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Reduced Cortical Gray Matter Volume In Male Adolescents With Substance And Conduct Problems

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Abstract

Boys with serious conduct and substance problems (“Antisocial Substance Dependence” (ASD)) repeatedly make impulsive and risky decisions in spite of possible negative consequences. Because prefrontal cortex (PFC) is involved in planning behavior in accord with prior rewards and punishments, structural abnormalities in PFC could contribute to a person's propensity to make risky decisions.

Methods—We acquired high-resolution structural images of 25 male ASD patients (ages 14–18 years) and 19 controls of similar ages using a 3T MR system. We conducted whole-brain voxel-based morphometric analysis ($p < 0.05$, corrected for multiple comparisons at whole-brain cluster-level) using Statistical Parametric Mapping version-5 and tested group differences in regional gray matter (GM) volume with analyses of covariance, adjusting for total GM volume, age, and IQ; we further adjusted between-group analyses for ADHD and depression. As secondary analyses, we tested for negative associations between GM volume and impulsivity within groups and separately, GM volume and symptom severity within patients using whole-brain regression analyses.

Results—ASD boys had significantly lower GM volume than controls in left dorsolateral PFC (DLPFC), right lingual gyrus and bilateral cerebellum, and significantly higher GM volume in right precuneus. Left DLPFC GM volume showed negative association with impulsivity within controls and negative association with substance dependence severity within patients.

Conclusions—ASD boys show reduced GM volumes in several regions including DLPFC, a region highly relevant to impulsivity, disinhibition, and decision-making, and cerebellum, a region important for behavioral regulation, while they showed increased GM in precuneus, a region associated with self-referential and self-centered thinking.

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Keywords

Antisocial; DLPFC; Inhibition; Dependence; Precuneus; Self-referential

1. INTRODUCTION

Conduct disorder (CD) and substance use disorders (SUD) are prevalent (Nock et al., 2006) in adolescence and are associated with serious consequences, including teen pregnancy and HIV-related risk behaviors (Deas-Nesmith et al., 1999), incarceration (Teplin et al., 2002), accidents (Junger et al., 2001), and violent or preventable deaths (Teplin et al., 2005). Despite available evidence-based treatments (Waldron and Turner, 2008; Henggeler et al., 1999), antisocial and substance use behaviors may persist or re-emerge after treatment (Crowley et al., 1998; Henggeler et al., 2002; Myers et al., 1998).

Although many studies of youths with CD have attempted to exclude those with SUD (Huebner et al., 2008; Sterzer et al., 2007; Kruesi et al., 2004) and vice-versa (Nagel et al., 2005), these disorders commonly co-occur within individuals (Grella et al., 2001). For example, in one recent large national epidemiological study, those with CD were 8.4 times more likely than other respondents to have a drug dependence diagnosis (Nock et al., 2006). Because antisocial behavior problems and SUD co-occur so often the combination sometimes is called “antisocial substance dependence” (ASD) (Crowley and Gelhorn, 2010). In fact, co-occurring CD and SUD are thought to represent separate behavioral manifestations of a single underlying liability (Young et al., 2000; Krueger et al., 2002), which is highly heritable (Young et al., 2000; Hicks et al., 2004). Therefore studying subjects with only one disorder, while excluding the other, may yield atypical, non-representative samples (Krueger, 1999).

Disinhibition is common among individuals with CD and SUD. Individuals with ASD are risk takers; they often show a lack of restraint in situations with uncertain outcomes (either punishment or reward) (Crowley et al., 2006), fail to inhibit well ingrained responses (Fillmore and Rush, 2002; Swann et al., 2002; Dougherty et al., 2000; Mathias et al., 2002) or continue to pursue rewards despite serious adverse consequences (Newman et al., 1987; Shapiro et al., 1988; Giancola et al., 1993). Adolescents with ASD score higher than controls on self-reported impulsivity, and tend to respond impulsively in the laboratory (Thompson et al., 2006), suggesting that such individuals may possess a diminished capacity for cognition-controlled reasoning essential to adaptive decision making.

A neurobiological contribution to ASD is supported by genetic studies of CD (Rhee and Waldman, 2002) and SUD (Rhee et al., 2003; Young et al., 2006), behavioral studies of damaged prefrontal cortex in humans (Anderson et al., 1999), and brain imaging in antisocial adults (Raine et al., 2000) and adolescents with CD (Huebner et al., 2008). The available evidence suggests that dysfunction of prefrontal cortex may play a role in the disinhibited, dysregulated behavior of ASD individuals. The prefrontal cortex (PFC), which includes the dorsal lateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC), is involved in critical roles such as executive function, decision-making and inhibition of impulses (Crews and Boettiger, 2009). More specifically, the DLPFC is involved with attentional control, sustained behavioral organization to solve complex issues, goal selection and, along with OFC, in behavioral regulation through maintenance and integration of sensory, affective, and associative information (Crews and Boettiger, 2009). OFC may subserve response to punishment or threat (Kringelbach, 2005), response inhibition (Goldstein and Volkow, 2002), and response reversal (Kringelbach and

Rolls, 2004), and may be integral to the experience of complex emotions such as regret (Camille et al., 2004), embarrassment, shame and guilt (Beer et al., 2003).

Importantly, PFC injury produces some behaviors similar to those observed in ASD subjects. Individuals with injury to the ventro-medial PFC pursue short-term rewards despite long-term negative consequences (Bechara, 2001). Multiple case reports link severe frontal brain injury to difficulty in self-regulation of emotion (Eslinger et al., 1992), impairments in complex social and moral behavior and reasoning (Anderson et al., 1999), and verbal aggression (Grafman et al., 1996).

Not surprisingly, PFC structure reportedly is different in individuals with substance dependence and antisocial behavior problems. *Adults* dependent on cocaine (Sim et al., 2007) or alcohol (Fein et al., 2002), or abusing multiple substances (Liu et al., 1998), or exhibiting violent or antisocial behavior (Tanabe et al., 2009) reportedly have reduced PFC gray matter (GM) volume. Among *adolescents and children*, smaller PFC GM volume has been demonstrated in youth with alcohol use disorders with other comorbid mental disorders (De Bellis et al., 2005), and CD (Heubner et al., 2008). However, not all studies agree (Medina et al., 2008; Sterzer et al., 2007; Kruesi et al., 2004; De Brito et al., 2009), and there is considerable between-study variation in exact locations of PFC volume differences. Despite these differences, many authors suggest that inhibitory dysfunction in PFC is a key neural mechanism underlying addiction (Dom et al., 2005; Jentsch and Taylor, 1999; Goldstein and Volkow, 2002).

Given the disagreement across studies on which portions of the PFC anatomy are affected in conduct-disordered or substance-dependent youth (Heubner et al., 2008; Medina et al., 2008; Sterzer et al., 2007; Kruesi et al., 2004; De Brito et al., 2009; De Bellis et al., 2005), we performed whole-brain voxel based morphometry (VBM) to examine prefrontal gray matter volume in male adolescents with ASD as compared to controls. VBM employs an automated segmentation procedure and standardized parametric statistics to avoid biases inherent in operator-dependent morphological operations (Ashburner and Friston, 2000). Based on prior findings that adults with ASD have smaller medial PFC GM volumes than controls, especially in OFC (Tanabe et al., 2009), we expected to observe similar effects. However, as adolescence has recently been shown to be a developmental period in which many changes in brain anatomy are occurring (Lenroot et al., 2009), we performed our investigation using whole-brain VBM to also examine possible volumetric abnormalities outside of the PFC.

Finally, it is important to stress that the current study utilizes a sample of male-only patients and controls (a separate female sample is currently being recruited). This choice to conduct analyses within-sex was made for several reasons. Developmental and sex differences in certain conduct disorder related symptoms are well known. For example, boys generally endorse more aggressive or other-harmful symptoms than girls (Tiet et al., 2001; Lahey et al., 2000). Previous work has also demonstrated sex differences in severity of substance use phenotypes (Derringer et al., 2010). And recent evidence supports sexual dimorphism in brain development (Lenroot et al., 2007). Gender may influence the impact of drug use on prefrontal neurodevelopment (Medina et al., 2008). Thus, to avoid the confounds of gender-specific morphometric pattern, we examine a homogenous male-only sample in this study.

2. Methods

2.1 Inclusion/Exclusion Criteria

Subjects were males, ages 14–18 years, with estimated intelligence quotient (IQ) score >80. Patients' inclusion criteria were: a patient in a university-based treatment program for adolescents with serious ASD, where most are referred by criminal-justice or social service

agencies; referred to treatment for “Conduct Problems” (CP), including symptoms of DSM-IV TR (American Psychiatric Association, 2000) CD, delinquent acts, arrests, school expulsions, or problems with the law; and at least one non-nicotine SUD diagnosis. Controls could have no DSM-IV-defined CD, nor any SUD except nicotine, nor court conviction, nor substance-related arrests, treatments, or school-expulsions. Patients and controls were excluded if they had non-prescribed substances present in urine (AccuTest™ for THC, cocaine, methamphetamine, amphetamine, barbiturates, benzodiazepines, MDMA, methadone, other opioids, PCP) or saliva (AlcoScreen™ for alcohol) either about 7 days before, or immediately before scanning. Subjects were excluded if they or their parents lacked sufficient English skills for assenting or consenting. Additional MRI *exclusion* criteria included left-handedness, reports (or evidence) of marked claustrophobia, orthodontic braces, color blindness, other contraindications to MR scanning (embedded metal, pacemakers, cochlear implants or other non-MR-compatible devices), history of head injury with loss of consciousness for more than 15 minutes, or history of significant neurological illness or neurosurgery. Color blindness was an exclusion criterion to ensure visual feasibility for a functional MRI task (Crowley et al., 2010) that immediately followed the structural acquisition.

2.2 Sample

Thirty-four patient boys were recruited as mentioned above from a university-based treatment program for adolescents with serious ASD; 25 male controls of similar age, race/ethnicity, and zip code of residence were recruited through a commercial firm and word-of-mouth. A subset of these subjects is included in a parallel functional imaging study (Crowley et al., 2010). For this study, we excluded 15 subjects: 9 patients and 6 controls; 6 due to excessive motion, 4 for being left-handed, 3 due to MRI contraindications, and 2 (patients) for reporting no non-nicotine SUD despite being in a substance treatment program. Final count included 19 controls and 25 patients, all right-handed. Previous VBM studies of similar design that demonstrated structural difference in the PFC of patients compared to controls have employed comparable sample sizes (Huebner et al., 2008; De Bellis et al., 2005). Using similar procedures a female adolescent (patient and control) sample is currently being collected and will be analyzed with results reported separately.

2.3 Assessments

Parents completed the Child Behavior Checklist (CBCL) (Achenbach, 1991a) for severity of attention-deficit hyperactivity disorder (ADHD) problems and a measure of socioeconomic status (SES) (Hollingshead, 1975). In a 2–3 hour session subjects completed the Diagnostic Interview Schedule for Children (Shaffer et al., 2000) for ADHD and CD diagnoses, Composite International Diagnostic Interview Substance Abuse Module (CIDI-SAM) (Robins et al., 1988) for SUD diagnoses and recency-of-use, and a Peak Aggression Scale (Crowley et al., 2001). Subjects also completed a number of self-report inventories, including Eysenck Junior Impulsiveness Scale (EIS) (Eysenck, 1981) for a measure of impulsivity, the Youth Self Report (YSR) (Achenbach, 1991b) for a measure of aggression and ADHD related problems (when CBCL unavailable), and Carroll Self Rating Scale (CRS) for depression score (Carroll et al., 1981). Finally, subjects completed two subtests (vocabulary and matrix reasoning) from the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) for estimated IQ. From the Composite International Diagnostic Interview Substance Abuse Module, we calculated SUMDEP, the across-drug number of substance dependence symptoms. This measure discriminates patients with ASD from comparison subjects and correlates significantly with the number of days (out of the last 180 days) of non-nicotine substance use (Crowley et al., 2001).

2.4 Image Acquisition

Subjects were scanned in a 3 Tesla MR scanner (General Electric) using a standard quadrature head coil. High-resolution 3D T1-weighted coronal slices were acquired using a SPGR-IR sequence and the following parameters: TR/TE/T1/Flip angle=9ms/1.9ms/500ms/10°, FOV=220 mm² in plane, slice thickness=1.7mm, 256² matrix, and number of slices=124. The total scan time for structural acquisition was 9 min 12 seconds.

2.5 Data Analyses

We compared patient and control groups on age, race/ethnicity, education, IQ, depression, ADHD, impulsivity, aggression, CD, SUD and recency of substance use using independent t-tests and chi-square tests; when appropriate, nonparametric analogues (Mann-Whitney tests and Fisher's Exact tests) were conducted. All tests were two-tailed with alpha level = 0.05.

The whole-brain VBM analyses generally followed standard pre-processing methods. In detail, we used statistical parametric mapping V5 (SPM5; The Wellcome Trust Centre for Neuroimaging at University College London) and Matlab (R2008a) (Mathworks Inc, Natick, MA, USA) software for data analyses. Structural images were reoriented and checked for motion by visual inspection. Structural images with artifacts caused by motion were excluded from the final analyses. VBM 5.1 (<http://dbm.neuro.unijena.de/vbm>) implemented in SPM5, combines tissue segmentation, bias correction, and spatial normalization into a unified model (Ashburner and Friston, 2005). VBM5's Hidden Markov Random Field Algorithm performed segmentation by separating the images into three compartments: gray, white and cerebrospinal fluid. Default values were maintained; segmented gray images were normalized to the ICBM space. Use of adult brain template for spatial normalization of a pediatric sample may not be optimum due to developmental differences between pediatric and adult samples (Wilke et al., 2003). We therefore conducted spatial normalization with a pediatric template (aged 13–18.8 years) (CCHMC2; Cincinnati Children's Hospital Medical Center, Cincinnati, OH) in the ICBM (International Consortium for Brain Mapping) space with voxel dimension 1×1×1 mm³. The modulated GM images generated from non-linear warping were smoothed by an 8 mm full-width half-maximum Gaussian filter. We chose 8mm as the optimum filter-width to emphasize the focal effects of regional differences.

The whole-brain analyses compared volume estimates between groups using analyses of covariance (ANCOVA). Statistical maps were set at a cluster-level threshold of $p < 0.05$, corrected for multiple comparisons with family-wise error (FWE) using alphasim Monte Carlo simulations (Ward, 2000), and a voxel-level threshold of $p < 0.005$. Alphasim Monte Carlo simulations estimated a critical cluster size of 1218 voxels (1mm³). To ensure the validity of cluster-level statistics, a non-isotropic smoothness correction was applied (Hayasaka et al., 2004). Absolute threshold masking (threshold: 0.15) minimized GM/white matter boundary effects. Previous studies suggest that total gray or total intracranial volume (TGV/TIV) (Pell et al., 2008) along with age (Pell et al., 2008; Isaacs et al., 2004), and IQ (Frangou et al., 2004; Isaacs et al., 2004), are important covariates in VBM. Therefore, all three variables were evaluated to ensure minimal multi-collinearity, and then included as covariates in subsequent analyses. We had some initial concern that substance dependence severity might be positively related to age and therefore, inclusion of age as a covariate might lead to false negative findings. However, bi-variate tests did not support a significant correlation between age and SUMDEP in our patient sample.

2.6 Secondary analyses

2.6.1 Secondary Analyses - ROI Analysis controlling for ADHD and

Depression—We conducted post-hoc secondary analyses to examine whether possible

brain regions showing between-group GM differences at the whole-brain voxel-level analysis remained significant while controlling for ADHD and depression. We conducted these analyses using ROIs generated from between-group analyses to assure that between-group differences in GM volume were not explained by between-group differences in severity of these commonly co-morbid disorders (i.e. ADHD, depression). We therefore generated GM volume estimates (intensities representing milliliters (mL)) for clusters where the whole-brain VBM group analyses showed GM differences using a region-of-interest toolbox called MarsBaR (MARSeille Boîte À Région d'Intérêt; Brett et al., 2002) for each subject. We then evaluated patient and control GM differences (dependent variable) in SAS 9.2 using Analysis of Covariance (Proc GLM; SAS Institute, 2008) that adjusted for severity of ADHD and depression (from CRS) as independent variables along with the other three covariates (i.e. age, IQ and total gray volume as nuisance variables) that were used at the whole-brain level analysis. For ADHD the Attention Deficit Hyperactivity Problems scale score from CBCL (completed by parents) was used when available; the corresponding YSR scale completed by the subject was used for three patients without CBCL.

2.6.2 Secondary Analyses - Whole-brain voxel-based regression analyses of GM with impulsivity within groups

—Previous reports support a negative association between brain volume (especially in frontal areas) and impulsivity (Boes et al., 2009, Matsuo et al., 2009). Therefore, we tested for negative associations between GM and impulsivity within groups using whole-brain regression analyses. Thus within controls and separately within patients, we conducted whole brain regression analyses examining possible negative associations between GM (dependent variable) and impulsivity scores obtained from Eysenck impulsivity scale (independent variable) and age, IQ and total gray volume (TGV) (nuisance variables). The statistical map was set at $p < 0.005$ with cluster size of 1218 voxels (obtained from alphasim Monte Carlo simulations as mentioned above). For controls ($n=19$), the critical t-value was -2.98 and the critical correlation coefficient r-value was -0.62 with 14 degrees of freedom; in other words among controls any voxel, in order to be considered here, first had to show a significant correlation between subjects' GM volume and their impulsivity scores ($r = -0.63$ or smaller, $t = -2.98$, $p = 0.005$); in addition, to further control for whole-brain multiple comparisons that voxel had to be part of a cluster of at least 1218 contiguous voxels, all meeting that same correlation threshold. For patients ($n=25$), the corresponding critical t-value was -2.84 and the corresponding critical correlation coefficient r-value was -0.537 with 20 degrees of freedom. Note, we did not test for negative association between impulsivity - and GM volume across groups to avoid bias as the groups differed significantly on impulsivity ($p=0.001$).

2.6.3 Secondary Analyses - Whole-brain voxel-based regression analyses of GM with symptom severity within patients

—We tested for negative associations between number of substance dependence symptoms (SUMDEP) and GM within patients and separately for number of conduct disorder symptoms (CDSX) and GM within patients; we focused on negative associations because the extant literature has generally supported lower GM volumes in patients with conduct and substance use disorders (see introduction). We conducted whole brain regression with (reduced) GM as the dependent variable and SUMDEP (or CDSX) as the independent variable and age, IQ and total gray volume (TGV) as nuisance variables. Again, we applied the same statistical threshold for significance (statistical map $p < 0.005$ with cluster size of 1218 voxels, based on the number of tests conducted in the whole-brain analysis). For patients ($n=25$), the corresponding critical t-value was -2.84 and the corresponding critical correlation coefficient r-value was -0.537 with 20 degrees of freedom; in other words, for a cluster to be significant these thresholds required that at least 1218 contiguous voxels all correlated at a correlation coefficient r-

value of -0.537 or smaller. For regression analyses with symptom severity, controls were not tested because they were selected for not having conduct and substance problems.

3. Results

3.1 Demographic and Clinical Symptoms Comparisons

Table 1 presents patient-control comparisons. Patients and controls were similar in age and ethnic distributions. As expected, patients had significantly lower IQ scores than controls. Also, patients obtained significantly worse scores on our measures of substance problems, depression, impulsivity, and aggression. Patients were significantly more likely to meet criteria for conduct disorder and multiple substance use disorder diagnoses.

3.2 Whole-Brain VBM GM comparisons

VBM analyses (Table 2) showed significantly lower GM volume in ASD boys compared with controls in the left DLPFC (Figure 1), right lingual gyrus and bilateral posterior lobe in the tuber region of the cerebellum. Patients had significantly higher GM volume in right precuneus (Figure 2; Table 2).

3.3 Secondary Analyses

3.3.1 ROI GM comparisons after adjusting for ADHD and depression—The pattern of results (and significance) was not substantively changed in secondary ROI analyses evaluating patient-control GM volume differences while adjusting for severity of ADHD and depression (data not shown).

3.3.2 Whole-brain voxel-based regression analyses of GM with impulsivity within groups—Controls showed significant negative association in several frontal regions (Table 3, Figure 3). Patients showed significant association between GM and impulsivity in right inferior parietal lobe at the selected threshold level (Maximum significant voxel (MNI): $X=45$, $Y=-34$, $Z=33$; $t=5.4$; cluster size=1861). However, patients' impulsivity scores had a skewed distribution requiring cautious interpretation of this result.

3.3.3 Whole-brain voxel-based regression analyses of GM with symptom severity within patients—Patients showed significant negative association of GM with SUMDEP in left DLPFC (Figure 4; Maximum significant voxel (MNI): $X=-45$, $Y=16$, $Z=33$; $t=6.69$; cluster size=4214). Patients showed no regions with significant negative association between GM and CDSX at the selected threshold level.

4. Discussion

4.1 Between-Group Analyses

CD and SUD commonly co-occur within individuals; this comorbidity has been explained by a significantly heritable predisposition to behavioral under-control or disinhibition (Young et al., 2000). Although there is a large literature of brain morphometry for adult samples (with SUD and antisocial behavior), there is a relative paucity for adolescents, especially with co-morbid conduct and substance problems. We will discuss two main findings of this study. First, compared to controls, ASD adolescents had smaller GM volume in brain regions believed to be highly relevant to cognition control and inhibition (DLPFC/inferior frontal junction), and to behavioral regulation (cerebellum). Second, patients had greater GM volume in a region involved in self-referential considerations (precuneus).

Four clusters (Table 2) survived cluster wise family-wise error threshold for the contrast control>patients in our between-group analyses. One of those clusters, the DLPFC and

inferior frontal gyrus (IFG) (Brodmann Area (BA) 9), was the only cluster in the frontal lobe and was over 1600 voxels ($1\text{mm}^3/\text{voxel}$) in size. This cluster (Figure 1) extended from the superior aspect of IFG BA 9/46 (i.e., pars opercularis) to caudal middle frontal gyrus, and posteriorly (“y” direction) through the precentral BA 6 to postcentral gyrus BA 2 up to the supramarginal gyrus BA 40. Brass et al. (2005) suggest that the “inferior frontal junction (IFJ)”, a region located more posterior than the mid-DLPFC in the fronto-lateral cortex with an anatomical location (see figure 1 in Brass et al., 2005) overlapping our DLPFC finding, can be structurally and functionally distinguished from the mid-DLPFC and plays a pivotal role in cognitive control. IFJ is located at the junction of three functional neuroanatomical domains (premotor, language and working memory); it integrates information coming from these domains and thereby allows flexibility in adjusting behavior to a complex and changing environment (Brass et al., 2005). Lesion studies further suggest that left inferior frontal gyrus (IFG) is critical for response inhibition (Swick et al., 2008). Left IFG and precentral gyrus are part of the mirror neuron system (MNS), mediating an understanding of others' actions, intentions, and emotions (Pfeifer et al., 2008; Molnar-Szakacs et al., 2005; Iacoboni 2005). The MNS, together with anterior insula and amygdala, may provide a neural substrate for empathy (Carr et al., 2003). Pfeifer et al. (2008) showed positive correlations between MNS activity (including IFG) and children's tendency to empathize. Lack of empathy is associated with antisocial behaviors and is a behavioral feature highly relevant to our patient population (Miller and Eisenberg, 1988).

The only cluster (Figure 2) with more GM volume in patients than controls involved cuneus and precuneus. About 80% of this cluster was in precuneus BA 7, while the rest was in BA 31, consisting of both precuneus and cuneus. Precuneus has connections with adjacent cortical regions but the principal extraparietal cortico-cortical connections are with the frontal lobes, mostly prefrontal cortex (BA 8, 9 and 46) (Cavanna and Trimble, 2006), including the DLPFC region mentioned above. Precuneus plays an important role in self-referent information processing, and discriminating self- and other- descriptive words/phrases (Platek et al., 2008). Precuneus (BA 7) is involved in self-relevant information processing (i.e., judgments on one's own versus another person's face or personality traits), and intentional self-processing (i.e., judgments on self-descriptive versus non-self-descriptive personality traits) (Kircher et al., 2002, 2000). Midline cortical structures including precuneus (BA 7) contribute to being self-aware (Keenan et al., 2003; Kjaer et al., 2002). Iacoboni et al. (2004) showed increased activity in precuneus and dorsomedial prefrontal cortex compared to a resting state baseline during viewing of social interactions. Left inferior frontal lobe and left inferior parietal lobe, parts of the MNS mentioned above, also contribute to the “self-other” processing network, including processes associated with mirroring other's action (Uddin et al., 2005).

Thus compared to controls, our patients had less GM volume in areas relevant to behavioral inhibition, impulsivity, and empathy toward others, and more GM volume in areas involved in self-referential processing. Perhaps consistent with this finding, youths with ASD act in ways quite disparate from normal adolescents, exhibiting disinhibited risky behaviors, failing to show affective empathy, and pursuing self-interest while harming others.

We also found decreased GM in patients' bilateral cerebellum (tuber and pyramis, right culmen, declive and left tonsil) and right lingual gyrus (BA19). Although cerebellum's role in ASD is unclear, the vermis is involved in cocaine- and other- incentive-related behaviors (Anderson et al., 2006). Indeed, cerebellum plays a role in reward-based learning; patients with focal vascular lesions have significantly impaired reward-based reversal learning (Thoma et al., 2008). Anderson et al (2006) suggest that cerebellar lesions may add to risks for alcoholism by impairing behavioral regulation and that delayed development of cerebellar structures may contribute to later alcohol dependence (Schmahmann et al., 2001).

Manzardo et al. (2005) agreed with the proposal that cerebellar deficits may play a causal role in the addiction process; they found that developmental markers of cerebellar functioning in infancy predicted alcoholic drinking at age 30.

A few studies have shown abnormal activation patterns in cerebellum and lingual gyrus in vulnerable, or already substance-dependent, populations. Teens with alcohol use disorders, compared with controls, showed significantly less spatial working-memory BOLD response in left lingual gyrus and bilateral cerebellum, including semilunar nodule, tonsil, uvula and right culmen and declive (Tapert et al., 2004). Young alcohol-naïve males at high risk for alcoholism had reduced GM volumes in many regions, including right cerebellum (Benegal et al., 2007). Mechtcheriakov et al. (2007) also reported GM cerebellar deficits in adults with alcohol addiction. Sim et al. (2007) showed reduced GM volume in bilateral cerebellum in cocaine-addicted men. Thus, our finding of reduced cerebellar GM volume in ASD youths supports numerous suggestions that cerebellar abnormalities antedate, or accompany, substance dependence.

4.2 Secondary Analyses

After adjusting for severity of ADHD and depression, the pattern of results (and significance) was not substantively changed in secondary ROI analyses evaluating patient-control GM volume differences.

As secondary analyses, we conducted four whole-brain regression analyses, one within controls and three within patients. Two of those within-group regression analyses demonstrated negative associations of left DLPFC (BA 9) GM volume with impulsivity (controls) and severity of substance dependence (patients). Interestingly, those clusters overlap with the left DLPFC cluster identified in our between-group analyses (Figure 1, 3, 4). In addition, our whole-brain regression analyses in controls (see Table 3) replicated findings by others of negative association between impulsivity and volume in several frontal lobe regions. Boes et al. (2009) showed a negative association between ventral prefrontal cortex and impulsivity in healthy boys (7–17 years); while Matsuo et al. (2009) showed inverse correlation in OFC volume and impulsivity in healthy adults (mean age 35.4 years).

Within-patients right inferior parietal lobe (BA40) GM volume showed negative association with impulsivity. The inferior parietal lobule (BA40) plays an important role in response inhibition components of impulse regulation (Menon et al., 2001; Garavan et al., 2006; Potenza, 2008). Horn et al. (2003) showed negative correlation between right inferior parietal lobule (BA40) activation during response inhibition in Go/No-Go paradigm and Eysenck's impulsivity scores. However, as mentioned in section 3.3.2, the skewed nature of patients' Eysenck impulsivity scores demands cautious interpretation.

The threshold used in this paper required over 1200 contiguous voxels all meeting the voxel-level threshold ($p < 0.005$); therefore smaller areas with strong between-group differences would not be identified with this approach. Hence, we felt it was important to test and report results utilizing a more stringent voxel-level threshold but smaller cluster size requirement than that set by alphasim. Therefore, in secondary analyses we set statistical maps at a cluster-level threshold of $p < 0.05$ (size 805 voxels), corrected for multiple comparisons with family-wise error (FWE), and a voxel-level threshold of $p < 0.001$. There were no group differences at this cluster- and voxel- level threshold combination. Much larger samples may be needed to satisfy a more stringent voxel-level threshold criterion. While we are confident that our results using a voxel-level threshold of $p < 0.005$ with alphasim cluster correction adequately control for type I error rates, we are less confident about our ability to exclude false negative results. For example, between-group differences for very small regions are

likely not to be identified with our alphasim cluster correction approach to setting threshold, and perhaps would not be identified without larger samples.

4.3 Limitations

Our findings should be considered within the context of these limitations. First, we cannot determine the causality of the observed associations. Patients may have relatively less GM volume across these brain regions because of multiple environmental insults, such as regular use of alcohol, tobacco and/or illicit substances. However, the adolescents studied here have relatively few years of heavy substance use compared with adult substance-using samples. This could mean that SUDs of relatively brief duration in adolescence induce brain changes that are easily demonstrated and occur in regions which are likely to reinforce further disinhibition, impulsivity, and behavioral problems. If true, this would have major public health consequence given that the first drug dependence treatment often occurs years after onset of the disorder (Compton et al., 2007). Alternatively, observed brain differences might be caused primarily by between-individual genetic differences as recent studies of normal adolescents support the high heritability of GM volume (Lenroot et al., 2009). This finding might suggest that brain differences mediate the between-individual genetic variations that predispose adolescents to behavioral disinhibition (Young et al., 2000), affective dysregulation (Tarter et al., 1999), and later externalizing behaviors and SUD (Iacono et al., 2008). Future studies should attempt to clarify whether brain volume differences predate onset of substance use in externalizing, at-risk youth.

Second, processes that lead to volume differences cannot be determined here; differences might relate to changes in neuropil, neuronal size, dendritic or axonal arborisation. Third, although it is tempting to declare lower GM volume as suggestive of less functional activity, the relationship between structural abnormality and corresponding direction of functional activity (i.e., hyperfunction versus hypofunction) is complex and not fully understood. For example, both excitatory and inhibitory activity contribute to the Blood-oxygen-level dependence (BOLD) signal in functional MRI (Logothetis, 2008; Tomassini et al., 2010), which in turn is positively correlated to local synaptic activity (Logothetis et al., 2001; Tomassini et al., 2010). Thus we should exercise caution in neurobiological interpretations of our results and should not expect a simple one-to-one relationship between imaging measures and underlying physiological or anatomical features (Tomassini et al., 2010). However, there is some evidence that smaller GM volume seen here may result in reduced functional activity. First, using a subset of this sample, patients compared with controls showed decreased fMRI activation while playing a risk-based decision making task in many key areas of the decision making network, including left DLPFC (Crowley et al., 2010). Second, impulsivity was negatively correlated with DLPFC volume in our within-control whole-brain regression analyses. Thus, it may be that our patients show lower inhibition, higher impulsivity and therefore lower functional activity and that this is in part demonstrable in smaller gray matter volume in left DLPFC. Still our results cannot provide direct information about functional activity or whether any activation differences represent deficits in inhibitory or excitatory processes.

Fourth, although automated VBM is a widely used tool for examining between-group structural brain differences and has advantages over traditional region of interest manual-based approach which can have operator bias, the VBM procedure can be sensitive to imperfectly registered images, for example, VBM cannot differentiate real changes in tissue volume from local mis-registration of images (Ashburner and Friston, 2001; Bookstein, 2001); another important caveat is that there is no agreed upon method for automated volumetrics and different approaches may yield different conclusions (Klauschen et al., 2009). However in recent years, iterative normalization and optimized segmentation procedures and algorithms have been developed to improve the final tissue classification

(Ashburner and Friston, 2005). Emerton et al. (2009) showed convergence in the VBM method in comparison with tracing-based volumetry methods; however they advocated the two methods to be considered complementary rather than interchangeable methods, due to different statistical approaches. Furthermore the same authors suggested that convergence depends on various factors such as inter-subject anatomical variability of the region of interest and/or the VBM preprocessing protocol employed. Fifth, results from these males cannot be generalized to female adolescents with ASD. However, the advantage of sample homogeneity (gender, handedness) is likely reduced confounds in our analyses, given recent findings of sexual dimorphism in adolescent brain development (Lenroot et al., 2007). Sixth, power is difficult to estimate without knowing effect size, or the expected differences in gray matter volume between patients and controls. Without such knowledge, it is not possible to estimate the most appropriate sample size. However, the sample size used in this VBM study is comparable to the other studies of similar phenotypes (i.e., Heubner et al., 2008; Sterzer et al., 2007; Kruesi et al., 2004; De Brito et al., 2009).

In sum, our results suggest that the brains of male youth with ASD are notably different from youth of similar age and zip code of residence. There is reduced gray matter volume in areas involved in cognitive and emotional control and increased gray matter in region associated with self-referential and self-centered thinking. The brain abnormalities in these regions could contribute to the antisocial and substance dependent behaviors of these youth.

References

- Achenbach, TM. Manual for the child behavior checklist/4–18 and 1991 profile. University of Vermont Department of Psychiatry; Burlington, VT: 1991a.
- Achenbach, TM. Manual for the Youth Self-Report and 1991 profile. University of Vermont Department of Psychiatry; Burlington, VT: 1991b.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Edition (DSM-IV). American Psychiatric Association; Washington, D.C.: 2000.
- Anderson CM, Maas LC, Frederick B, Bendor JT, Spencer TJ, Livni E, Lukas SE, Fischman AJ, Madras BK, Renshaw PF, Kaufman MJ. Cerebellar vermis involvement in cocaine-related behaviors. *Neuropsychopharmacology*. 2006; 31:1318–1326. [PubMed: 16237382]
- Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat. Neurosci*. 1999; 2:1032–1037. [PubMed: 10526345]
- Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage*. 2000; 11:805–821. [PubMed: 10860804]
- Ashburner J, Friston KJ. Why voxel-based morphometry should be used. *Neuroimage*. 2001; 14:1238–1243. [PubMed: 11707080]
- Ashburner J, Friston KJ. Unified segmentation. *Neuroimage*. 2005; 26:839–851. [PubMed: 15955494]
- Bechara A. Neurobiology of decision-making: risk and reward. *Semin. Clin. Neuropsychiatry*. 2001; 6:205–216. [PubMed: 11447572]
- Beer JS, Heerey EA, Keltner D, Scabini D, Knight RT. The regulatory function of self-conscious emotion: insights from patients with orbitofrontal damage. *J. Pers. Soc. Psychol*. 2003; 85:594–604. [PubMed: 14561114]
- Benegal V, Antony G, Venkatasubramanian G, Jayakumar PN. Gray matter volume abnormalities and externalizing symptoms in subjects at high risk for alcohol dependence. *Addict. Biol*. 2007; 12:122–132. [PubMed: 17407506]
- Boes AD, Bechara A, Tranel D, Anderson SW, Richman L, Nopoulos P. Right ventromedial prefrontal cortex: a neuroanatomical correlate of impulse control in boys. *Soc. Cogn. Affect. Neurosci*. 2009; 4:1–9. [PubMed: 19015086]
- Bookstein FL. “Voxel-based morphometry” should not be used with imperfectly registered images. *Neuroimage*. 2001; 14:1454–1462. [PubMed: 11707101]

- Brass M, Derrfuss J, Forstmann B, von Cramon DY. The role of the inferior frontal junction area in cognitive control. *Trends Cogn. Sci.* 2005; 9:314–316. [PubMed: 15927520]
- Brett, M.; Anton, J.; Valabregue, R.; Poline, J. Region of interest analysis using an SPM toolbox. 8th International Conference on Functional Mapping of the Human Brain; Sendai, Japan. 2002.
- Camille N, Coricelli G, Sallet J, Pradat-Diehl P, Duhamel JR, Sirigu A. The involvement of the orbitofrontal cortex in the experience of regret. *Science.* 2004; 304:1167–1170. [PubMed: 15155951]
- Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc. Natl. Acad. Sci. U S A.* 2003; 100:5497–5502. [PubMed: 12682281]
- Carroll BJ, Feinberg M, Smouse PE, Rawson SG, Greden JF. The Carroll rating scale for depression. I. Development, reliability and validation. *Br. J. Psychiatry.* 1981; 138:194–200. [PubMed: 7272609]
- Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain.* 2006; 129:564–583. [PubMed: 16399806]
- Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch. Gen. Psychiatry.* 2007; 64:566–576. [PubMed: 17485608]
- Crews FT, Boettiger CA. Impulsivity, frontal lobes and risk for addiction. *Pharmacol. Biochem. Behav.* 2009; 93:237–247. [PubMed: 19410598]
- Crowley, TJ.; Gelhorn, H. Antisocial substance dependence. In: Koob, G.; Le Moal, M.; Thompson, RF., editors. *Encyclopedia of Behavioral Neuroscience.* Elsevier Science; Oxford: 2010. p. 101-108.
- Crowley TJ, Dalwani MS, Mikulich-Gilbertson SK, Du YP, Lejuez CW, Raymond KM, Banich MT. Risky decisions and their consequences: neural processing by boys with Antisocial Substance Disorder. *PLoS One.* 2010; 5:e12835. [PubMed: 20877644]
- Crowley TJ, Mikulich SK, Ehlers KM, Whitmore EA, MacDonald MJ. Validity of structured clinical evaluations in adolescents with conduct and substance problems. *J. Am. Acad. Child Adolesc. Psychiatry.* 2001; 40:265–273. [PubMed: 11288767]
- Crowley TJ, Mikulich SK, MacDonald M, Young SE, Zerbe GO. Substance-dependent, conduct-disordered adolescent males: severity of diagnosis predicts 2-year outcome. *Drug Alcohol Depend.* 1998; 49:225–237. [PubMed: 9571387]
- Crowley TJ, Raymond KM, Mikulich-Gilbertson SK, Thompson LL, Lejuez CW. A risk-taking “set” in a novel task among adolescents with serious conduct and substance problems. *J. Am. Acad. Child. Adolesc. Psychiatry.* 2006; 45:175–183. [PubMed: 16429088]
- De Bellis MD, Narasimhan A, Thatcher DL, Keshavan MS, Soloff P, Clark DB. Prefrontal cortex, thalamus, and cerebellar volumes in adolescents and young adults with adolescent-onset alcohol use disorders and comorbid mental disorders. *Alcohol. Clin. Exp. Res.* 2005; 29:1590–1600. [PubMed: 16205359]
- De Brito SA, Mechelli A, Wilke M, Laurens KR, Jones AP, Barker GJ, Hodgins S, Viding E. Size matters: increased grey matter in boys with conduct problems and callous-unemotional traits. *Brain.* 2009; 132:843–852. [PubMed: 19293245]
- Deas-Nesmith D, Brady KT, White R, Campbell S. HIV-risk behaviors in adolescent substance abusers. *J. Subst. Abuse Treat.* 1999; 16:169–172. [PubMed: 10023616]
- Derringer J, Krueger RF, Iacono WG, McGue M. Modeling the impact of age and sex on a dimension of poly-substance use in adolescence: a longitudinal study from 11- to 17-years-old. *Drug Alcohol Depend.* 2010; 110:193–199. [PubMed: 20456876]
- Dom G, Sabbe B, Hulstijn W, van den Brink W. Substance use disorders and the orbitofrontal cortex: systematic review of behavioural decision-making and neuroimaging studies. *Br. J. Psychiatry.* 2005; 187:209–220. [PubMed: 16135857]
- Dougherty DM, Bjork JM, Marsh DM, Moeller FG. A comparison between adults with conduct disorder and normal controls on a continuous performance test: differences in impulsive response characteristics. *Psychol. Rec.* 2000; 50:203–219.

- Emerton BC, Jerram M, Deckersbach T, Dougherty DD, Fulwiler C, Gansler DA. A comparison of voxel-based morphometry and volumetry methods in the context of the neural basis of aggression. *Brain Imaging Behav.* 2009; 3:332–341.
- Eslinger PJ, Grattan LM, Damasio H, Damasio AR. Developmental consequences of childhood frontal lobe damage. *Arch. Neurol.* 1992; 49:764–769. [PubMed: 1497505]
- Eysenck SB. Impulsiveness and antisocial behaviour in children. *Curr. Psychol. Res.* 1981; 1:31–37.
- Fein G, Di Sclafani V, Cardenas VA, Goldmann H, Tolou-Shams M, Meyerhoff DJ. Cortical gray matter loss in treatment-naïve alcohol dependent individuals. *Alcohol. Clin. Exp. Res.* 2002; 26:558–564. [PubMed: 11981133]
- Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend.* 2002; 66:265–273. [PubMed: 12062461]
- Frangou S, Chitins X, Williams SC. Mapping IQ and gray matter density in healthy young people. *Neuroimage.* 2004; 23:800–805. [PubMed: 15528081]
- Garavan H, Hester R, Murphy K, Fassbender C, Kelly C. Individual differences in the functional neuroanatomy of inhibitory control. *Brain Res.* 2006; 1105:130–142. [PubMed: 16650836]
- Giancola PR, Peterson JB, Pihl RO. Risk for alcoholism, antisocial behavior, and response perseveration. *J. Clin. Psychol.* 1993; 49:423–428. [PubMed: 8315046]
- Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am. J. Psychiatry.* 2002; 159:1642–1652. [PubMed: 12359667]
- Grafman J, Schwab K, Warden D, Pridgen A, Brown HR, Salazar AM. Frontal lobe injuries, violence, and aggression: a report of the Vietnam Head Injury Study. *Neurology.* 1996; 46:1231–1238. [PubMed: 8628458]
- Grella CE, Hser YI, Joshi V, Rounds-Bryant J. Drug treatment outcomes for adolescents with comorbid mental and substance use disorders. *J. Nerv. Ment. Dis.* 2001; 189:384–392. [PubMed: 11434639]
- Hayasaka S, Phan KL, Liberzon I, Worsley KJ, Nichols TE. Nonstationary cluster-size inference with random field and permutation methods. *Neuroimage.* 2004; 22:676–687. [PubMed: 15193596]
- Henggeler SW, Clingempeel WG, Brondino MJ, Pickrel SG. Four-year follow-up of multisystemic therapy with substance-abusing and substance-dependent juvenile offenders. *J. Am. Acad. Child Adolesc. Psychiatry.* 2002; 41:868–874. [PubMed: 12108813]
- Henggeler SW, Pickrel SG, Brondino MJ. Multisystemic treatment of substance-abusing and dependent delinquents: outcomes, treatment fidelity, and transportability. *Ment. Health Serv. Res.* 1999; 1:171–184. [PubMed: 11258740]
- 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]
- Hollingshead, A.d.B. Four Factor Index of Social Status. Yale University, Dept. of Sociology; New Haven, CT: 1975.
- Horn NR, Dolan M, Elliott R, Deakin JF, Woodruff PW. Response inhibition and impulsivity: an fMRI study. *Neuropsychologia.* 2003; 41:1959–1966. [PubMed: 14572528]
- Huebner T, Vloet TD, Marx I, Konrad K, Fink GR, Herpertz SC, Herpertz-Dahlmann B. Morphometric brain abnormalities in boys with conduct disorder. *J. Am. Acad. Child Adolesc. Psychiatry.* 2008; 47:540–547. [PubMed: 18356764]
- Iacoboni, M. Understanding others: imitation, language, empathy. In: Hurley, S.; Chater, N., editors. *Perspectives on Imitation: From Cognitive Neuroscience to Social Science.* Vol. Vol. 1. MIT Press; Cambridge, MA: 2005. p. 77-99.
- Iacoboni M, Lieberman MD, Knowlton BJ, Molnar-Szakacs I, Moritz M, Throop CJ, Fiske AP. Watching social interactions produces dorsomedial prefrontal and medial parietal BOLD fMRI signal increases compared to a resting baseline. *Neuroimage.* 2004; 21:1167–1173. [PubMed: 15006683]
- Iacono WG, Malone SM, McGue M. Behavioral disinhibition and the development of early-onset addiction: common and specific influences. *Annu. Rev. Clin. Psychol.* 2008; 4:325–348. [PubMed: 18370620]

- Isaacs EB, Edmonds CJ, Chong WK, Lucas A, Morley R, Gadian DG. Brain morphometry and IQ measurements in preterm children. *Brain*. 2004; 127:2595–2607. [PubMed: 15371289]
- Jentsch JD, Taylor JR. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl.)*. 1999; 146:373–390. [PubMed: 10550488]
- Junger M, van der Heijden P, Keane C. Interrelated harms: examining the associations between victimization, accidents, and criminal behavior. *Int. J. Inj. Contr. Saf. Promot.* 2001; 8:13–28.
- Keenan, JP.; Wheeler, MA.; Ewers, M. The neural correlates of self-awareness and self-recognition. In: Kircher, T.; David, A., editors. *The Self in Neuroscience and Psychiatry*. Cambridge University Press; Cambridge, UK: 2003. p. 166-179.
- Kircher TT, Brammer M, Bullmore E, Simmons A, Bartels M, David AS. The neural correlates of intentional and incidental self processing. *Neuropsychologia*. 2002; 40:683–692. [PubMed: 11792407]
- Kircher TTJ, Senior C, Phillips ML, Benson PJ, Bullmore ET, Brammer M, Simmons A, Williams SCR, Bartels M, David AS. Towards a functional neuroanatomy of self processing: effects of faces and words. *Cognitive Brain Res.* 2000; 10:133–144.
- Kjaer TW, Nowak M, Lou HC. Reflective self-awareness and conscious states: PET evidence for a common midline parietofrontal core. *Neuroimage*. 2002; 17:1080–1086. [PubMed: 12377180]
- Klauschen F, Goldman A, Barra V, Meyer-Lindenberg A, Lundervold A. Evaluation of automated brain MR image segmentation and volumetry methods. *Hum. Brain Mapp.* 2009; 30:1310–1327. [PubMed: 18537111]
- Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat. Rev. Neurosci.* 2005; 6:691–702. [PubMed: 16136173]
- Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog. Neurobiol.* 2004; 72:341–372. [PubMed: 15157726]
- Krueger RF. The structure of common mental disorders. *Arch. Gen. Psychiatry*. 1999; 56:921–926. [PubMed: 10530634]
- Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. *J. Abnorm. Psychol.* 2002; 111:411–424. [PubMed: 12150417]
- Kruesi MJ, Casanova MF, Mannheim G, Johnson-Bilder A. Reduced temporal lobe volume in early onset conduct disorder. *Psychiatry Res.* 2004; 132:1–11. [PubMed: 15546698]
- Lahey BB, Schwab-Stone M, Goodman SH, Waldman ID, Canino G, Rathouz PJ, Miller TL, Dennis KD, Bird H, Jensen PS. Age and gender differences in oppositional behavior and conduct problems: a cross-sectional household study of middle childhood and adolescence. *J. Abnorm. Psychol.* 2000; 109:488–503. [PubMed: 11016118]
- Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, Blumenthal JD, Lerch J, Zijdenbos AP, Evans AC, Thompson PM, Giedd JN. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage*. 2007; 36:1065–1073. [PubMed: 17513132]
- Lenroot RK, Schmitt JE, Ordaz SJ, Wallace GL, Neale MC, Lerch JP, Kendler KS, Evans AC, Giedd JN. Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. *Hum. Brain Mapp.* 2009; 30:163–174. [PubMed: 18041741]
- Liu X, Matochik JA, Cadet JL, London ED. Smaller volume of prefrontal lobe in polysubstance abusers: a magnetic resonance imaging study. *Neuropsychopharmacology*. 1998; 18:243–252. [PubMed: 9509492]
- Logothetis NK. What we can do and what we cannot do with fMRI. *Nature*. 2008; 453:869–878. [PubMed: 18548064]
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature*. 2001; 412:150–157. [PubMed: 11449264]

- Manzardo AM, Penick EC, Knop J, Nickel EJ, Hall S, Jensen P, Gabrielli WF Jr. Developmental differences in childhood motor coordination predict adult alcohol dependence: proposed role for the cerebellum in alcoholism. *Alcohol. Clin. Exp. Res.* 2005; 29:353–357. [PubMed: 15770110]
- Mathias CW, Dougherty DM, Marsh DM, Moeller FG, Hicks LR, Dasher K, Bar-Eli L. Laboratory measures of impulsivity: a comparison of women with or without childhood aggression. *Psychol. Rec.* 2002; 52:289–303.
- Matsuo K, Nicoletti M, Nemoto K, Hatch JP, Peluso MA, Nery FG, Soares JC. A voxel-based morphometry study of frontal gray matter correlates of impulsivity. *Hum. Brain Mapp.* 2009; 30:1188–1195. [PubMed: 18465751]
- Mechtcheriakov S, Brenneis C, Egger K, Koppelstaetter F, Schocke M, Marksteiner J. A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. *J. Neurol. Neurosurg. Psychiatry.* 2007; 78:610–614. [PubMed: 17088334]
- Medina KL, McQueeney 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]
- Menon V, Adelman NE, White CD, Glover GH, Reiss AL. Error-related brain activation during a Go/NoGo response inhibition task. *Hum. Brain Mapp.* 2001; 12:131–143. [PubMed: 11170305]
- Miller PA, Eisenberg N. The relation of empathy to aggressive and externalizing/antisocial behavior. *Psychol. Bull.* 1988; 103:324–344. [PubMed: 3289071]
- Molnar-Szakacs I, Iacoboni M, Koski L, Mazziotta JC. Functional segregation within pars opercularis of the inferior frontal gyrus: evidence from fMRI studies of imitation and action observation. *Cereb. Cortex.* 2005; 15:986–994. [PubMed: 15513929]
- Myers MG, Stewart DG, Brown SA. Progression from conduct disorder to antisocial personality disorder following treatment for adolescent substance abuse. *Am. J. Psychiatry.* 1998; 155:479–485. [PubMed: 9545992]
- Nagel BJ, Schweinsburg AD, Phan V, Tapert SF. Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. *Psychiatry Res.* 2005; 139:181–190. [PubMed: 16054344]
- Newman JP, Patterson CM, Kosson DS. Response perseveration in psychopaths. *J. Abnorm. Psychol.* 1987; 96:145–148. [PubMed: 3584663]
- Nock MK, Kazdin AE, Hiripi E, Kessler RC. Prevalence, subtypes, and correlates of DSM-IV conduct disorder in the National Comorbidity Survey Replication. *Psychol. Med.* 2006; 36:699–710. [PubMed: 16438742]
- Pell GS, Briellmann RS, Chan CH, Pardoe H, Abbott DF, Jackson GD. Selection of the control group for VBM analysis: influence of covariates, matching and sample size. *Neuroimage.* 2008; 41:1324–1335. [PubMed: 18467131]
- Pfeifer JH, Iacoboni M, Mazziotta JC, Dapretto M. Mirroring others' emotions relates to empathy and interpersonal competence in children. *Neuroimage.* 2008; 39:2076–2085. [PubMed: 18082427]
- Platek SM, Wathne K, Tierney NG, Thomson JW. Neural correlates of self-face recognition: an effect-location meta-analysis. *Brain Res.* 2008; 1232:173–184. [PubMed: 18656465]
- Potenza MN. Review. The neurobiology of pathological gambling and drug addiction: an overview and new findings. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 2008; 363:3181–3189. [PubMed: 18640909]
- Raine A, Lencz T, Bihle S, LaCasse L, Colletti P. Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Arch. Gen. Psychiatry.* 2000; 57:119–127. discussion 128–119. [PubMed: 10665614]
- Rhee SH, Hewitt JK, Young SE, Corley RP, Crowley TJ, Stallings MC. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Arch. Gen. Psychiatry.* 2003; 60:1256–1264. [PubMed: 14662558]
- Rhee SH, Waldman ID. Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. *Psychol. Bull.* 2002; 128:490–529. [PubMed: 12002699]
- Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, Farmer A, Jablenski A, Pickens R, Regier DA, 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]
- SAS Institute Inc.. SAS/STAT User's Guide. Version 9.2. SAS Institute Inc; Cary, NC: 2008. The PROC GLM Procedure.
- Schmahmann JD, Anderson CM, Newton N, Ellils R. The function of the cerebellum in cognition, affect and consciousness. *Conscious. Emot.* 2001; 2:273–309.
- 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. *J. Am. Acad. Child Adolesc. Psychiatry*. 2000; 39:28–38. [PubMed: 10638065]
- Shapiro SK, Quay HC, Hogan AE, Schwartz KP. Response perseveration and delayed responding in undersocialized aggressive conduct disorder. *J. Abnorm. Psychol.* 1988; 97:371–373. [PubMed: 3192833]
- Sim ME, Lyoo IK, Streeter CC, Covell J, Sarid-Segal O, Ciraulo DA, Kim MJ, Kaufman MJ, Yurgelun-Todd DA, Renshaw PF. Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. *Neuropsychopharmacology*. 2007; 32:2229–2237. [PubMed: 17299505]
- Sterzer P, Stadler C, Poustka F, Kleinschmidt A. A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. *Neuroimage*. 2007; 37:335–342. [PubMed: 17553706]
- Swann AC, Bjork JM, Moeller FG, Dougherty DM. Two models of impulsivity: relationship to personality traits and psychopathology. *Biol. Psychiatry*. 2002; 51:988–994. [PubMed: 12062883]
- Swick D, Ashley V, Turken AU. Left inferior frontal gyrus is critical for response inhibition. *BMC Neurosci.* 2008; 9:102. [PubMed: 18939997]
- Tanabe J, Tregellas JR, Dalwani M, Thompson L, Owens E, Crowley T, Banich M. Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. *Biol. Psychiatry*. 2009; 65:160–164. [PubMed: 18801475]
- Tapert SF, Schweinsburg AD, Barlett VC, Brown SA, Frank LR, Brown GG, Meloy MJ. Blood oxygen level dependent response and spatial working memory in adolescents with alcohol use disorders. *Alcohol. Clin. Exp. Res.* 2004; 28:1577–1586. [PubMed: 15597092]
- Tarter R, Vanyukov M, Giancola P, Dawes M, Blackson T, Mezzich A, Clark DB. Etiology of early age onset substance use disorder: a maturational perspective. *Dev. Psychopathol.* 1999; 11:657–683. [PubMed: 10624720]
- Teplin LA, Abram KM, McClelland GM, Dulcan MK, Mericle AA. Psychiatric disorders in youth in juvenile detention. *Arch. Gen. Psychiatry*. 2002; 59:1133–1143. [PubMed: 12470130]
- Teplin LA, McClelland GM, Abram KM, Mileusnic D. Early violent death among delinquent youth: a prospective longitudinal study. *Pediatrics*. 2005; 115:1586–1593. [PubMed: 15930220]
- Thoma P, Bellebaum C, Koch B, Schwarz M, Daum I. The cerebellum is involved in reward-based reversal learning. *Cerebellum*. 2008; 7:433–443. [PubMed: 18592331]
- Thompson LL, Whitmore EA, Raymond KM, Crowley TJ. Measuring impulsivity in adolescents with serious substance and conduct problems. *Assessment*. 2006; 13:3–15. [PubMed: 16443715]
- Tiet QQ, Wasserman GA, Loeber R, McReynolds LS, Miller LS. Developmental and sex differences in types of conduct problems. *J. Child. Fam. Stud.* 2001; 10:181–197.
- Tomassini V, Jbabdi S, Kincses ZT, Bosnell R, Douaud G, Pozzilli C, Matthews PM, Johansen-Berg H. Structural and functional bases for individual differences in motor learning. *Hum. Brain Mapp.* 2010; 32:494–508. [PubMed: 20533562]
- Uddin LQ, Kaplan JT, Molnar-Szakacs I, Zaidel E, Iacoboni M. Self-face recognition activates a frontoparietal “mirror” network in the right hemisphere: an event-related fMRI study. *Neuroimage*. 2005; 25:926–935. [PubMed: 15808992]
- Waldron HB, Turner CW. Evidence-based psychosocial treatments for adolescent substance abuse. *J. Clin. Child Adolesc. Psychol.* 2008; 37:238–261. [PubMed: 18444060]
- Ward, BD. AFNI 3dDeconvolve Documentation. Medical College of Wisconsin; Milwaukee, WI: 2000. Simultaneous inference for FMRI data.

- Wechsler, D. Wechsler Abbreviated Scale of Intelligence. Psychological Corp; San Antonio, TX: 1999.
- Wilke M, Schmithorst VJ, Holland SK. Normative pediatric brain data for spatial normalization and segmentation differs from standard adult data. *Magn. Reson. Med.* 2003; 50:749–757. [PubMed: 14523961]
- Young SE, Rhee SH, Stallings MC, Corley RP, Hewitt JK. Genetic and environmental vulnerabilities underlying adolescent substance use and problem use: general or specific? *Behav. Genet.* 2006; 36:603–615. [PubMed: 16619135]
- 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]

Figure 1.

Color map (X coordinate: 51 mm left of midline) showing increased gray matter in left dorsolateral prefrontal cortex (DLPFC) /Inferior Frontal Gyrus (IFG) and left cerebellum in control male adolescents compared with antisocial substance dependent (ASD) male adolescents, after co-varying for total gray matter, age and IQ. Statistical maps were set at a cluster-level threshold of $p < 0.05$, corrected for multiple comparisons with family-wise error (FWE) using alphasim Monte Carlo simulations and a voxel-level threshold of $p < 0.005$. Color Bar represents t-value.

Figure 2. Color map (X coordinate: 20 mm right of midline) showing increased gray matter in right Precuneus/Cuneus BA 7,31 in antisocial substance dependence (ASD) male adolescents compared with control male adolescents, after co-varying for total gray matter, age and IQ. Statistical maps were set at a cluster-level threshold of $p < 0.05$, corrected for multiple comparisons with family-wise error (FWE) using alphasim Monte Carlo simulations and a voxel-level threshold of $p < 0.005$. Color Bar represents t-value.

Figure 3.

Color map (X coordinate: 48 mm left of midline) showing negative association between the left DLPFC GM and impulsivity in controls after co-varying for total gray matter, age and IQ. Statistical maps were set at a cluster-level threshold of $p < 0.05$, corrected for multiple comparisons with family-wise error (FWE) using alphasim Monte Carlo simulations and a voxel-level threshold of $p < 0.005$. Color Bar represents t-value. The crosshair marks the voxel with maximum negative association and the regression plot below the color map shows the negative association ($r = -0.85$) between GM and impulsivity for that maximum voxel.

Figure 4.

Color map (X coordinate: 45 mm left of midline) showing negative association between the left DLPFC GM and number of substance dependent symptoms (SUMDEP) in patients after co-varying for total gray matter, age and IQ. Statistical maps were set at a cluster-level threshold of $p < 0.05$, corrected for multiple comparisons with family-wise error (FWE) using alphasim Monte Carlo simulations and a voxel-level threshold of $p < 0.005$. Color Bar represents t-value. The crosshair marks the voxel with maximum negative association and the regression plot below the color map shows the negative association between GM and SUMDEP ($r = -0.83$) for that maximum voxel.

Table 1

Patient-Control Comparisons

	Controls (n=19)	Patients (n=25)	test statistic	p-value
<u>Demographics:</u>				
Age (sem)	16.59(0.37)	16.64(0.23)	t = -0.13	0.89
Race				
Caucasian	15	16		
African American	1	4		
Hispanic	2	5		
Other	1	0		
Caucasian vs. Non-caucasian			X ² = 1.16	0.28
Education				
Highest grade completed (sem)	9.74(0.39)	9.12(0.22)	Mann-Whitney	0.18
Ever repeated grade (n)	1	8	Fischer's Exact	0.06
<u>Diagnostic and other measures:</u>				
IQ (sem)	105.21(2.08)	98.08(1.68)	t = 2.69	0.001
Carroll rating of depression (sem)	4.11(0.95)	8.76(1.21)	Mann-Whitney	0.003
CBCL (or YSR n=3)				
Attention Deficit Hyperactivity				
Problems t-score (sem)	53.32(1.05)	58.44(1.57)	t = 2.54	0.01
DISC Lifetime ADHD diagnosis (n)	2	3	Fischer's Exact	1.0
<u>Impulsivity, Aggression And Conduct Disorder</u>				
Eysenck Impulsivity Scale (sem)	6.95(1.04)	12.76(1.23)	t = -3.47	0.001
Peak Aggression Scale	0.37(0.23)	5.66(0.62)	Mann-Whitney	0.001
Lifetime CD diagnosis (n)	0	22	Chi-Square	<0.001
<u>Substance Use Disorders</u>				
SUMDEP (sem)	0.15(0.16)	11.88(0.62)	Mann-Whitney	<0.0005
Lifetime Substance Abuse or Dependence (n):				
Alcohol	0	21	X ² = 30.53	<0.001
Cannabis	0	21	X ² = 30.53	<0.001
Tobacco	1	13	X ² = 10.87	0.001
Club drugs	0	9	Fischer's Exact	0.006
Cocaine	0	8	Fischer's Exact	0.007
Hallucinogens	0	5	Fischer's Exact	0.06
Amphetamine	0	3	Fischer's Exact	0.25
# Days Used in Past 180 Days:				
Tobacco	5.16(4.72)	119.88(9.75)	t = -10.59	<0.0001
Cannabis	0.21(0.12)	82.60(13.60)	t = -6.06	<0.0001
Alcohol	0.89(0.37)	34.80(8.14)	t = -4.16	0.0003
Amphetamines ^a	15.79(11.09)	16.04(9.95)	t = -0.02	0.98
Cocaine	0	8.68(6.39)		NA
MDMA/Ectasy	0	8.32(3.77)		NA

	Controls (n=19)	Patients (n=25)	test statistic	p-value
Hallucinogens	0	6.28(3.48)		NA
Opiate	0	0.84(0.43)		NA
Ketamine	0	0.12(0.09)		NA
PCP	0	0.04(0.04)		NA

Abbreviations in Table 1: ADHD = DSM-IV-defined attention-deficit/hyperactivity disorder; CD = at least three lifetime DSM-IV conduct disorder symptoms; CBCL = child behavior checklist; DISC = Diagnostic Interview Schedule for Children; IQ = intelligence quotient measured by the two subtests from the Wechsler Abbreviated Scale of Intelligence; on the Carroll a score of ≥ 10 is suggestive of clinical depression; SUMDEP = total number of substance dependence symptoms; sem = standard error of the mean; t = t-value for the t-test; X^2 = Chi-square value for the Chi-square test; YSR = Youth Self-Report.

^aTwo control subjects were on medication for ADHD (one for 180 days and one for 120 days) and hence the number of days amphetamines used in past 180 days shows a relatively high level for controls.

Table 2

Regions in which groups significantly differed in GM Volume

Contrast 1: Controls>Patients						
Region	Laterality/BA	# Voxels	t	X	Y	Z
DLPFC Inf Fr Gy ^a	Left; 9, 46	1628	4.02	-53	5	32
Lingual Gy ^b	Right; 19	1270	4.53	12	-58	-2
Tuber, Pyramis and Tonsil	Left	2532	3.93	-39	-68	-40
Tuber, Pyramis	Right	1232	4.20	39	-68	-39
Contrast 2: Patients>Controls						
Cuneus/Precuneus	Right; 7, 31	1989	4.25	20	-77	23

Abbreviations in Table 2: BA = Brodmann Area; DLPFC = Dorsolateral Prefrontal Cortex; Inf = Inferior; Fr = Frontal; Gy = Gyrus. Coordinates are given for the maximally significant voxel. The coordinates are reported in Montreal Neurological Space (MNI). Statistical maps were corrected for multiple comparisons using family-wise-error cluster level threshold ($p < 0.05$) and were set at a voxel-level threshold $P < 0.005$.

^aThis cluster also includes voxels in the middle frontal gyrus, pre/post-central gyrus, inferior parietal lobule, and supramarginal gyrus (BA 6, 2 and 40).

^bThis cluster also includes voxels in the culmen and declive.

Table 3
Whole-Brain Regression Between GM volume and Impulsivity score in Controls

Region	Laterality/BA	# Voxels	t	X	Y	Z
DLPFC Middle Fr Gy ^a	Left; 9	5179	6.16	-48	11	36
DLPFC Inf Fr Gy ^b	Left; 44	3160	4.40	-51	1	20
OFC Medial Fr Gy	Right; 10, 11	2071	5.75	12	54	-9
Frontopolar Sup Fr Gy	Right; 10	1258	5.25	20	61	14
Middle Frontal Gy	Right; 10	1522	5.07	32	54	7
OFC Medial Fr Gy	Left; 10	2478	4.60	-12	57	3
Middle Fr Gy	Right; 10	1622	4.59	42	53	0
OFC, Middle/Inf Fr. Gy	Left; 10, 47	1801	4.13	-43	44	6

Abbreviations in Table 3: BA = Brodmann Area; DLPFC = Dorsolateral Prefrontal Cortex; OFC = Orbito Frontal Cortex Inf = Inferior; Fr = Frontal; Gy = Gyrus, Sup = Superior. Coordinates are given for the maximally significant voxel. The coordinates are reported in Montreal Neurological Space (MNI). Statistical maps were corrected for multiple comparisons using family-wise-error cluster level threshold ($p < 0.05$) and were set at a voxel-level threshold $P < 0.005$.

^aThis cluster also includes voxels in the precentral gyrus (BA 6).

^bThis cluster also includes voxels in the precentral gyrus (BA 6).