environmental influences on behavioral disinhibition. Am J Med Genet. 2000; 96:684–695. [PubMed: 11054778]

19. Hicks BM, Krueger RF, Iacono WG, McGue M, Patrick CJ. Family transmission and heritability of externalizing disorders: a twin-family study. Arch Gen Psychiatry. 2004; 61:922–928. [PubMed: 15351771]
20. Mountcastle VB. The columnar organization of the neocortex. Brain. 1997; 120:701–722. [PubMed: 9153131]
21. Rakic P. Specification of cerebral cortical areas. Science. 1988; 241:170–176. [PubMed: 3291116]
22. Rakic P. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. Trends Neurosci. 1995; 18:383–388. [PubMed: 7482803]
23. Rakic P. The radial edifice of cortical architecture: from neuronal silhouettes to genetic engineering. Brain Res Rev. 2007; 55:204–219. [PubMed: 17467805]
24. Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage. 2010; 53:1135–1146. [PubMed: 20006715]
25. Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, et al. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex. 2009; 19:2728–2735. [PubMed: 19299253]
26. Pakkenberg B, Gundersen H. Neocortical neuron number in humans: effect of sex and age. J Comp Neurol. 1997; 384:312–320. [PubMed: 9215725]
27. Schilling C, Kühn S, Romanowski A, Schubert F, Kathmann N, Gallinat J. Cortical thickness correlates with impulsiveness in healthy adults. Neuroimage. 2012; 59:824–830. [PubMed: 21827861]
28. Durazzo TC, Tosun D, Buckley S, Gazdzinski S, Mon A, Fryer SL, et al. Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: relationships to relapse and extended abstinence. Alcohol Clin Exp Res. 2011; 35:1187–1200. [PubMed: 21410483]
29. Lopez-Larson MP, Bogorodzki P, Rogowska J, McGlade E, King JB, Terry J, et al. Altered prefrontal and insular cortical thickness in adolescent marijuana users. Behav Brain Res. 2011; 220:164–172. [PubMed: 21310189]
30. Squeglia LM, Sorg SF, Schweinsburg AD, Wetherill RR, Pulido C, Tapert SF. Binge drinking differentially affects adolescent male and female brain morphometry. Psychopharmacology. 2012; 220:529–539. [PubMed: 21952669]
31. Hyatt CJ, Haney-Caron E, Stevens MC. Cortical thickness and folding deficits in conduct-disordered adolescents. Biol Psychiatry. 2012; 72:207–214. [PubMed: 22209639]
32. Fahim C, He Y, Yoon U, Chen J, Evans A, Pérusse D. Neuroanatomy of childhood disruptive behavior disorders. Aggress Behav. 2011; 37:326–337. [PubMed: 21538379]
33. Ameis SH, Ducharme S, Albaugh MD, Hudziak JJ, Botteron KN, Lepage C, et al. Cortical thickness, cortico-amygdalar networks, and externalizing behaviors in healthy children. Biol Psychiat. 2013; 75:65–72. [PubMed: 23890738]
34. Wallace GL, White SF, Robustelli B, Sinclair S, Hwang S, Martin A, et al. Cortical and subcortical abnormalities in youths with conduct disorder and elevated callous-unemotional traits. J Am Acad Child Psy. 2014; 53:456–465.
35. Elliott R, Dolan RJ, Frith CD. Dissociable functions in medial and lateral OFC: evidence from human neuroimaging studies. Cereb Cortex. 2000; 10:308–317. [PubMed: 10731225]
36. Tamm L, Menon V, Reiss AL. Maturation of brain function associated with response inhibition. J Am Acad Child Psy. 2002; 41:1231–1238.
37. Ridderinkhof RK, van den Wildenberg WPM, Segalowitzd SJ, Cartere CS. Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain Cognition. 2004; 56:129–140. [PubMed: 15518930]
38. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn Sci. 2014; 18:177–185. [PubMed: 24440116]
39. Achenbach, T. Manual for the Youth Self-Report and 1991 Profile. Burlington, VT: University of Vermont, Department of Psychiatry; 1991.

40. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. Journal of the American Academy of Child & Adolescent Psychiatry. 2000; 39(1):28–38. [PubMed: 10638065]
41. Robins LN, Wing J, Witchen HU, Helzer JE, Babor TF, Burke J, et al. The composite international diagnostic interview: An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry. 1988; 45:1069–1077. [PubMed: 2848472]
42. Cottler LB, Schuckit MA, Helzer JE, Crowley TJ, Woody G, Nathan P, et al. The DSM-IV field trial for substance use disorders: Major results. Drug Alcohol Depend. 1995; 38:59–69. [PubMed: 7648998]
43. Wechsler, D. Wechsler Abbreviated Scale of Intelligence. Psychological Corp; San Antonio, TX: 1999.
44. Eysenck SBG. Impulsiveness and anti-social behaviour in children. Current Psychological Research. 1981; 1:31–37.
45. Lewis DO, Pincus JH, Shanok SS, Glaser GH. Psychomotor epilepsy and violence in a group of incarcerated adolescent boys. Am J Psychiatry. 1982; 139:882–887. [PubMed: 6807111]
46. Achenbach, T. Manual for the Child Behavior Checklist/4-18 and 1991 profile. Burlington, VT: University of Vermont Department of Psychiatry; 1991.
47. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 1999; 9:179–194. [PubMed: 9931268]
48. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II. Inflation, flattening, and a surface-based coordinate system. Neuroimage. 1999; 9:195–207. [PubMed: 9931269]
49. Fischl B, Sereno MI, Tootell RB, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum Brain Mapp. 1999; 8:272–284. [PubMed: 10619420]
50. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006; 31:968–980. [PubMed: 16530430]
51. Narr KL, Woods RP, Thompson PM, Szeszko P, Robinson D, Dimtcheva T, et al. Relationships between IQ and regional cortical gray matter thickness in healthy adults. Cereb Cortex. 2007; 17:2163–2171. [PubMed: 17118969]
52. Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, et al. Neurodevelopmental trajectories of the human cerebral cortex. J Neurosci. 2008; 28:3586–3594. [PubMed: 18385317]
53. Makris N, Gasic GP, Kennedy DN, Hodge SM, Kaiser JR, Lee MJ, et al. Cortical thickness abnormalities in cocaine addiction--a reflection of both drug use and a pre-existing disposition to drug abuse? Neuron. 2008; 60:174–188. [PubMed: 18940597]
54. Koenen KC, Caspi A, Moffitt TE, Rijsdijk F, Taylor A. Genetic influences on the overlap between low IQ and antisocial behavior in young children. J Abnorm Psychol. 2006; 115:787–97. [PubMed: 17100536]
55. Hagler DJ Jr, Saygin AP, Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. Neuroimage. 2006; 33:1093–1103. [PubMed: 17011792]
56. Shaw P, Lalonde F, Lepage C, Rabin C, Eckstrand K, Sharp W, et al. Development of cortical asymmetry in typically developing children and its disruption in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2009; 66:888–896. [PubMed: 19652128]
57. Blanton RE, Levitt JG, Thompson PM, Narr KL, Capetillo-Cunliffe L, Nobel A, et al. Mapping cortical asymmetry and complexity patterns in normal children. Psychiatry Research: Neuroimaging. 2001; 107:29–43. [PubMed: 11472862]
58. Luders E, Narr KL, Thompson PM, Rex DE, Jancke L, Toga AW. Hemispheric asymmetries in cortical thickness. Cereb Cortex. 2006; 16:1232–1238. [PubMed: 16267139]
59. Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, et al. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biol Psychiat. 2001; 50:943–951. [PubMed: 11750890]

60. Chikazoe J. Localizing performance of go/no-go tasks to prefrontal cortical subregions. Curr Opin Psychiatry. 2010; 23:267–272. [PubMed: 20308899]
61. Tops M, Boksem MA. A potential role of the inferior frontal gyrus and anterior insula in cognitive control, brain rhythms, and event-related potentials. Front Psychol. 2011; 2:330. [PubMed: 22084637]
62. Shamay-Tsoory SG. The neural bases for empathy. Neuroscientist. 2011; 17:18–24. [PubMed: 21071616]
63. Yalachkov Y, Kaiser J, Naumer MJ. Functional neuroimaging studies in addiction: Multisensory drug stimuli and neural cue reactivity. Neurosci Biobehav Rev. 2012; 36:825–835. [PubMed: 22198678]
64. Raine A, Yang Y. Neural foundations to moral reasoning and antisocial behavior. Soc Cogn Affect Neurosci. 2006; 1:203–213. [PubMed: 18985107]
65. Mar RA. The neural bases of social cognition and story comprehension. Annu Rev Psychol. 2011; 62:103–134. [PubMed: 21126178]
66. Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev. 2011; 35:1219–1236. [PubMed: 21185861]
67. Pardoe HR, Abbott DF, Jackson GD. Sample size estimates for well-powered cross-sectional cortical thickness studies. Hum Brain Mapp. 2013; 34:3000–3009. [PubMed: 22807270]
68. Medina KL, McQueeny T, Nagel BJ, Hanson KL, Schweinsburg AD, Tapert SF. Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. Alcohol Clin Exp Res. 2008; 32:386–394. [PubMed: 18302722]
69. Rose RJ, Dick DM, Viken RJ, Pulkkinen L, Kaprio J. Genetic and environmental effects on conduct disorder and alcohol dependence symptoms and their covariation at age 14. Alcohol Clin Exp Res. 2004; 28:1541–1548. [PubMed: 15597087]
70. Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, et al. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage. 2007; 36:1065–1073. [PubMed: 17513132]
71. Raznahan A, Shaw P, Lalonde F, Stockman M, Wallace GL, Greenstein D, et al. How does your cortex grow? J Neurosci. 2011; 31:7174–7177. [PubMed: 21562281]
72. Dalwani MS, Tregellas JR, Andrews-Hanna JR, Mikulich-Gilbertson SK, Raymond KM, Banich MT, et al. Default mode network activity in male adolescents with conduct and substance use disorder. Drug alcohol depen. 2014; 134:242–250.
73. Dalwani MS, McMahon MA, Mikulich-Gilbertson SK, Young SE, Regner MF, Raymond KM, et al. Female adolescents with severe substance and conduct problems have substantially less brain gray matter volume. PLoS one. (in press).
74. Bodensteiner JB, Schaefer GB. Wide cavum septum pellucidum: a marker of disturbed brain development. Pediatr Neurol. 1990; 6:391–4. [PubMed: 1705800]
75. McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer IA, et al. MRI anatomy of schizophrenia. Biol Psychiatry. 1999; 45:1099–119. [PubMed: 10331102]
76. White SF, Brislin S, Sinclair S, Fowler KA, Pope K, Blair RJ. The relationship between large cavum septum pellucidum and antisocial behavior, callous-unemotional traits and psychopathy in adolescents. J Child Psychol Psychiatry. 2013; 54:575–81. [PubMed: 22934662]
77. Blair RJ, Leibenluft E, Pine DS. Conduct disorder and callous-unemotional traits in youth. N Engl J Med. 2014; 371:2207–16. [PubMed: 25470696]
78. Porter JN, Collins PF, Muetzel RL, Lim KO, Luciana M. Associations between cortical thickness and verbal fluency in childhood, adolescence, and young adulthood. Neuroimage. 2011; 55:1865–1877. [PubMed: 21255662]
79. Rhee SH, Boeldt DL, Friedman NP, Corley RP, Hewitt JK, Young SE, et al. The role of language in concern and disregard for others in the first year of life. Dev Psychol. 2013; 49:197–214. [PubMed: 22545842]
80. Short SJ, Lubach GR, Shirtcliff EA, Styner MA, Gilmore JH, Coe CL. Population variation in neuroendocrine activity is associated with behavioral inhibition and hemispheric brain structure in young rhesus monkeys. Psychoneuroendocrinology. 2014; 47:56–67. [PubMed: 24954302]

81. Alexander-Bloch A, Giedd JN, Bullmore E. Imaging structural co-variance between human brain regions. Nat Rev Neurosci. 2013; 14:322–36. DOI: 10.1038/nrn3465 [PubMed: 23531697]

82. Lerch JP, Worsley K, Shaw WP, Greenstein DK, Lenroot RK, Giedd J, et al. Mapping anatomical correlations across cerebral cortex (MACACC) using cortical thickness from MRI. Neuroimage. 2006; 31:993–1003. [PubMed: 16624590]

83. Gong G, He Y, Chen ZJ, Evans AC. Convergence and divergence of thickness correlations with diffusion connections across the human cerebral cortex. Neuroimage. 2012; 59:1239–1248. [PubMed: 21884805]

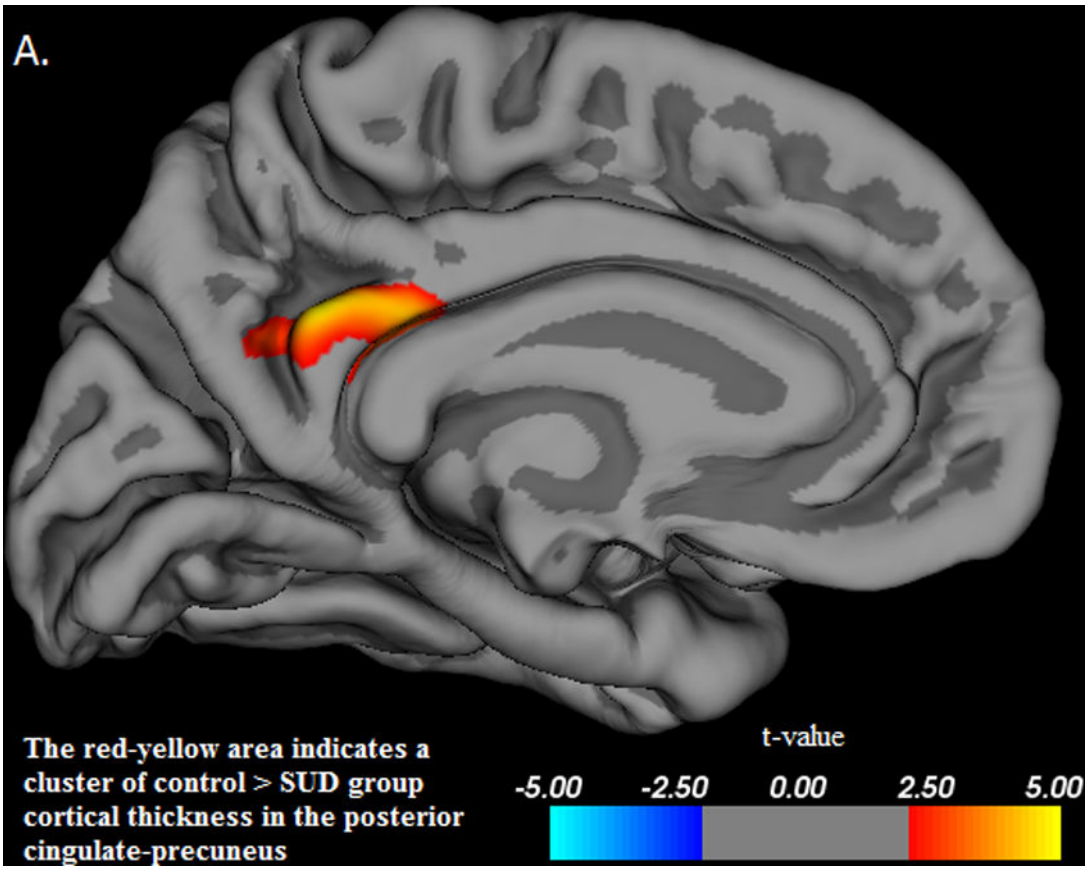

Figure 1a

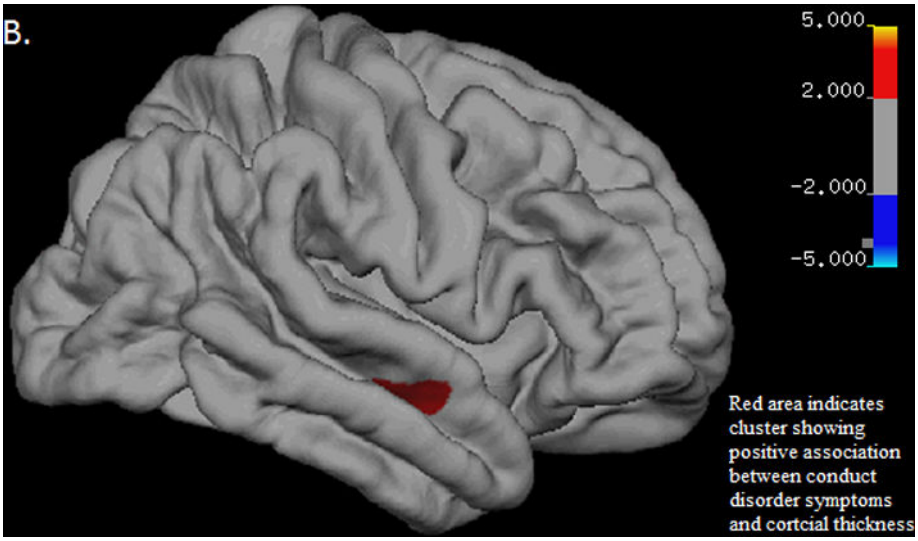

Figure 1b

Figure 1.

Panel A. Whole-cerebrum Analyses in QDEC (controls > experimental group adolescents; n=44, degrees of freedom=38), controlling for IQ and average cortical thickness across the whole cerebrum, using cluster-wise family-wise error correction of $p < 0.05$ (going in p-

value 0.005 at vertex-level with 10,000 Monte Carlo simulations); one cluster of 1,009 vertexes, maximum vertex at Talaraich x, y, z of −5.6, −44.2, 30.0. Color scale (horizontal bar, lower right of figure) indicates t-value, where t=2.5 required for vertex-level threshold). Panel B. Within SUD group adolescents, showing a positive association between lifetime conduct disorder symptom count and cortical thickness in superior temporal gyrus of the right hemisphere (same threshold enforced; cluster size is 679 vertexes).

Table 1

Values presented are the number of participants of the given group that fit the given criterion, or mean with parenthetic standard deviation; MW = Mann-Whitney U Test; FE = Fisher's Exact Test; SUMDEP the sum of DSM-IV dependence symptoms across drug categories.

		Experimental group (n=25)	Controls (n=19)	Statistic; p-value
Demographics:				
	Age	16.6 (1.15) yrs	16.6 (1.62) yrs	$t_{31.15}$=−0.13; p=0.90
	Race: White	16	15	χ^2=1.16; p=0.28
	Race: All others	9	4	
	Estimated IQ	98.1 (1.68)	105.2 (2.08)	t_{42}=2.69; p=0.01
	Years of schooling completed	9.36 (1.15)	9.84 (1.80)	$t_{28.79}$=1.02; p=0.32
Nicotine dependence diagnosis		13	1	χ^2=10.9; p=0.001
SUMDEP		11.9 (7.05)	0.2 (0.69)	MW; p<0.001
Conduct disorder symptom count (lifetime)		6.4 (2.83)	0.4 (0.61)	$t_{26.86}$=−10.33; p<0.001
Eysenck Impulsivity scale		12.8 (6.13)	7.0 (4.53)	$t_{41.98}$=−3.62; p=0.001
Peak Aggression		5.7 (3.11)	0.4 (1.01)	MW; p<0.001
YSR Aggressive behavior t-score		61.6 (10.65)	52.6 (5.22)	$t_{36.70}$=−3.71; p=0.001

Table 2a

Mean and standard deviation within SUD group adolescents and controls of average cortical thickness (both left and right hemispheres and of the regions of interest) (in mm) and intracranial volume (ICV, in cm3). Number of controls = 19, number of experimental group adolescents = 25. Asymm. is asymmetry, computed as the mean of experimental group adolescents' or controls' differences in the ROI (or hemispheric) left and right cortical thicknesses, divided by the mean of the left and right ROI (or hemispheric) cortical thicknesses (see section 3.2).

	Hemispheric			Inferior Frontal Gyrus			Orbitofrontal cortex			Insula			ICV
	L CT	R CT	asymm.	L CT	R CT	asymm.	L CT	R CT	asymm.	L CT	R CT	asymm.	
Controls Mean (SD)	2.478 (0.10)	2.487 (0.11)	−0.003	2.657 (0.13)	2.754 (0.14)	−0.035	2.594 (0.14)	2.569 (0.18)	0.011	3.206 (0.14)	3.246 (0.14)	−0.013	1876.3 (131)
SUD group Mean (SD)	2.478 (0.07)	2.477 (0.07)	0.000	2.690 (0.10)	2.701 (0.10)	−0.004	2.586 (0.15)	2.536 (0.13)	0.019	3.122 (0.14)	3.176 (0.14)	−0.017	1841.2 (137)

Table 2b

Pearson correlations between several covariates and either other covariates or cortical thickness of several regions of interest are presented, as well as (in the last row) the significance of SUD adolescent-control difference in correlations between the given ROI's cortical thickness and the whole cerebrum cortical thickness.

ALL SUBJECTS (n=44)								
	Age	**IQ**	**LIFG**	**RIFG**	**LOFC**	**ROFC**	**LINS**	**RINS**
Whole-cerebrum CT	−0.35*	0.10	0.53**	0.68**	0.65**	0.69**	0.31*	0.31*
ICV	0.16	0.30*	−0.28	−0.03	−0.08	−0.06	0.18	0.19
Age	1	0.22	−0.24	−0.16	−0.07	−0.12	−0.10	0.02
Estimated IQ	0.22	1	−0.03	0.08	−0.04	0.03	0.14	0.22
WITHIN-CONTROLS (n=19)								
Whole-cerebrum CT	−0.34	0.18	0.50*	0.83**	0.84**	0.84**	0.54*	0.59**
ICV	0.16	0.20	−0.15	0.29	0.18	0.15	0.27	0.09
Age	1	0.24	−0.25	−0.33	−0.26	−0.22	−0.34	0.04
Estimated IQ	0.24	1	−0.12	0.21	0.22	0.18	−0.09	0.10
WITHIN-SUD GROUP (n=25)								
Whole-cerebrum CT	−0.37	−0.002	0.63**	0.45*	0.49*	0.43*	0.05	−0.002
ICV	0.17	0.34	−0.37	−0.40*	−0.26	−0.30	0.07	0.22
Age	1	0.25	−0.23	0.09	0.12	0.04	0.16	0.01
Estimated IQ	0.25	1	0.19	−0.23	−0.26	−0.23	0.14	0.18
TESTING FOR DIFFERENES IN THE MAGNITUDE OF SUD GROUP vs. CONTROL CORRELATIONS (P VALUES PRESENTED)								
ROI to whole-cerebrum CT correlations (SUD group vs. control)			0.559	0.032*	0.037*	0.021*	0.092	0.039*

Abbreviations: CT = cortical thickness; ICV = intracranial volume; LIFG = average cortical thickness of the left inferior frontal gyrus (pars opercularis, triangularis and orbitalis); LINS = average cortical thickness of the left insula; LOFC = average cortical thickness of the left OFC; RIFG = average cortical thickness of the right inferior frontal gyrus; RINS = average cortical thickness of the right insula; ROFC = average cortical thickness of the right OFC; Whole-cerebrum CT = Average cortical thickness across the entire cerebrum. An * indicates $p<0.05$; ** indicates $p<0.01$.

Table 3

Standardized regression coefficients (β) and associated p values of group (SUD group adolescent vs control) status or the model's covariates (IQ and age) versus mean thickness of regions of interest (L and R delineate the left and right hemisphere's given ROI). All values given are not corrected for multiple comparisons.

	LIFG	RIFG	LOFC	ROFC	LINS	RINS
Group	β=0.19 (p=0.26)	β=−0.20 (p=0.24)	β=−0.04 (p=0.81)	β=−0.10 (p=0.58)	β=−0.26 (p=0.13)	β=−0.19 (p=0.27)
IQ	β=0.10 (p=0.54)	β=0.04 (p=0.80)	β=−0.04 (p=0.82)	β=0.03 (p=0.89)	β=0.07 (p=0.70)	β=0.16 (p=0.37)
Age	β=−0.26 (p=0.10)	β=−0.17 (p=0.30)	β=−0.06 (p=0.37)	β=−0.13 (p=0.44)	β=−0.10 (p=0.51)	β=−0.01 (p=0.93)