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Abnormal Striatal Circuitry and Intensified Novelty Seeking among Adolescents Who Abuse Methamphetamine and Cannabis

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Key Words
Adolescence · Methamphetamine · Cannabis · Magnetic resonance imaging · Striatum · Novelty seeking

Abstract
It has been hypothesized that changes in striatal-mediated dopamine modulation during adolescence may increase the 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 (Meth) or Meth and cannabis (CA) abuse to regional striatal morphology, we acquired structural magnetic resonance images, using a 3T Siemens Trio scanner, from three groups of adolescents composed of healthy controls (n = 10), Meth abusers (n = 9) and combined Meth and CA abusers (Meth+CA, n = 8). We also assessed novelty seeking using the novelty seeking subscale of 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 the controls. The degree of Meth exposure was also positively correlated with regional striatal volume and novelty seeking in both the 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 the initiation of, or sustained, drug use.

Introduction

Worldwide, methamphetamine (Meth) and cannabis (CA) are extensively abused. According to the United Nations Office on Drugs and Crime World Drug Report 2010 [1], it is estimated that there were between 13.7 and 52.9 million individuals using amphetamine-type substances in the previous year, while CA remains the most prevalently abused substance globally with an estimated 129–191 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

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abused substances [for review, see 3], and CA abuse may specifically increase the 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 the initiation of substance abuse behaviors. However, the 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 the rate of increase in CA use during high school [16], and preclinical research has shown that responsiveness to novelty is related to the 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, 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 CA users aged 18–21 [20]. Moreover, evidence from functional magnetic resonance imaging (MRI) studies have shown altered reward signaling in the STR of CA users during probabilistic decision tasks [21, 22]. Abnormalities in the STR 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 DA transporter [25, 26] and reduced DA receptor availability in the caudate and putamen of adult Meth users have been reported [27]. Altered STR BOLD response in the caudate and putamen of adult Meth users has also been observed during the 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 are 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 drug 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 the degree of drug exposure. To test these hypotheses we acquired structural MRIs from a group of healthy controls, Meth abusers and combined Meth+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]. NS was determined using a self-report inventory [33].

Methods

Procedure

The University of Stellenbosch institutional review board approved the study. All the 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 the participants were interviewed using the Schedule for Affective Disorders and Schizophrenia for School Aged Children (6–18 years) Lifetime Version [34], a semistructured clinical diagnostic interview based on DSM-IV criteria [35]

Table 1. Demographic and clinical characteristics of adolescent controls, Meth users and Meth+CA users

	Controls (n = 10)	Meth (n = 9)	Meth+CA (n = 8)
Female, %	70.0	62.5	62.5
Age, years	15.65 ± 1.48	15.60 ± 1.43	16.20 ± 1.15
Right hand dominant, %	100	100	100
HAM-D	1.30 ± 1.33	3.33 ± 1.41	3.75 ± 4.09
HAM-A	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
CA use, %	10	66.66	100
Age of first CA use, years	15 ± 0.00	14.13 ± 1.41	13.78 ± 1.32
Age of first regular CA use, years	–	–	14.00 ± 1.37
Duration of CA use, months	–	–	26.50 ± 10.21
CA average frequency, days per month	–	–	13.63 ± 8.34
CA average daily quantity, units per day	–	–	2.88 ± 1.45
CA estimated lifetime doses	0.10 ± 0.32	6.33 ± 5.32	1,099.13 ± 865.66

Data are expressed as means ± SD. HAM-D = Hamilton Rating Scale for Depression; HAM-A = Hamilton Rating Scale for Anxiety.

(see table 1). All the subjects in the Meth group met the criterion for Meth abuse/dependence and all the subjects in the Meth+CA group met the criterion for both Meth and CA abuse/dependence. None of the participants met the criterion for nicotine or alcohol abuse/dependence. NS was assessed using the novelty seeking scale of 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 a T_1-weighted 3D MPRAGE sequence. Acquisition parameters were as follows: field of view – 256 mm, TR – 3 ms, TE – 3.38 ms, flip angle – 8° and slice thickness – 1 mm.

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 T_1 MPRAGE volumes in DICOM format were anonymized and imported into the FreeSurfer image analysis environment. Semiautomated methods employing the default surface-based and volume-based pipelines were used. Processing included registration with the Talairach and Tornoux atlas, intensity normalization, skull stripping, segmentation of white and deep gray matter volumetric structures, gray and white matter boundary delineation, 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 an 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 was conducted to assess changes between the 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). The total segmented brain volumes included all brain regions identified in FreeSurfer aseg.mgz, BrainSegVol, which excludes the dura but includes the cerebellum and ventricles.

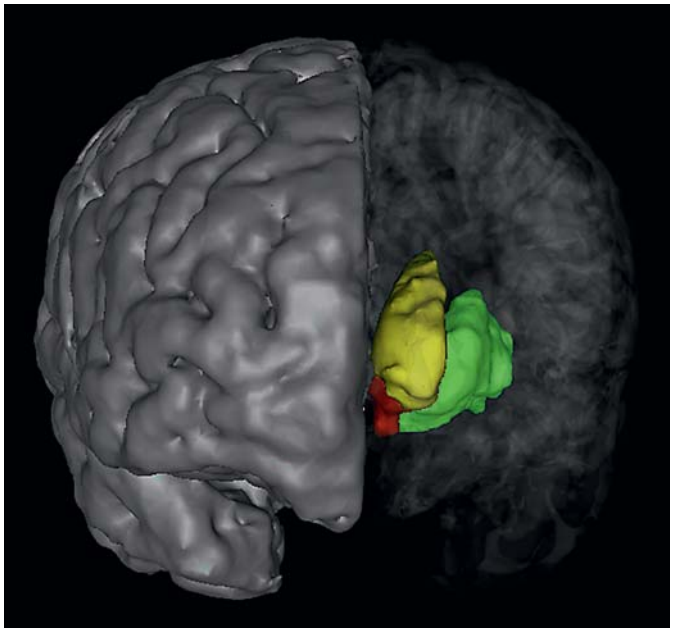

Fig. 1. Anterior view of the whole brain in a single subject who abused Meth+CA. The left hemisphere shows a semitransparent cortical gray matter surface superimposed over a 3-D rendering of ROIs in the STR, including the caudate in yellow, putamen in green, and accumbens in red.

Table 2. Regional striatal volumes for controls, Meth users and Meth+CA users

	Controls (n = 10)	Meth (n = 9)	Meth+CA (n = 8)
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 ± 0.02

Data are expressed as means ± SD.

Results

Our analyses indicated a significant difference between the 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 the controls and the Meth+CA users (level of significance 0.05) for left putamen volume and NS. Inspection of the mean values for these tests indicated that the Meth+CA users had larger left putamen volume and higher levels of self-reported NS than the controls (fig. 2, 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 group: $r(9) = 0.56$, $p = 0.05$ and the 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: $r(17) = 0.39$, $p = 0.05$ (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: $r(8) = 0.57$, $p = 0.08$ (fig. 5). 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 NS. The present investigation used quantitative morphometric analysis to determine regional striatal differences among healthy controls, Meth and Meth+CA adolescent users. We hypothesized that the adolescent Meth users would have increased STR volume in contrast to the controls and that these changes would be exacerbated in the Meth+CA users. We also hypothesized that the 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 the subjects who 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, the adolescents who abused both Meth and CA reported significantly greater NS in contrast to the controls. NS significantly correlated with life-

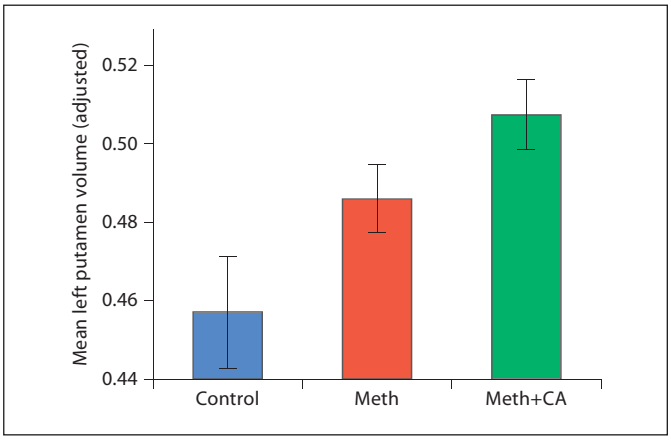

Fig. 2. Mean corrected values for left putamen volume in the control, Meth and Meth+CA groups. A significant difference between the groups was observed: $F(2, 24) = 4.94$, $p < 0.02$ for left putamen volume, and post hoc tests demonstrated a significant difference between controls and Meth+CA users at the 0.05 level of significance. Error bars +/– SE.

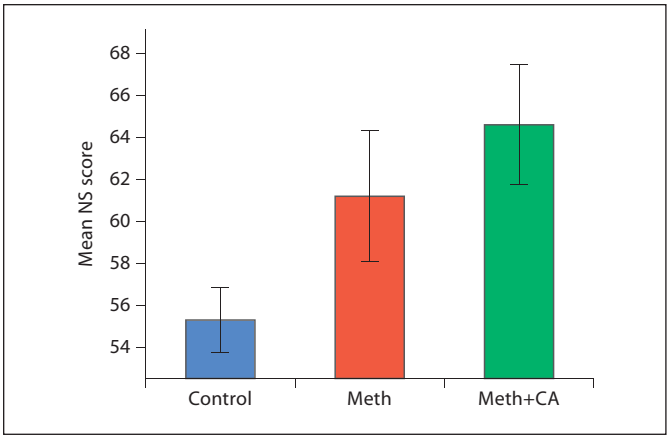

Fig. 3. Mean NS scores in the control, Meth and Meth+CA groups. A significant difference between the groups was observed for NS: $F(2, 24) = 3.56$, $p < 0.04$, and post hoc tests demonstrated a significant difference between controls and Meth+CA users at the 0.05 level of significance. Error bars +/– SE.

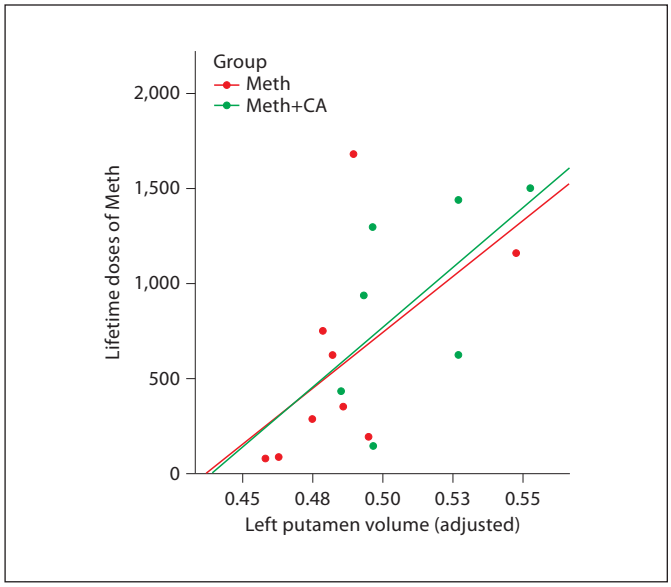

Fig. 4. Correlation between lifetime doses of Meth and left putamen volume for both Meth and Meth+CA users. For the combined groups, $r(17) = 0.63$, $p < 0.01$. When the groups were analyzed separately, Meth $r(9) = 0.56$, $p = 0.05$ and Meth+CA $r(8) = 0.65$, $p = 0.04$.

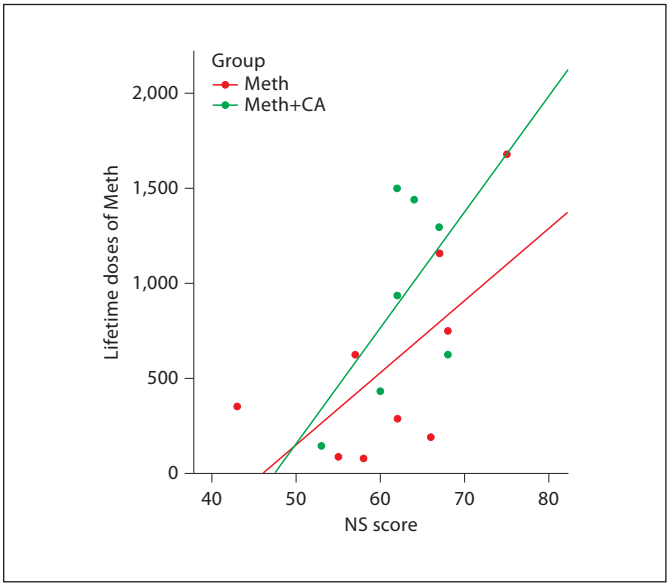

Fig. 5. Correlation between lifetime doses of Meth and NS for both Meth and Meth+CA users. For the combined groups, $r(17) = 0.39$, $p = 0.05$. When the groups were analyzed separately, Meth $r(9) = 0.64$, $p < 0.03$ and Meth+CA $r(8) = 0.57$, $p = 0.08$.

time doses of Meth when both the 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 the subjects who 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 the accumbens, cau-

date, 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 (aged 18–25) were shown to have increased functional activation in the STR during the uncertainty condition of a card prediction task and were also found to be more impulsive [42].

Cannabis use has been associated with neurochemical and functional changes in the STR. For example, acute administration of Δ^9-tetrahydrocannabinol reduces [^{11}C] raclopride binding in both ventral STR and the dorsal putamen in human subjects [14] and facilitates the release of DA in the dorsolateral STR of rats [43]. Metabolic changes in the STR of CA users have also been observed. For example, a PET study found decreased glucose metabolism in the putamen of a small sample of recently abstinent CA users aged 18–21 [20]. Functional MRI 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 the 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 to amphetamine in the ventral tegmental area [49]. Investigation of Meth and Meth+CA abuse using PET techniques suggests that the 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 an altered STR function which exceeds that found in individuals who abuse Meth alone [32].

High levels of motivation for NS during adolescence is thought to result from an increased or decreased response to anticipation and consumption of rewards mediated by the STR [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 in that of adults [53]. Meth treatment also enhances NS in adolescents but not in adults [54], indicating that Meth abuse during adolescence may exert a specific influence on the STR DA systems that increase NS. Further, in a large sample of college-aged CA users, it was found that as the 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 STR during the peripubertal period, with a marked increase in DA receptors at adolescence and a reduction from adolescence into early adulthood. This pattern was not mirrored in the ventral STR where DA receptor density peaked during the periadolescent period but remained level 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 [^{11}C]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 D_2 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 who abuse Meth+CA in contrast to controls, and further showed a relationship between the degree of Meth exposure and putamen volume in subjects who abuse Meth or Meth+CA. The results also demonstrate a relationship between NS and the 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 the initiation of, or sustained, drug use. However, future studies utilizing larger sample sizes and longitudinal study designs are needed to confirm and extend these initial findings.

Acknowledgements

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