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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-naive 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 mid-insula. 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.



## 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 et al. (2007) estimated 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

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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 h 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 min before scanning may produce apparent decreases in cortical volume on $T_1$-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)

**Table 1**

| 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 $X^2$ (df = 5 and 1, respectively).
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

### 2.2. MRI acquisition and voxel-based morphometry

A high resolution, $T_1$-weighted, anatomical brain scan (spoiled gradient recalled (SPGR), TR = 8 ms, TE = 3 ms, FOV = 25 cm, approximately 1 $mm^3$ 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.,