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A Voxel-Based Morphometry Study of Young Occasional Users of Amphetamine-Type Stimulants and Cocaine

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Abstract

BACKGROUND: Although the interaction of brain volume with amphetamine-type stimulants (ATS) and cocaine has been investigated in chronically dependent individuals, little is known about structural differences that might exist in individuals who consume ATS and cocaine occasionally but are not dependent on these drugs.

METHODS: Regional brain volumes in 165 college aged occasional users of ATS (namely: amphetamine, methamphetamine, methylphenidate, and 3,4-methylenedioxymethamphetamine; MDMA) and cocaine were compared by voxel-based morphometry with 48 ATS/cocaine-naïve controls.

RESULTS: Grey matter volume was significantly higher in the left ventral anterior putamen of occasional users, and lower in the right dorsolateral cerebellum and right inferior parietal cortex. A regression in users alone on lifetime consumption of combined ATS (namely: amphetamine, methamphetamine, methylphenidate and MDMA) and cocaine use revealed that individuals who used more ATS/cocaine had greater volume in the right ventromedial frontal cortex. A second regression on lifetime consumption of ATS with cocaine as a covariate revealed that individuals with a greater history of ATS use alone had more grey matter volume in the left midinsula. Interestingly, structural changes in the ventromedial prefrontal cortex, insula and striatum have been consistently observed in volumetric studies of chronic ATS and cocaine dependence.

CONCLUSION: The present results suggest that these three brain regions may play a role in stimulant use even in early occasional users.

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Conflict of Interest No conflict declared.

Keywords

Voxel-based Morphometry; Structural Neuroimaging; Amphetamine-type Stimulants; Cocaine; Occasional

1. INTRODUCTION

Amphetamine-type stimulants (ATS), including l-amphetamine, d-amphetamine, methamphetamine, methylphenidate, and 3,4-methylenedioxymethamphetamine (MDMA) are a family of psychoactive compounds that share common elements in their chemical structure (Sulzer et al., 2005). ATS and cocaine, which act on the nervous system by increasing the synaptic availability of catecholamines (e.g., dopamine, norepinephrine) and serotonin, have profound effects on mind and body, including appetite suppression, intense feelings of well-being, and increased energy, heart rate, and mental alertness. Although ATS and cocaine are categorized as controlled substances, amphetamine (e.g., Aderall), methamphetamine (e.g., Desoxyn), and methylphenidate (e.g., Ritalin) are prescribed to treat a variety of neuropsychiatric conditions including attention deficit disorder, treatment-resistant depression and narcolepsy. Non-medical use of these stimulants is widespread (Substance Abuse and Mental Health Services Administration, 2011).

Approximately 13% of individuals who use stimulants non-medically will subsequently develop a clinical dependence on the drug (McCabe et al., 2007). Numerous developmental, sociodemographic and behavioral risk factors for dependence have been identified. For example, age at first exposure to alcohol and drugs is a significant predictor of substance dependence (Anthony and Petronis, 1995; Chen et al., 2009; McCabe et al., 2007). McCabe and colleagues (2007) estimate that the lifetime likelihood of developing a dependence on prescription drugs is decreased by 2% for each year that onset of non-medical use of prescription drugs is delayed. Demographic attributes that contribute to risk, include youth, being unmarried, low-income and fewer years of education (Compton et al., 2007; Huang et al., 2006; von Sydow et al., 2002). Stimulant dependent individuals are also more behaviorally disinhibited, e.g. they score higher on questionnaires probing impulsivity and sensation seeking (Ersche et al., 2010; Moeller et al., 2002; Patkar et al., 2004) and are less willing to trade immediate gratification for larger delayed rewards (Hoffman et al., 2006; Schwartz et al., 2010).

Recently, closer attention has been paid to the heightened prevalence of non-medical ATS use among college students, who use ATS primarily to enhance academic performance (Teter et al., 2005). Several studies indicate that college students who use ATS without a prescription have lower grades on average, skip more classes, and spend more time socializing relative to their stimulant naïve peers (Arria, 2008; McCabe et al., 2005; Reske et al., 2010). Also, occasional ATS use in college students has been associated with below normal cognitive ability, including deficits in verbal learning and memory (Reske et al., 2010).

To date, studies on the interaction between brain volume and ATS/cocaine consumption have focused almost exclusively on the effects of chronic abuse/dependence (e.g., Barros-Loscertales et al., 2011; Bartzokis et al., 2002; Connolly et al., 2013; Franklin et al., 2002; Narayana et al., 2010). While most parts of the brain have been implicated in at least one study, a recent literature review indicates that three brain regions are consistently linked to chronic ATS/cocaine use, namely the striatum, the insula and the frontal cortex –in particular, the ventromedial prefrontal cortex (vmPFC; Mackey and Paulus, 2013). This is interesting because of evidence suggesting that the anterior striatum, vmPFC and insula

participate in a network of brain regions that are important for decision-making processes related to substance use (Naqvi and Bechara, 2009).

Relatively little is known, however, about the structural differences that might exist in individuals that have used ATS and cocaine occasionally but are not dependent on them. In the present study, optimized voxel-based morphometry (VBM) was performed in college students who occasionally used ATS and cocaine 1) to explore differences with ATS and cocaine naïve control subjects, and 2) to investigate whether regional brain volumes are differentially related to the lifetime amount of combined ATS/cocaine use or to lifetime amount of ATS use alone.

2. METHODS

2.1 Subject Behavioral Assessment

The experimental protocol was reviewed by the University of California, San Diego Human Subjects Review Board and all aspects of the study were performed in accordance with the Declaration of Helsinki. The selection of subjects has been described elsewhere (Stewart et al., 2012). Briefly, volunteers were recruited by internet and newspaper ads as well as flyers mailed to university students in the San Diego region. Subjects were assessed by the Semi Structured Assessment for the Genetics of Alcoholism (SSAGA) which generates a detailed substance use history and includes timeline follow-back methods to quantify lifetime drug use based on the number of distinct sessions each drug was used (Bucholz et al., 1994). Decisions to include/exclude subjects were made at consensus meetings that consisted of a clinician specialized in substance use disorders (MPP) and the study personnel. There were seven exclusion criteria: (1) diagnosis of Attention Deficit Hyperactivity Disorder (ADHD); (2) medically prescribed use of stimulants; (3) current (and past 6 months) Axis I panic disorder, social phobia, post-traumatic stress disorder, major depressive disorder; (4) lifetime bipolar disorder, schizophrenia or other cognitive disorders, including obsessive compulsive disorder; (5) antisocial personality disorder and conduct disorder; (6) current positive urine toxicology test (exception: marijuana) and (7) head injuries or loss of consciousness for longer than 5 min. Subjects were classified as occasional users on the basis of three conditions: 1) 2 or more non-medical uses of oral prescription ATS (i.e. amphetamine, methamphetamine, methylphenidate) or cocaine in the past 6 months, 2) no lifetime history of ATS or cocaine dependence, and 3) no treatment seeking for other substance related problems. Occasional users were compared to control subjects who had no lifetime history of non-medical ATS or cocaine use and no use of any drug (with the exception of marijuana, alcohol or nicotine) in the previous six months. Occasional users were matched with ATS/cocaine naïve controls in terms of age, gender, ethnicity, and years of education (Table 1). Informed consent was obtained from all participants. Subjects were asked not to consume any illicit substances for a period of 72 hours prior to scanning to eliminate the possibility of the acute substance effects. A recent study has suggested that a 20 mg dose of baclofen, a GABA_B receptor agonist, administered 110 minutes before scanning may produce apparent decreases in cortical volume on T₁-weighted anatomical images (Franklin et al., 2013). To verify current drug status, subjects were assessed by a urine toxicology test immediately prior to scanning. Subjects were also scored on the Barratt Impulsivity Scale (BIS-11; Patton et al., 1995), the Sensation Seeking Scale (SSS; Zuckerman et al., 1978), and Beck's Depression Index (BDI-II; Beck et al., 1996). Group differences on demographic and behavioral variables were assessed by t-test or chi-squared test (see Table 2). The level of significance for the multiple t-tests on the BIS, SSS, BDI totals and subscales was adjusted by Bonferroni correction for multiple comparisons, i.e. $\alpha = 0.004$ (i.e., $0.05/13$).

2.2 MRI acquisition and voxel-based morphometry

A high resolution, T₁-weighted, anatomical brain scan [spoiled gradient recalled (SPGR), TR=8 ms, TE=3 ms, FOV=25 cm, approximately 1 mm³ voxels] was collected from each subject on a 3.0 Tesla Signa EXCITE scanner (GE Healthcare, Milwaukee, WI). Images were reconstructed then preprocessed for voxel-based morphometry with FSL-VBM (Douaud et al., 2007) using an optimized VBM protocol (Ashburner and Friston, 2000; Good et al., 2001) performed with FSL tools (FSL-4.1.6; Smith et al., 2004). The optimized protocol uses an iterative approach to segmentation and normalization that results in a more accurate identification of grey and white matter. Brain extraction was performed with BET (Smith, 2002). Despite careful manipulation of the BET extraction parameters, considerable amounts of non-brain tissue remained in the vicinity of the eyeballs and other ventral parts of the brain continuing posteriorly to the pons. In these regions, the images were masked manually to remove non-brain material (e.g., vasculature, bone etc.). Non-brain tissue was identified 1) by its appearance in locations that were anatomically unlikely (this included consideration of adjacent serial sections to ensure continuity of anatomical structures in 3 dimensions), and 2) a heterogeneity of pixel values that were dissimilar from the more uniform gray matter. In most places, identification was facilitated by a dark, though sometimes interrupted, line of pixels visible along the outer edge of the brain. Subsequent to brain extraction, tissue-types were segmented with FAST4 (Zhang et al., 2001). Segmented grey matter maps were aligned with the MNI-152 standard space by affine registration (d.f.=12) using the FLIRT tool (Jenkinson and Smith, 2001; Jenkinson et al., 2002) followed by non-linear registration using FNIRT (Andersson et al., 2007). A study-specific template was created by averaging the grey matter maps of the 46 control subjects with a matching number of subjects randomly selected from the occasional stimulant user group. Segmented grey matter images in native space were then re-registered to this template. To preserve information about absolute volume, partial volume images were modulated by multiplying by the Jacobian determinants generated during spatial normalization (Good et al., 2001) to compensate for expansion or contraction due to the non-linear part of the transformation (<http://dbm.neuro.uni-jena.de/vbm/segmentation/modulation/>) thus obviating the need to correct for total intracranial volume (Scorzin et al., 2008). The resulting images were smoothed by an isotropic Gaussian kernel, $\sigma = 3 \text{ mm} \approx 7.06 \text{ mm FWHM}$, and visualized with Analysis of Functional Neuroimages (AFNI) software (Cox, 1996).

2.3 Statistical Analysis

Statistical analyses of the processed images were performed in R (<http://www.r-project.org/>). All substance use variables were log transformed. Three whole-brain voxelwise analyses were performed. 1) Volumetric differences between users and controls were assessed statistically by a linear mixed effects (LME) model (Pinheiro, 2011). 2) A robust regression (Fox, 2010; Huber, 1964) in the user group alone identified voxels related to the combined lifetime amount (number of distinct occasions) of ATS and cocaine use. 2) A second robust regression in the user group alone was conducted to identify voxels related to the lifetime amount (number of distinct occasions) of prescription ATS (i.e., oral doses of amphetamine, methamphetamine, and methylphenidate) consumed with the lifetime amount of cocaine and MDMA entered as covariates. Voxelwise significance was established at an uncorrected global threshold in the LME at $F_{1, 209} = 8.04$, $p < 0.005$ and in the regressions at $t_{151} = 2.85$, $p < 0.005$, then multiple comparisons were controlled by cluster-extent correction to an a posteriori probability of $p < 0.01$ (AlphaSim; AFNI), i.e., thresholded at 1056 μL (132 voxels). Average grey matter volume was calculated for each significant region-of-interest (ROI) identified by the LME and the two regression analyses. Pearson correlations in SPSS (IBM, version 20) were then calculated in the occasional user group alone: i) to determine whether the ROI volumes were related to lifetime use of marijuana (number of distinct occasions), alcohol (number of alcoholic drinks per week) or nicotine (number of

cigarettes per week) and ii) to explore whether the ROI volumes were related to behavioral measures or age of initial ATS or cocaine use. To minimize multiple comparisons, only behavioral measures that were significantly different between users and controls were examined (Table 2). Furthermore, a Bonferroni correction was applied to the behavioral correlations to control for false positives due to multiple comparisons. Since there were eight ROIs identified and six behavioral measures including age of initial ATS or cocaine use, the significance threshold was adjusted to $\alpha = 0.001$ (i.e. $0.05/48$).

3. RESULTS

3.1 Demographic, Substance Use and Behavioral Characteristics

Phone interviews were conducted on 1025 individuals, 229 of whom met the inclusion criteria. The brain scans of eighteen participants were excluded because of low image quality due to motion artifact. A summary of demographic and substance use characteristics as determined by the SSAGA interview is presented in Table 1. Subjects with ($N = 165$) and without ($N = 46$) ATS and cocaine experience did not differ significantly in terms of age, race/ethnicity, sex, IQ, or education. Occasional ATS and cocaine users consumed significantly more marijuana, drank more alcohol and smoked more cigarettes during a typical week. After adjusting for multiple comparisons, occasional ATS and cocaine users scored significantly higher on BIS and SSS totals but not on the BDI (Table 2). In particular, the ATS and cocaine users scored significantly higher on the Motor sub-scale of the BIS and the Experience-Seeking and Disinhibition subscales of the SSS.

3.2 Linear Mixed Effects Model comparing Users and Controls

Differences in regional grey matter volume between occasional ATS and cocaine users and controls were assessed statistically with an LME model. Three significant clusters were identified: the volume of the most anterior part of the left putamen lateral to the nucleus accumbens was greater in ATS and cocaine users compared to controls (Figure 1); there was also significantly less volume in the right dorsolateral cerebellum and the right inferior parietal cortex. Cluster coordinates are provided in Table 3. The average volume within each cluster ROI was extracted. To determine whether use of other addictive substances (i.e., substance use that differed significantly between users and controls listed in Table 1) represent a potential confound in the interpretation of the ROI volumes, Pearson correlations between these variables were examined. ROI volumes did not correlate with marijuana, alcohol or nicotine use, $p > 0.05$. An alternate LME model analysis which included marijuana, alcohol and nicotine use as covariates generated similar results (see Supplemental Material). To help interpret volume differences, correlations between ROI volumes and behavioral measures as well as initial age of ATS or cocaine use were examined in occasional users alone. No significant correlations between ROI volumes and the behavioral measures were detected. Subjects who started to use ATS and cocaine earlier in life had larger putamen volumes ($r_{165} = -0.15$, $p < 0.05$) but this difference failed to reach significance after removing outliers and adjusting for multiple comparisons.

3.3 Regression on the Amount of Combined ATS and Cocaine Use in Users

A whole-brain voxelwise robust regression on combined lifetime consumption of ATS and cocaine was performed in the user group alone. Two regions of the brain were positively correlated with combined ATS and cocaine use: the right ventromedial prefrontal cortex and the right dorsal cerebellum (Table 3, Figure 2), while a third region encompassing parts of the post central gyrus and inferior parietal cortex was negatively correlated with use. The average volume of these ROIs was not significantly correlated with the behavioral measures or initial age of ATS or cocaine use. Alternate whole brain robust regressions with additional covariates produced similar results (see Supplemental Material).

3.4 Regression on the Amount of ATS Use Alone in Users

In a second whole-brain robust regression performed in users alone, two regions of the brain were positively correlated with the total lifetime amount of ATS consumed with cocaine as a covariate: the left mid-insula and the right occipital pole (Table 3) (Figure 3). A large cluster that passed the voxelwise threshold of significance but not the cluster extent correction was noted in the right mid-insula region that was symmetrical to the significant cluster in the left hemisphere. The average volumes of the left mid-insula and right occipital pole ROIs were not significantly correlated with the behavioral measures or the initial age of ATS use. Additional whole brain robust regressions with alternate covariates produced similar results (see Supplemental Material).

3.5 Covariation between ROI volumes

Lastly, correlations between the ROI volumes identified in the LME and two regression analyses were explored in the users alone to determine whether the volumes of the identified ROIs were related within individuals. The volumes of the left mid-insula and subthreshold right mid-insula ROIs were significantly correlated ($r_{165} = 0.459$, $p < 0.01$). Also, the volume of the ventromedial ROI was positively correlated with the volume of the left mid-insula and the right inferior parietal cortex ROIs in users ($r_{165} = 0.231$ and 0.296 , respectively, $p < 0.01$).

4. DISCUSSION

This study examined whether individuals who occasionally use ATS and cocaine exhibit structural brain differences relative to healthy comparison subjects and yielded two main findings. Firstly, occasional users of ATS and cocaine exhibit more grey matter volume in the anterior striatum and less volume in the inferior parietal cortex compared to stimulant naïve controls. Secondly, the volumes of the mid-insula and the vmPFC were positively correlated with lifetime amount of ATS use and lifetime amount of combined ATS/cocaine use, respectively. Moreover, the mean volumes of the vmPFC and insula ROIs were positively correlated within individuals.

It is interesting to note that the brain regions identified here resemble the findings of a recent review of the literature on brain volume effects associated with chronic use of ATS and cocaine (Mackey and Paulus, 2013). This review determined that the most consistent findings across studies of chronic ATS and cocaine use were higher striatal and lower vmPFC and insula volumes in older chronic users compared to age-matched controls. Considerable independent evidence suggests that the anterior striatum, vmPFC and insula participate in a network of brain regions that are important for decision-making processes related to substance use (Naqvi and Bechara, 2009). But why would the volumes of the vmPFC and insula be lower in chronic users of ATS and cocaine relative to controls (e.g., Franklin et al., 2002; Barros-Loscertales et al., 2011; Ersche et al., 2011; Hanlon et al., 2011; Alia-Klein et al., 2011; Connolly et al., 2013) while in the present data greater use in young occasional users of ATS and cocaine (Figures 2 and 3) is associated with higher volume? A clue with regard to why increased volume may be related to greater stimulant use in young occasional users is provided by the finding that repeated low doses of amphetamine or cocaine in rats cause synaptic reorganization selectively in the ventral striatum and the medial frontal cortex (Robinson and Kolb, 2004). In young rats, low doses of amphetamine produce increases in spine density and dendritic branching (Diaz Heijtz et al., 2003). It is possible that the relation between ATS/cocaine use and the volumes of the vmPFC and insula in young occasional users observed in the present study may be related to excessive proliferation of neuronal processes. In normal development, cortical and striatal grey matter volume increases during early childhood and then in adolescence begins a lifelong decline (Gogtay et al., 2004; Ostby et al., 2009; Sowell et al., 2003). It has been

hypothesized that these volume changes are related to early exuberant synaptogenesis followed by an extended period of pruning and myelination (Sowell et al., 2003). Moreover, it has been reported that the temporal dynamic of the maturational decline in cortical thickness is related to intellectual development in adolescents and young adults (Shaw et al., 2006; Sowell et al., 2004). While the present cross-sectional study cannot determine cause and effect, greater ATS and cocaine use in young individuals co-occurs with a disruption of an indicator of normal brain maturation (i.e., decreasing grey matter volume) in several key brain regions. Developmental delay may incur cognitive penalties that place individuals at greater risk of developing abusive patterns of stimulant consumption. This could point toward a biological explanation for the recurrent finding that, the earlier initial consumption occurs, the more likely an individual will subsequently develop a substance dependency (Anthony and Petronis, 1995; Chen et al., 2009; McCabe et al., 2007). Prospective studies will be required to determine the specific details of what is likely a complex dynamic relation between the vmPFC and insula volumes and ATS/cocaine use in young occasional users.

Three recent brain volumetric studies on recreational stimulant use are worth discussing in light of the present findings (Ersche et al., 2013; Cowan et al., 2003; Daumann et al., 2011). Ersche et al. (2013) found several regions of increased grey matter volume, including the vmPFC, in recreational cocaine users (mean age 29.1 years, s.d. ± 7.6 years) relative to cocaine-naïve control subjects. The observation of higher cortical volumes in recreational users is consistent with the present study, although it should be noted that the subjects in the Ersche et al. study were on average more than eight years older than those described here (Table 1).

A second study that investigated younger subjects more comparable in age to the present study (mean age 21.7 years old, s.d. ± 3.3 years) but focused on recreational MDMA use noted lower grey matter volumes compared to controls in the inferior frontal gyrus, occipital lobe, cerebellum and brain stem (Cowan et al., 2003). In this latter study, subjects were selected on the basis of MDMA use unlike the present study in which subjects were selected for use of cocaine and oral prescription ATS, namely: amphetamine, methamphetamine and methylphenidate. Although MDMA is classified as an ATS due to its chemical structure, it has a different behavioral and pharmacological profile in rats, monkeys and humans (e.g., Bankson et al 2009; Fantegrossi et al 2009; Gozoulis-Mayfrank and Daumann, 2009) than cocaine or the oral prescription ATS studied here. The effects of MDMA appear to be mediated principally by increased intracellular concentrations of serotonin. MDMA use, however, was minimal in the present sample (see Table 1) and including or excluding MDMA use in the analysis did not have any substantive effect on the results (see Supplemental Materials).

A third study compared experienced users of MDMA and amphetamine with individuals who had either low or no lifetime exposure to these drugs (Daumann et al., 2011). Subjects who used cocaine frequently were excluded. Most individuals from the low exposure group would not have been included in the present study due to insufficient amphetamine use. Not inconsistent with the present findings, no volumetric differences between the low exposure and control groups were detected. The older experienced users (mean age 26.6 years old; standard deviation of ± 7.17 years) in the Daumann et al. study consumed larger quantities of MDMA and amphetamine over significantly longer periods to a degree that would be more similar to subjects described in the literature on chronic cocaine and ATS use than to the present study. Indeed, like most volumetric studies on chronic cocaine and ATS use (Mackey and Paulus, 2013), Daumann et al. observed several regions of significantly lower cortical volume, including the vmPFC, relative to ATS-naïve controls. A re-analysis of the same data presented by Daumann et al. provides a parallel set of results with regard to

cortical thickness (Koester et al., 2012). Taken together, these studies are not inconsistent with the present findings and suggest that it may be worthwhile to examine the volumetric effects of recreational MDMA separately from oral prescription ATS and cocaine.

In the following paragraphs, the anatomical connections between the anterior striatum, vmPFC and mid-insula as well as evidence supporting their role in decision-making processes related to stimulant use are considered. Occasional ATS and cocaine users exhibited greater grey matter volume in the most anterior part of the putamen encroaching both on the ventral (limbic) striatum, which is ventral to the internal capsule, and the associative striatum located in the putamen rostral to the anterior commissure but slightly lateral and dorsal to the ventral striatum (Haber and Knutson, 2010). In the macaque, both striatal regions receive projections from the amygdala and hippocampus while more segregated inputs arrive at the limbic striatum from the vmPFC and from the lateral orbitofrontal and dorsal cingulate cortex in the associative striatum. Importantly, there is also a projection from the middle part of the insula to the anterior putamen (Chikama et al., 1997).

The cluster peak in the ventromedial prefrontal cortex related to greater lifetime ATS and cocaine consumption was located in area 32 anterior to the genu of the corpus callosum (Figure 2). The cluster extended ventrally where, especially under a relaxed threshold, it also included a large portion of area 14m (Mackey and Petrides, 2010). The locations of these findings are significant because of evidence suggesting that the transition from occasional drug use to dependence is represented at the neural level by a shift from frontal cortical and ventral striatal processing during initial drug experimentation to more dorsal striatal processing when drug-seeking becomes compulsive (Everitt et al., 2008). Relevant findings have been reported in macaques allowed to self-administer cocaine (Porrino et al., 2004). During a period of exposure to cocaine similar to the level of occasional use in the present study, significant decreases in glucose utilization as measured by autoradiography spread from the medial striatum to more lateral and dorsal parts of the anterior striatum overlapping the anatomically comparable anterior ventral part of the putamen identified here in human subjects (Figure 1). In the cortex, decreased glucose utilization was restricted during the initial stages of cocaine exposure to the vmPFC before progressing to other parts of the frontal lobe (Porrino et al., 2007).

The volume of the left mid-insula was also correlated with lifetime amount of ATS use (Figure 3). In the primate brain, the mid-insula region sends a projection to the putamen at the location of the ROI identified in this study suggesting that these regions are functionally related (Chikama et al., 1997). Moreover, in the present data the volume of the mid-insula was significantly correlated with the volume of the identified vmPFC ROI within individuals. Anatomical and functional investigations indicate that the insula is located at the center of a network of brain structures involved in the perception and regulation of the internal state of the body (Craig, 2002). It has been hypothesized that altered perception of the bodily state may motivate drug consumption as a maladaptive response to anticipated challenges to physiological homeostasis (Paulus et al., 2009). Naqvi and colleagues found in a sample of brain lesioned patients that a majority of individuals with lesions involving the insular cortex, but not other parts of the brain, who had a prior addiction to cigarette smoking, lost the urge to smoke and were able to stop smoking easily and without relapse following damage to the insula (Naqvi et al., 2007). In rats also, amphetamine-conditioned place preference can be disrupted by transient chemical lesions of the insula (Contreras et al., 2007). Although cause and effect cannot be determined due to the cross-sectional design of the present study, greater insula volume in those who have consumed more ATS and cocaine, may be related to nascent drug urges that, to some extent, drive use in young occasional non-dependent users after initial exposure.

There have been relatively few reports of lower grey matter volume in the cerebellum, or parietal and occipital lobes in association with ATS and cocaine use (Mackey and Paulus, 2013). In addition, the automated segmentation of the brain from surrounding tissue performed during this study was often questionable near the falx cerebri in the region of the occipital pole and the cerebellum which would suggest caution with regard to findings in this region. The parietal ROI is perhaps the most interesting of these three because of corollary evidence provided by other neuroimaging modalities suggesting a role in substance abuse (Barros-Loscertales et al., 2011; Chang et al., 2002; Garavan et al., 2000; Paulus et al., 2005; Volkow et al., 2001). Functional disruption of the parietal cortex in ATS and cocaine users may mediate a decline in cognitive control over behavior that increases the risk of dependence (Paulus et al., 2003).

The interpretation of the present study is limited by several factors. First, since the study is cross-sectional, it cannot be determined whether volume effects are, directly or indirectly, a cause or result of drug-taking behavior. Second, the effects of specific substances cannot be isolated statistically from other drug-taking behavior (see Miller and Chapman, 2001). Consequently, a regression that attempts to “control” for different substances by including them as covariates should be approached with care. While a study could be performed to select subjects who use a single substance and excludes use of all others (e.g., selecting subjects that exclusively use cocaine but not ATS, alcohol or nicotine, etc.), the extrapolation of findings to the general population where polysubstance use is the norm would be problematic. Third, tissue segmentation in the posterior part of the brain near the falx cerebri in the occipital and cerebellar regions was frequently incomplete. For this reason, volumetric findings in the occipital cortex and cerebellum in the present study should be interpreted cautiously. Fourth, this study did not directly measure brain function. While it is an important exercise to speculate how the present findings may be related to brain function and behavior, further study would be required to test such hypotheses. Moreover, the volumetric effects associated with ATS/cocaine use were not directly related to other behavioral and personality measures (e.g., BIS or SSS) obtained during the study which may have further elucidated the significance of these results.

In summary, several areas were identified that either distinguish occasional ATS and cocaine users from naïve controls (anterior putamen and inferior parietal cortex) or correlate with the lifetime amount of ATS and cocaine use (insula and ventromedial frontal cortex). Interestingly, multiple volumetric studies have found higher volume in the striatum (e.g., Chang et al., 2005; Jernigan et al., 2005; Ersche et al., 2011) and lower volumes in the insula (e.g., Franklin et al., 2002; Barros-Loscertales et al., 2011; Ersche et al., 2011; Nakama et al., 2011; Connolly et al., 2013) and the vmPFC (e.g., Alia-Klein et al., 2011; Daumann et al., 2011; Ersche et al., 2011; Hanlon et al., 2011) in chronic ATS and cocaine users compared to controls (reviewed in Mackey and Paulus, 2013). Unlike these findings on chronic use, the present study in younger college-aged occasional users found grey matter volumes in the vmPFC and insula were positively correlated with total amount of ATS and cocaine consumed. This contrasts with a well documented age-related decline in grey matter volume in the healthy developing brain, suggesting that grey matter development may be delayed in young occasional ATS and cocaine users. The present results support the existence of a network of brain regions that warrant further investigation by longitudinally designed studies to determine whether patterns of regional brain volume can be used to predict individuals at risk of transitioning from occasional use to dependence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Coronal (A), axial (B) and sagittal (C) sections demonstrating the location of the region of higher grey matter volume in the left anterior ventral putamen of young occasional users of ATS and cocaine compared to controls.

Figure 2. Coronal (A), axial (B) and sagittal (C) sections illustrating the region in the right ventromedial prefrontal cortex in which grey matter volume is significantly correlated with combined ATS and cocaine use in the user group alone.

Figure 3. Coronal (A), axial (B) and sagittal (C) sections illustrating the region in the left mid-insula in which cortical grey matter volume is significantly correlated with prescription ATS use (i.e. amphetamine, methamphetamine, methylphenidate) in the user group alone.

Table 1**Demographics, Substance Use, and Behavior**

Demographics	Users N=165	Controls N=46	Statistical Tests
Age (years)	20.85±1.52	21.02±2.17	-0.62
Race/Ethnicity			
White – Not Hispanic origin	111	28	
Hispanic	14	1	
Asian/Asian American	19	8	10.14
Pacific Islander	1	3	
African/African American	2	1	
Other	17	5	
Sex (male/female)	101/64	21/25	3.57
Education (years)	14.59±1.32	14.52±1.41	0.30
Verbal IQ	109.0 (7.3)	110.3(6.7)	-1.1
Substance Use Characteristics			
Prescription stimulants	24.5 (63.6)	--	--
Onset Age	18.6 (2.0)	--	--
Cocaine	21.4(36.8)	--	--
Onset Age	18.8(1.7)	--	-
MDMA	3.1(5.1)	--	--
Onset Age	19.0(1.7)	--	--
Marijuana	897.6 (1391.1)	66.5 (147.0)	4.3 ***
Alcoholic drinks in a typical week	19.7 (14.9)	4.6 (3.3)	5.8 ***
Cigarettes smoked in a typical week	17.3 (30.7)	6.0 (28.3)	2.3 **

Substance use amount represents number of distinct sessions with the exception of alcohol and nicotine. Reported substance use characteristics are obtained in the SSAGA interview. Brackets indicate standard deviation; all statistical tests are t-tests (df=209) except for race and sex which are χ^2 (df=5 and 1, respectively);

* = $p < 0.05$,

** = $p < 0.01$, and

*** = $p < 0.001$.

Table 2

Behavior	Users N=165	Controls N=46	t-value
Barratt Impulsiveness Scale (BIS) Total	65.5 (9.5)	60.2 (6.7)	3.5 *
Attention	10.8 (2.6)	9.7 (2.3)	2.6
Motor	16.3 (3.2)	14.5 (2.6)	3.6 *
Self Control	13.1 (2.8)	12.6 (2.3)	2.1
Cognitive Complexity	11.6 (2.2)	10.9 (1.9)	1.8
Perseverance	7.7 (1.9)	6.9 (1.7)	2.4
Cognitive Instability	6.1 (1.6)	6.0 (1.9)	0.2
Sensation-Seeking Scale (SSS) Total	25.2 (4.6)	19.6 (6.4)	6.7 *
Thrill and Adventure Seeking	8.0 (1.8)	7.5 (2.4)	1.3
Experience Seeking	6.7 (1.7)	5.2 (1.9)	5.2 *
Disinhibition	7.0 (2.1)	4.0 (2.9)	7.8 *
Boredom Susceptibility	3.5 (2.0)	2.9 (1.9)	1.9
Beck Depression Inventory	2.6 (3.5)	1.5 (2.5)	1.9

Brackets indicate standard deviation; all statistical tests are t-tests (df=209) Statistical threshold adjusted by Bonferroni correction for multiple comparisons,

* = p<0.004.

Table 3

Cluster Size and Peak Voxel Coordinates

Brain Region	Coordinates			Size (μL)
	X	Y	Z	
Analysis 1: LME Comparison Users (N=165) V. Controls (N=46)				
1 R. Dorsolateral Cerebellum (Pyramis)	23	−67	−29	6744
2 R. Inferior Parietal Cortex	49	−37	53	1528
3 L. Anterior Ventral	−23	15	−1	1368
Analysis 2: Robust Regression Lifetime Use of ATS and Cocaine in Users				
1 R. Dorsal Cerebellum (Declive)	20	−87	−24	3136
2 R. Ventromedial Frontal Cortex	9	42	14	1968
3 L. Postcentral Gyrus	−38	−25	49	1232
Analysis 3: Robust Regression Lifetime Use of Prescription ATS (i.e. amphetamine, methamphetamine, methylphenidate) in Users with Lifetime Use of Cocaine and MDMA as covariates				
1 L. Mid Insular Cortex	−38	5	4	2352
2 R. Occipital Polar Cortex	20	−93	−16	1616

Brain coordinates are in Talairach space, LPI.