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Abnormal Striatal Circuitry and Intensified Novelty Seeking Among Adolescents that Abuse Methamphetamine and Cannabis

John C. Churchwell^{1,2}, Paul D. Carey³, Helen L. Ferrett³, Dan J. Stein³, and Deborah A. Yurgelun-Todd^{1,2}

¹The Brain Institute, University of Utah, Salt Lake City, UT, 84105

²Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT, 84105

³Department of Psychiatry, University of Stellenbosch, Tygerberg, South Africa, 7505

Abstract

It has been hypothesized that changes in striatal-mediated dopamine modulation during adolescence may increase risk for initiating substance abuse as a result of its fundamental role in arbitrating reward sensitivity and motivation during learning and decision making. However, substance abuse during adolescence may also significantly modify striatal structure and function and concomitantly alter reward sensitivity and action control while this brain region is undergoing remodeling. In the present investigation, to assess the relationship of methamphetamine or methamphetamine and cannabis abuse to regional striatal morphology, we acquired structural magnetic resonance images (MRI), using a 3T Siemens Trio scanner, from three groups of adolescents composed of healthy controls (N=10), methamphetamine abusers (Meth, N=9), and combined methamphetamine and cannabis abusers (Meth+CA, N=8). We also assessed novelty seeking using the novelty seeking subscale from Cloninger's Tridimensional Character Inventory. The results indicate that adolescent Meth+CA abusers have increased regional striatal volume and show intensified novelty seeking in contrast to controls. Degree of Meth exposure was also positively correlated with regional striatal volume and novelty seeking in both Meth and Meth+CA users. These preliminary findings support theories that propose a role for the striatum in adolescent substance abuse and further indicate that novelty seeking may be related to initiation or sustained drug use.

Keywords

Adolescence; Methamphetamine; Cannabis; MRI; Striatum; Novelty Seeking

Introduction

Worldwide, Methamphetamine (Meth) and cannabis (CA) are extensively abused. According to the United Nations Office on Drugs and Crime World Drug Report [1], it is estimated that there were between 13.7 and 52.9 million individuals to use amphetamine-type substances in the previous year, while CA remains the most prevalently abused substance globally with an estimated 129 to 191 million users. Adolescents may be at greater risk for establishing substance abuse behaviors than adults, as individuals with early

onset of substance use, including CA and psychostimulant use, are more likely to become drug dependent [2]. Preclinical models indicate that adolescents are more responsive to the rewarding effects of abused substances [for review, see 3] and CA abuse may specifically increase risk for using a range of illicit substances including psychostimulants [4].

Adolescents may be especially susceptible to initiating substance abuse behaviors due to neurodevelopmental changes occurring in brain regions involved in reward perception, goal-directed behavior, and habit formation such as the striatum (STR). There is evidence that STR plasticity is enhanced during adolescence as both cannabinoid [5] and dopamine (DA) receptor availability in the STR peak during adolescence [6]. Thus, changes in the STR may contribute to initiation of substance abuse behaviors. However, abuse of substances that affect STR DA and cannabinoid systems during a period of enhanced plasticity may contribute to an increased risk for progression to drug dependence [7].

Novelty preference also peaks during adolescence and may be an important trait related to initiating and maintaining substance abuse behaviors [8-10]. It has been proposed that individual differences in both novelty seeking (NS) and drug abuse are mediated by the mesolimbic DA system [for review, see 11]. Consistent with this view, NS has been associated with DA [12] and cannabinoid [13] receptor availability in the STR. Both amphetamine and CA also appear to be capable of modulating DA release in the STR [14, 15]. Moreover, NS during middle school predicts rate of increase in CA use during high school [16] and preclinical research has shown that responsiveness to novelty is related to self-administration of amphetamine [17].

There have been intense efforts to understand the relationship of Meth and CA abuse to structural, functional, and metabolic changes in the human brain [18, 19]. Several lines of evidence indicate that CA abuse is related to changes in the STR. For example, a positron emission tomography (PET) study showed that Δ^9 -tetrahydrocannabinol (THC), the main psychoactive component in CA, increases DA release in the STR [14]. A separate PET study found decreased glucose metabolism in the putamen of a small sample of recently abstinent cannabis users aged 18-21 [20]. Moreover, evidence from functional magnetic resonance imaging (fMRI) studies have shown altered reward signaling in the STR of CA users during probabilistic decision tasks [21, 22]. Abnormalities in the striatum of Meth users have also been observed using a range of neuroimaging techniques [see 19, 23]. For example, alterations in neurotransmitter systems such as reduced density of STR vesicular monoamine [24], reduced dopamine transporter [25, 26], and reduced dopamine receptor availability in the caudate and putamen of adult Meth users has been reported [27]. Altered STR BOLD response in the caudate and putamen of adult Meth users has also been observed during completion of a delay discounting procedure [28]. In terms of morphology, specific evidence for volumetric increases in the accumbens, caudate, and putamen of adult Meth users relative to controls has been demonstrated [29, 30] and preclinical evidence indicates that a single high dose of Meth can lead to increased STR volume [31]. Relative to individuals solely using Meth, Meth+CA abusers show STR metabolic abnormalities [32]. However, neuroimaging studies examining the relationship of abnormal STR circuitry to Meth and Meth+CA abuse in adolescents is lacking.

In summary, both STR DA and STR cannabinoid receptor density peak during adolescence. Both Meth and CA abuse have been associated with altered STR function, and Meth abuse has been specifically associated with increased regional STR volume. There is also evidence that individuals who abuse Meth+CA have abnormal STR function compared to those that solely abuse Meth. Lastly, STR DA and cannabinoid receptor availability correlate with NS, which peaks during adolescence, as does vulnerability to drugs use.

We hypothesized that Meth use would be related to increased STR volume and that this effect would be exacerbated in Meth+CA users. We also hypothesized that Meth and Meth+CA users would show increased levels of self-reported NS relative to controls. Lastly, we expected that self-reported NS and STR volume would be associated with degree of drug exposure. To test these hypotheses we acquired structural MRIs from a group of healthy controls, Meth abusers, and combined Meth and CA abusers. We used quantitative volumetric analysis to assess STR morphology using regions of interest (ROI) in the accumbens, caudate, and putamen, as enlargement in these regions have previously been observed in Meth abusers and preclinical models [29-31]. Novelty Seeking was determined using a self-report inventory [33].

Methods

Procedure

The University of Stellenbosch institutional review board approved the study. All participants read the informed consent and assented to participate in the study. Parents were required to consent for participants less than 18 years of age. In order to clarify diagnostic status and determine drug use history abuse/dependence status, all participants were interviewed using the Schedule for Affective Disorders and Schizophrenia for School Aged Children (6–18 years) Lifetime Version [K-SADS-PL; 34], a semi-structured clinical diagnostic interview based on DSM-IV criteria [See Table 1; 35]. All subjects in the Meth group met criterion for Meth abuse/dependence and all subjects in the Meth+CA group met criterion for both Meth and CA abuse/dependence. None of the participants met criterion for, nicotine, or alcohol abuse/dependence. Novelty seeking was assessed using the Novelty Seeking Scale from Cloninger's Tridimensional Character Inventory [33].

MRI Acquisition

Structural images were acquired with a Siemens 3-T Trio magnet using a 12-channel head coil and T-1 weighted 3D MPRAGE sequence. Acquisition parameters were as follows: field of view 256 mm, TR 3 m sec, TE 3.38 m sec, flip angle 8°, and 1 mm slice thickness.

Image Analysis

Analyses were completed using the standard FreeSurfer processing stream (<http://surfer.nmr.mgh.harvard.edu/>). The following workflow procedures were used for the standard analysis. High-resolution T1 MPRAGE volumes in DICOM format were anonymized and imported into the FreeSurfer image analysis environment. Semi-automated methods employing the default surface-based and volume-based pipelines were used. Processing included registration with the Talairach and Tournoux atlas, intensity normalization, skull stripping, segmentation of white and deep gray matter volumetric structures, gray and white matter boundary tessellation, and intensity normalization [36-38]. Cortical white matter surfaces were used in a deformation procedure that assigns gray and white matter borders by following intensity gradients to the position at which the maximum shift in intensity designates the transition to the other tissue class [39]. Several deformation procedures including inflation, spherical registration, and cortical parcellation were performed [40]. An automated registration procedure was used to label each voxel in a MRI volume based on probabilities estimated from a manually labeled training set [41]. Standard predefined (ROI) labels in STR subregions (caudate, accumbens, and putamen; (Fig. 1) were used in the final statistical analysis. After image processing was completed, volume data for ROIs were extracted from the image analysis environment, adjusted for total segmented brain volume, and submitted to statistical analysis.

An Analysis of Variance (ANOVA) was conducted to assess changes between groups associated with Meth or Meth+CA abuse on STR subregional volumes, as well as group differences in NS. One-tailed Pearson's correlations were used to evaluate the relationships between STR subregions and estimated lifetime doses of Meth, in addition to self-reported NS.

Data Reduction

Adjusted volumes for the ROIs were obtained by taking the ratio of regional (ROI) to total segmented brain volume for each subject and multiplying the obtained quotient by 100 (see Table 2). Total segmented brain volumes included all brain regions identified in FreeSurfer aseg.mgz, BrainSegVol, which excludes the dura but includes the cerebellum and ventricles.

Results

Our analyses indicated a significant difference between groups for left putamen volume $F(2, 24) = 4.94, p < 0.02$ and NS $F(2, 24) = 3.56, p < 0.04$. Specifically, Tukey's HSD post-hoc tests found a significant difference between controls and Meth+CA users (0.05 level of significance) for left putamen volume and NS. Inspection of the mean values for these tests indicated that Meth+CA users had greater left putamen volume and higher levels of self-reported NS than controls (Fig 2. and Fig. 3). A significant positive relationship was seen between lifetime doses of Meth and left putamen volume for the combined groups $r(17) = 0.63, p < 0.01$, an association which persisted for the Meth using group $r(9) = 0.56, p = 0.05$ and Meth+CA group $r(8) = 0.65, p = 0.04$, when considered separately (Fig. 3). Similarly, there was a significant positive relationship between lifetime doses of Meth and NS when both drug-using groups were considered collectively $r(17) = 0.39, p = .05$ (Fig. 4). When analyzed separately, lifetime doses of Meth was positively correlated with NS in the Meth group $r(9) = 0.64, p < 0.03$, whereas in the Meth+CA group the correlation between lifetime doses of Meth and NS was not apparent $r(8) = -0.16, p > 0.47$. However, visual inspection of the data revealed a potential outlier in the Meth+CA group. When the data were analyzed excluding this subject, a positive correlation approached, but still did not reach significance $r(8) = 0.57, p = 0.08$. Finally, we assessed whether the left putamen volume was correlated with NS and found no significant effects for the combined group or separate group analyses ($p > 0.05$).

Discussion

There is limited evidence to date assessing the relationship of Meth or Meth+CA to structural brain development of reward systems and novelty seeking. The present investigation used quantitative morphometric analysis to determine regional striatal differences among healthy controls, Meth, and Meth+CA abusing adolescents. We hypothesized that adolescents Meth users would have increased STR volume in contrast to controls and that these changes would be exacerbated in Meth+CA users. We also hypothesized that Meth and Meth+CA users would show increased levels of self-reported NS relative to controls. The current results provide evidence that adolescents who use Meth and CA in combination have increased left putamen volume relative to controls. The results also show a strong positive relationship between the number of lifetime doses of Meth and left putamen volume in subjects that either used Meth alone or in combination with CA, suggesting that Meth may be primarily responsible for the observed volumetric changes or that factors related to volume in this region encourage Meth use. In addition, adolescents that abused both Meth and CA reported significantly greater NS in contrast to controls. Novelty seeking significantly correlated with lifetime doses of Meth when both Meth and Meth+CA groups were combined. However, the relationship between Meth+CA abuse and NS only showed a trend towards significance when the Meth+CA group was analyzed

separately. The significant correlation between lifetime doses of Meth and NS was preserved for subjects that solely abused Meth.

Investigations using a range of neuroimaging techniques have shown the STR to be altered in adult Meth users, which included increases in accumbens, caudate, and putamen volume [29, 30]. Further, a PET study conducted using non-human primates found that the correlation between amphetamine dose and change in [^{11}C]raclopride binding, which is indicative of increased DA release, was most significant in the putamen, among several STR regions assessed [15]. Congruent with these findings, young adult stimulant users (age 18-25) were shown to have increased functional activation in the STR during the uncertainty condition of a card prediction task and also were found to be more impulsive [42]. Thus, NS, or response to novelty, may be importantly related to adolescent CA abuse and the transition to other abused substances such as Meth.

Cannabis use has been associated with neurochemical and functional changes in the STR. For example, acute administration of THC reduces [^{11}C]raclopride binding in both ventral striatum and the dorsal putamen in human subjects [14] and facilitates release of DA in the dorsolateral striatum of rats [43]. Metabolic changes in the STR of cannabis users have also been observed. For example, a PET study found decreased glucose metabolism in the putamen of a small sample of recently abstinent cannabis users aged 18-21 [20]. fMRI studies have also shown altered STR activity in adult CA users during completion of reward tasks [21, 22].

It has been reported that CA is the most commonly used secondary illicit drug of abuse among Meth users [44]. Although the development of Meth abuse behavior is complex and likely linked to a variety of factors [45], early initiation of CA abuse has been associated with increased risk for using stimulants and other drugs of abuse [4, 46]. Sequential and common factor models may account for the relationship between CA and abuse of other drugs [47], but preclinical models suggest that exposure to cannabinoid agonists induces behavioral sensitization to amphetamine [48]. Further, adolescent, but not adult, animals pretreated with cannabinoid agonists show an enhanced DA neuronal response in the ventral tegmental area to amphetamine [49]. Investigation of Meth and Meth+CA abuse using PET techniques suggest that combined use of these drugs is related to reduced STR metabolism during completion of a continuous performance task, indicating that simultaneous abuse of these drugs may be linked to altered STR function that exceeds what is found in individuals that abuse Meth alone [32].

High levels of motivation for NS during adolescence is thought to result from increased or decreased response to anticipation and consumption of rewards mediated by the striatum [50-52]. This hypothesis has implications for understanding the initiation of substance abuse during adolescence, as reduced or enhanced experience of reward following drug use may escalate drug-taking behavior. Conversely, there is evidence from preclinical models to suggest that Meth treatment induces sensitization of DA release in the STR of adolescents, but not adults [53]. Meth treatment also enhances NS in adolescents, but not adults [54], indicating that Meth abuse during adolescence may exert a specific influence on the STR DA systems that increases NS. Further, in a large sample of college-aged CA users, it was found that as frequency of CA use increased NS also increased [55]. Although the direction of influence among drug abuse, neurodevelopment, and NS is unclear, it is possible that these factors may reciprocally influence each other [10].

Evidence from preclinical studies have demonstrated a distinct trajectory of dopaminergic (D_1 and D_2) synaptogenesis and pruning in the dorsal striatum during the peripubertal period, with a marked increase in DA receptors at adolescence and reductions from

adolescence into early adulthood. This pattern was not mirrored in the ventral striatum where DA receptor density peaked during the periadolescent period but remained flat following the peak [56]. In a preclinical model of CA and amphetamine exposure, it was shown that treatment with either substance results in altered STR dendritic morphology, though these changes were observed in the accumbens, the only STR region examined [57, 58]. It is also noteworthy that activated microglial density is significantly greater in the STR of Meth abusers than in healthy controls, as indicated by [11C](R)-PK11195 binding potential [59]. This study suggests that alterations in microglial density are related to the neurotoxic effects of Meth and it has been proposed that abnormal striatal volumes observed in Meth users is a consequence of this cellular change [19]. There is relatively little data relating DA function to STR morphology. However, analysis of STR volume prior to and following modulation of DA function using a D₂ receptor antagonist in healthy human subjects indicated that pharmacological challenge can induce immediate and detectable volumetric changes in the STR that correlate with motor disturbances [60]. These findings were interpreted as demonstrating a relationship between STR volumetric measures, DA function, and action control. Consistent with this finding, a preclinical study showed that a single high dose of Meth could induce increased STR volume, which returned to pretreatment levels 8-12 weeks later [31]. Thus, modulation of DA function through substance abuse activity, while the STR is still undergoing development, may lead to alterations in this region that are sustained and detectable with quantitative morphometric neuroimaging techniques.

In summary, adolescence is a time of notable neurodevelopmental susceptibility to the influence of substance abuse and the STR is a crucial component within a neural network involved in drug exposure risk. This study found altered STR morphology and intensified NS in adolescents that abuse Meth+CA in contrast to controls, and further showed a relationship between the degree of Meth exposure and putamen volume in subjects that abuse Meth or Meth+CA. The results also demonstrate a relationship between NS and degree of Meth exposure. These preliminary findings support theories that propose a role for the STR in adolescent substance abuse and further indicate a possible role for NS related to initiation or sustained drug use. However, future studies utilizing larger sample sizes and longitudinal study designs are needed to confirm and extend these initial findings.

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Figure 1.

Shows the anterior view of the whole brain in a single subject that abused methamphetamine and cannabis. The left hemisphere shows a semi-transparent cortical gray matter surface superimposed over a 3-D rendering of regions of interest in the striatum, including the caudate in yellow, putamen in green, and accumbens in red.

Figure 2.

Shows mean corrected values for left putamen volume in controls, methamphetamine users (Meth), and methamphetamine and cannabis users (Meth+CA). A significant difference between groups was observed $F(2, 24) = 4.94$, $p < 0.02$ for left putamen volume and post-hoc tests demonstrated a significant difference between controls and Meth+CA users at the 0.05 level of significance.

Figure 3.

Shows mean NS scores in controls, methamphetamine users (Meth), and methamphetamine and cannabis users (Meth+CA). A significant difference between groups was observed for NS $F(2, 24) = 3.56$, $p < 0.04$ and post-hoc tests demonstrated a significant difference between controls and Meth+CA users at the 0.05 level of significance.

Figure 4.

Shows correlation between lifetime doses of methamphetamine and left putamen volume for both methamphetamine (Meth) and methamphetamine+cannabis (Meth+CA) users. For the combined groups, $r(17) = 0.63$, $p < 0.01$. When groups were analysed separately, Meth $r(9) = 0.56$, $p = 0.05$ and Meth+CA group $r(8) = 0.65$, $p = 0.04$.

Figure 5.

Shows correlation between lifetime doses of methamphetamine and NS for both methamphetamine (Meth) and methamphetamine+cannabis (Meth+CA) users. For the combined groups $r(17) = 0.39$, $p = .05$. When groups were analysed separately, Meth $r(9) = 0.64$, $p < 0.03$ and Meth+CA $r(7) = 0.57$, $p = 0.08$.

Table 1

Demographic and clinical characteristics of adolescent controls, methamphetamine (Meth) users, and methamphetamine and cannabis (Meth+CA) users.

	Controls (n=10)	Meth (n=9)	Meth+CA (n=8)
Female (%)	70.0	62.5	62.5
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	15.65 (1.48)	15.60 (1.43)	16.20 (1.15)
Right Hand Dominant (%)	100	100	100
HAM-D ¹	1.30 (1.33)	3.33 (1.41)	3.75 (4.09)
HAM-A ²	2.10 (1.19)	3.44 (1.67)	5.0 (3.25)
Alcohol Use (%)	50	55.60	75
Age of First Alcohol Use (years)	13.25 (1.92)	10.8 (6.0)	12.54 (5.65)
Nicotine Use (%)	40	88.9	87.5
Age of First Nicotine Use (years)	14.41 (1.19)	12.60 (2.38)	13.64 (1.10)
Age of First Meth Use (years)	-	13.42 (1.34)	13.90 (1.38)
Age of Regular Meth Use (years)	-	14.18 (1.37)	14.09 (1.40)
Duration of Meth use (months)	-	21.67 (12.46)	22.00 (10.29)
Meth Average Frequency (days per month)	-	12.56 (8.96)	13.50 (7.61)
Meth Average Daily Quantity (units per day)	-	2.33 (1.18)	2.88 (0.35)
Meth Estimated Lifetime Doses	-	579.33 (542.80)	837.00 (531.369)
Cannabis Use (%)	10	66.66	100
Age of First Cannabis Use (years)	15 (0.00)	14.13 (1.41)	13.78 (1.32)
Age of First Regular Cannabis Use (years)	-	-	14.00 (1.37)
Duration of Cannabis use (months)	-	-	26.50 (10.21)
Cannabis Average Frequency (days per month)	-	-	13.63 (8.34)
Cannabis Average Daily Quantity (units per day)	-	-	2.88 (1.45)
Cannabis Estimated Lifetime Doses	0.10 (0.32)	6.33 (5.32)	1099.13 (865.66)

¹ Hamilton Rating Scale for Depression

² Hamilton Rating Scale for Anxiety

* SD = Standard Deviation

Table 2

Regional striatal volumes for controls, methamphetamine users (Meth), and methamphetamine+cannabis (Meth+CA) users.

	Controls (n=10)	Meth (n=9)	Meth+CA (n=8)
	Mean (SD)	Mean (SD)	Mean (SD)
Left Accumbens	0.042 (0.002)	0.042 (0.006)	0.043 (0.011)
Right Accumbens	0.048 (0.004)	0.049 (0.005)	0.049 (0.007)
Left Caudate	0.294 (0.038)	0.306 (0.036)	0.316 (0.029)
Right Caudate	0.298 (0.043)	0.318 (0.039)	0.315 (0.023)
Left Putamen	0.456 (0.045)	0.486 (0.025)	0.507 (0.025)
Right Putamen	0.456 (0.047)	0.487 (0.024)	0.479 (0.023)