Brain Advance Access published May 13, 2015

doi:10.1093/brain/awv113 BRAIN 2015: Page 1 of 13 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Smaller amygdala and medial prefrontal cortex predict escalating stimulant use

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Drug addiction is a chronic, relapsing brain disorder. The identification of biomarkers that render individuals vulnerable for the transition from occasional drug use to addiction is of key importance to develop early intervention strategies. The aim of the present study was to prospectively assess brain structural markers for escalating drug use in two independent samples of occasional amphetamine-type stimulant users. At baseline occasional users of amphetamine and 3,4-methylenedioxymethamphetamine (cumulative lifetime use $\leqslant$10 units) underwent structural brain imaging and were followed up at 12 months and 24 months (Study 1, $n = 38$; Study 2, $n = 28$). Structural vulnerability markers for escalating amphetamine-type drug use were examined by comparing baseline grey matter volumes of participants who increased use with those who maintained or reduced use during the follow-up period. Participants in both samples who subsequently increased amphetamine-type drugs use displayed smaller medial prefrontal cortex volumes and, additionally, in the basolateral amygdala (Study 1) and dorsal striatum (Study 2). In both samples the baseline volumes were significantly negatively correlated with stimulant use during the subsequent 12 and 24 months. Additional multiple regression analyses on the pooled data sets revealed some evidence of a compound-specific association between the baseline volume of the left basolateral amygdala and the subsequent use of amphetamine. These findings indicate that smaller brain volumes in fronto-striato-limbic regions implicated in impulsivity and decision-making might render an individual vulnerable for the transition from occasional to escalating amphetamine-type stimulant use.

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Keywords: vulnerability; brain structure; addiction; stimulant drugs; biomarker

Abbreviations: ATS = amphetamine-type stimulants; MDMA = 3,4-methylenedioxymethamphetamine; PFC = prefrontal cortex

Received November 3, 2014. Revised February 8, 2015. Accepted March 6, 2015.

Introduction

Amphetamine-type stimulants (ATSs) are the world's second most widely used illicit drugs and have become one of the most significant drug problems worldwide (UNODC, 2011). ATSs, which include amphetamine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA, also known as ecstasy), refer to a group of structurally similar psychoactive substances that exert their effects primarily through increasing the synaptic concentrations of monoamine neurotransmitters, including dopamine, serotonin and noradrenaline (de la Torre *et al.*, 2004; Sulzer *et al.*, 2005). ATSs are used by individuals across a wide socio-demographic range and for a variety of reasons. Patterns of ATS use can be correspondingly diverse, ranging from occasional to highly compulsive and dependent (EMCDDA, 2008). During recent years socially marginalized chronic users of methamphetamine have attracted considerable public and research interest. However, use of ATSs has become increasingly popular among socially well-integrated young adults to enhance cognitive performance and increase recreational well-being (Gouzoulis-Mayfrank and Daumann, 2009). The majority of these individuals occasionally use amphetamine and MDMA and never escalate to problematic use and dependence (Herman-Stahl *et al.*, 2007; Mackey and Paulus, 2013). Nevertheless, increasing numbers of ATS users seeking treatment for drug addiction suggest that a significant proportion of these occasional users will escalate their use and develop an addiction (UNODC, 2011).

Preclinical studies have provided compelling evidence of individual differences in the vulnerability to the transition to addiction (Everitt *et al.*, 2008; George and Koob, 2010). Both genetic (~50% risk) and environmental (e.g. drug availability, amount of previous drug use) factors are predictive of addiction risk (Brewer and Potenza, 2008). Recent animal models for the transition from occasional to escalating ATS use suggest that individual differences in limbic cortical-striatal brain circuits and associated functions predict the propensity to escalate drug use and develop addictive use patterns (Everitt *et al.*, 2008; George and Koob, 2010).

In line with these findings, human ATS users show profound structural and functional abnormalities in multiple brain regions, most notably in prefrontal, limbic and striatal regions (Ersche *et al.*, 2013*b*; Mackey and Paulus, 2013). However, previous studies in human users have used cross-sectional approaches focusing mostly on chronic ATS users and have numerous methodological problems, including retrospective designs and an absence of baseline data. Such studies are unable to resolve whether observed abnormalities represent addiction-related adaptations, neurotoxic drug effects, compensatory adjustments or predisposing alterations that render an individual vulnerable to the transition into ATS addiction. Given the individual and societal harm associated with problematic ATS use (Nutt *et al.*, 2007), and the lack of efficient treatment strategies for ATS addiction (van den Brink, 2012), it is of great importance to establish biological vulnerability markers, using prospective longitudinal designs in occasional ATS users, which can reliably identify individuals at greatest risk of developing an addiction (Berman *et al.*, 2008; Mackey and Paulus, 2013).

Against this background we prospectively assessed brain structural markers of an escalation in ATS use in two independent samples of occasional ATS users. At study inclusion participants had only recently begun using ATS and had not been exposed to substantial amounts (cumulative lifetime use $\leqslant$10 units of amphetamine and/or MDMA). After enrolment, brain structural MRI data and a comprehensive set of potential confounders, including previous substance use, neurocognitive performance and psychological distress were assessed (baseline). Participants were then followed-up to assess drug use in the 12-months (Follow-up 1) and 24-months (Follow-up 2) after the baseline examination. Structural vulnerability markers for escalating ATS use were examined by comparing baseline grey matter volumes of participants who increased ATS use during the follow-up period (Cumulative Units $ATS_{follow\text{-}up}$ > Cumulative Units $ATS_{baseline}$; escalating stimulant user) with those who maintained the same or reduced level after baseline examination (Cumulative Units $ATS_{follow\text{-}up} \leqslant$ Cumulative Units $ATS_{baseline}$; non-escalating stimulant user). Previous studies suggest differential acute and long-term effects of amphetamine and MDMA, including the development of addiction and brain structural alterations (Berman *et al.*, 2009; Gouzoulis-Mayfrank and Daumann, 2009; Mackey and Paulus, 2013). An additional analysis on the pooled data sets therefore aimed to explore whether the prospective structural differences between escalating stimulant users and non-escalating stimulant users were specifically associated with the subsequent use of amphetamine or MDMA.

Materials and methods

Inclusion and exclusion criteria

The main inclusion criterion at baseline was occasional (ATS use $\geqslant$1 occasion), but very limited use of ATS (cumulative lifetime use of $\leqslant$10 units of MDMA and/or amphetamine).

For the present study ATS units were defined on the basis of typical quantities that the compounds are supplied in (one unit MDMA = 1 tablet; one unit amphetamine = 1 g). In addition the following exclusion criteria were used: lifetime use of any other illicit psychotropic substances $\geqslant$5 occasions (except for cannabis, which is widely used among recreational ATS users) (Gouzoulis-Mayfrank and Daumann, 2009), history of alcohol abuse or dependence (according to DSM-IV criteria), regular medication (once or more a week, except for contraceptives), use of any psychotropic substances in the 7 days before the examination (exception: cannabis, tobacco), use of cannabis on the day of the examination, current or previous history of neurological or psychiatric disorder (Axis I and II according

to DSM-IV criteria), any other general medical condition, history of traumatic brain injury with loss of consciousness or amnesia, left-handedness, unable to give informed consent, age < 18 years, childhood diagnosis of attention-deficit hyperactivity disorder, pregnancy and MRI contraindications.

Procedure

At baseline, brain structure, drug use and potential confounders were assessed in occasional ATS users (Study 1, $n = 48$; Study 2, $n = 42$). Participants were then followed to assess ATS use over the course of 12 months (Follow-up 1) and 24 months (Follow-up 2). The screening procedure included a structured interview to assess Diagnostic and Statistical Manual of Mental Disorders-Fourth edition (DSM-IV) Axis I and II disorders, the Wender Utah Rating Scale (Ward *et al.*, 1993) to assess childhood attention-deficit hyperactivity disorder, a detailed structured drug-history interview for ATS and other prevalent psychotropic substances. Randomly taken hair samples and urine screens were used to verify self-reported substance use patterns. In addition, the following potential confounding variables were assessed: neuropsychological functioning, including memory, executive functioning, mental flexibility, non-verbal intelligence, use of alcohol and tobacco, overall psychological distress (Global Severity Index from the Symptom Checklist-90-R, SCL90R). The study had full ethical approval from the ethics committee of the Medical Faculty of the University of Cologne and was carried out in compliance with the latest revision of the Declaration of Helsinki. Participants were recruited in Cologne (Germany). After participants had received a full description of the study they all provided written informed consent.

Subjects

Both studies were part of a larger research project on the long-term effects of ATS use on brain structure and function. Participants in Study 1 were part of a larger prospective study on the long-term effects of ATS use on brain function (Becker *et al.*, 2013; Wagner *et al.*, 2013). Participants in Study 2 had participated as controls with low ATS exposure in a previous cross-sectional study on the effects of heavy ATS use on brain structure (Daumann *et al.*, 2011; Koester *et al.*, 2012). In contrast to the previous studies examining the effects of substantial ATS use, the present study aimed to identify markers that predispose subjects to develop substantial ATS use.

Study 1

Of the initial 48 occasional ATS users who participated in the baseline assessment, 40 could be re-examined after 12 months. Based upon a quality check procedure for the structural MRI images the data from two participants had to be excluded (Supplementary material). For the remaining 38 participants, 23 reported decreased or stable ATS use during the 12-months follow-up (Cumulative Units $ATS_{follow\text{-}up} \leqslant$ Cumulative Units $ATS_{baseline}$; non-escalating stimulant user group). Fifteen participants had increased ATS use during the follow-period and were classified as vulnerable to escalating ATS use (Cumulative Units $ATS_{follow\text{-}up} >$ Cumulative Units $ATS_{baseline}$; escalating stimulant user group). Thirty-three participants could be re-examined 24 months after baseline.

Study 2

At baseline, 42 occasional ATS users were enrolled in the cross-sectional study using the same screening procedure and criteria as in Study 1 (for details see Daumann *et al.*, 2011). For the present study, participants were followed up to re-assess drug use in the subsequent 12 and 24 months. After excluding five participants ($n = 4$ had also participated in Study 1; $n = 1$ due to MRI data quality), 28 participants could be re-examined after 12 months. From the remaining participants 14 reported increased ATS use and 14 reported decreased or stable use, and were classified as non-escalating stimulant users or escalating stimulant users, respectively. Twenty-three participants could be re-examined 24 months after baseline. Brain structural vulnerability markers for escalating ATS use were assessed by a direct comparison of baseline grey matter volumes between participants in the non-escalating and escalating stimulant user groups.

Potential confounds at baseline

To control for potential confounds at baseline the experimental groups (non-escalating and escalating stimulant user) within each study were compared by means of independent samples *t*-tests (or χ^2-tests) regarding age, gender distribution, cognitive functioning, cannabis, alcohol and tobacco use parameters and overall psychological distress assessed at baseline. Differences of $P < 0.05$ were considered significant.

MRI data acquisition and data processing

MRI data in Study 1 were acquired on a Philips 1.5 T Gyroscan Intera with a Powertrak 6000 gradient amplifier using a standard quadrature head coil MRI system (flip angle = 25°, repetition time = 20 ms, echo time = 4.6 ms, slice thickness = 1 mm, voxel size = 1 × 1 × 1 mm). MRI data in Study 2 were acquired on a 3.0 T Magnetom Tim Trio system using a standard quadrature head coil (flip angle = 18°, repetition time = 1930 ms, echo time = 5.8 ms, slice thickness = 1.25 mm, voxel size = 1.0 × 1.0 × 1.25 mm). MRI images were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm), and the voxel-based morphometry toolbox VBM8 (http://dbm.neuro.uni-jena.de/vbm). To improve image registration, we used the diffeomorphic anatomic registration through an exponentiated lie algebra algorithm (DARTEL) (Ashburner, 2007).

Voxel-based morphometry analysis

Differences in baseline grey matter volumes between escalating stimulant users and non-escalating stimulant users in both studies were analysed using independent sample *t*-tests incorporated in SPM8. To further explore associations between baseline volumes and subsequent ATS use individual baseline volumes were extracted from regions differentiating between escalating and non-escalating stimulant users. Associations between the z-standardized baseline volumes and ATS use during the 12-months (Cumulative Units $ATS_{follow\text{-}up1} >$ Cumulative Units $ATS_{baseline}$) and 24-months (Cumulative Units $ATS_{follow\text{-}up1}$ + Cumulative Units $ATS_{follow\text{-}up2} >$ Cumulative Units $ATS_{baseline}$) follow-up periods were examined using

Pearson correlations ($P < 0.05$). Additional covariance and regression analyses were used to explore whether the observed differences between escalating stimulant users and non-escalating stimulant users were specifically associated to subsequently escalating amphetamine or MDMA use. To increase the statistical power to detect compound-specific associations, participants from both studies were pooled. Differences between escalating and non-escalating stimulant users across both samples were mapped using SPM8 independent samples *t*-tests with the covariate 'study' (Study 1, Study 2) to account for the different scanner types used in the studies. Next, compound-specific associations were explored by (i) including subsequent amphetamine and MDMA use as separate covariates in the SPM8 analyses; and (ii) multiple regression models using the extracted individual baseline volumes from regions differentiating escalating stimulant users and non-escalating stimulant users as dependent variable and amphetamine use, MDMA use, age, gender and study as independent variables (for details on the analyses see Supplementary material)

To increase the power to detect brain structural vulnerability markers statistical analyses focused on key brain structures associated with increased vulnerability for problematic drug use (Makris *et al.*, 2004; Wrase *et al.*, 2008; Daumann *et al.*, 2011) and meta-analytic findings in stimulant dependent individuals (Ersche *et al.*, 2013*b*; Mackey and Paulus, 2013): basal ganglia, amygdala, medial prefrontal cortex (PFC), inferior frontal gyrus, and insula. Structural regions of interest were defined using the Anatomy Toolbox version 1.8 (Eickhoff *et al.*, 2005) and the WFU Pickatlas Toolbox (Maldjian *et al.*, 2003). Between-group differences within the *a priori* regions of interest were computed using a threshold of $P < 0.05$ (family-wise error-corrected, FWE; minimum cluster size $\geqslant 10$ voxels). ATS use data for both follow-up periods were left skewed and were log transformed to normal distribution for the correlational and regression analyses. One participant in Study 2 reported a substantially higher increase in ATS use (>150 units ATS during Follow-up 1). Consequently, the ATS use data from this participant were excluded from the ATS use reports during follow-up, the correlational and regression analyses.

Results

Cumulative ATS use patterns and potential confounds

In line with current drug use surveys suggesting that MDMA and amphetamine are the most commonly used ATSs in Europe (UNODC, 2011) none of the participants reported methamphetamine use during the study period. MDMA was typically used orally in tablet form, whereas amphetamine was predominantly administered intranasally in powder form. At study inclusion, escalating and non-escalating stimulant users in both studies had used comparable cumulative amounts of ATS [cumulative ATS use (units): Study 1; escalating stimulant users, 6.32 (±2.44); non-escalating stimulant users, 5.23 (±2.72); Study 2; escalating stimulant users, 5.74 (±2.95); non-escalating stimulant users, 5.41 (±2.95)]. Compared to the usage at baseline, escalating stimulant users in both studies increased ATS use over the course of the subsequent 12 months. Escalating stimulant users in Study 1 on average reported a 3-fold [ATS use (units): 21.03 (±14.94)], and in Study 2 a 5-fold [ATS use (units): 27.52 (±20.70)] increase in ATS usage, whereas in the non-escalating stimulant user groups there was a 3-fold decrease in usage [ATS use (units): Study 1; 1.62 (±2.71); Study 2; 1.25 (±1.51)] (all $P < 0.05$, paired *t*-tests). Data from the 24-month assessment confirmed that individuals in the non-escalating and escalating stimulant user groups continued to show similar low and high ATS usage, respectively ($P > 0.05$, paired *t*-tests; Tables 1 and 2). Importantly, at baseline, escalating and non-escalating stimulant users within both studies were comparable on a range of potential confounders, including demographics, general intelligence, psychological distress and the use of licit and illicit drugs (Tables 1 and 2; for detailed information on cognitive functioning and psychological distress see Supplementary Table 1). Moreover, cannabis, alcohol and nicotine use did not increase during the follow-up period, suggesting that only ATS use patterns changed during the study period (Tables 1 and 2).

Differences in grey matter volume at baseline

Study 1

Occasional users who subsequently increased ATS use (escalating stimulant users) displayed smaller regional grey matter volumes in the bilateral amygdala, particularly the basolateral amygdala subregion, and the left medial PFC compared to those who had a stable/decreased ATS use (non-escalating stimulant users) (Table 3). Extraction of individual amygdala and medial PFC baseline volumes revealed a negative association between right amygdala, left amygdala and left medial PFC volumes with subsequent increased or decreased use during the 12-month and 24-month follow-ups (Fig. 1 and Table 4).

Study 2

Occasional users who subsequently increased ATS use displayed smaller regional grey matter volumes in the right basal ganglia, located in the dorsal striatum (nucleus caudatus) and the left medial PFC compared to those who had stable/decreased use (Table 3). Extraction of individual grey matter volumes from these regions revealed a negative association between the regional baseline volumes with subsequent increased or decreased ATS use during 12-month and 24-month follow-ups (Fig. 2 and Table 4).

Patterns of MDMA and amphetamine use in the pooled sample

Most escalating stimulant users increased amphetamine as well as MDMA use (19 of 29 subjects). Compared to usage at baseline, escalating stimulant users increased

Table 1 Study 1: Socio-demographic and drug use data of escalating (ESU) and non-escalating (NSU) stimulant users

Characteristic at baseline	ESU (n=15)	NSU (n=23)	*P*-value
Socio-demographics			
Age (years)	23.27 (±3.01)	22.78 (±3.52)	0.66
Education (years)	15.41 (±2.41)	14.81 (±2.77)	0.48
Gender distribution (f:m)[a]	3:12	6:17	0.67
ATS use at baseline			
Cumulative ATS use (units)	6.32 (±2.44)	5.23 (±2.72)	0.22
Age of ATS onset (years)	20.07 (±3.46)	19.96 (±2.56)	0.91
ATS use during follow-up			
Cumulative ATS: months 0–12 (units)	21.03 (±14.29)	1.62 (±2.71)	<0.001
Cumulative ATS: months 13–24 (units)	17.30 (±21.77)	1.14 (±3.39)	0.003
Other drug use at baseline			
No. of alcoholic drinks per week[b]	7.86 (±2.92)	7.56 (2.31)	0.73
No. of cigarettes per day[b]	11.27 (±5.61)	9.67 (±6.44)	0.44
Years of tobacco use[c]	5.85 (±3.67)	4.72 (±4.08)	0.39
Cannabis use duration (months)[c]	56.60 (±41.58)	44.95 (±33.29)	0.35
Cannabis use frequency (days/month)[b]	13.23 (±11.06)	13.00 (±11.24)	0.95
Cannabis use dosage (joints/occasion)[b]	2.45 (±2.09)	2.34 (±1.39)	0.85
Other drug use during follow-up 1			
No. of alcoholic drinks per week[b]	8.47 (±1.92)	7.74 (±1.57)	0.21
No. of cigarettes per day[b]	6.60 (±8.01)	8.13 (±6.26)	0.45
Cannabis use frequency (days/month)[b]	11.97 (±11.39)	9.73 (±11.87)	0.57
Other drug use during follow-up 2			
No. of alcoholic drinks per week[b,d]	8.15 (±2.31)	7.65 (±2.36)	0.56
No. of cigarettes per day[b,d]	7.46 (±7.34)	9.75 (±6.22)	0.36
Cannabis use frequency (days/month)[b,d]	7.81 (±10.21)	9.36 (±11.71)	0.69

[a]Chi-square test.
[b]During the 12 months before the examination.
[c]lifetime.
[d]based on $n = 13$ ESU and $n = 20$ NSU.

amphetamine and MDMA use during the subsequent 12 month [amphetamine (grams): baseline, 3.19 (±1.54); 12-month follow-up, 12.54 (±11.42); MDMA (tablets): baseline, 2.94 (±1.52); 12-month follow-up, 11.50 (±12.89)] and continued use on a comparable level during the 24-month follow-up period [amphetamine (grams): 12.29 (±14.32); MDMA (tablets): 8.70 (±14.07)]. Details for the separate study samples are presented in Supplementary Table 2. Changes in amphetamine and MDMA use during the follow-up period were moderately correlated (log-transformed data, follow-up 1, $r = 0.51$; $P < 0.001$).

Compound-specific associations with grey matter volume at baseline

Findings from the pooled samples ($n = 66$; non-escalating stimulant user, $n = 37$; escalating stimulant user, $n = 29$) confirmed the pattern of smaller bilateral amygdala, particularly the basolateral amygdala subregion, and medial PFC volumes in users who subsequently increased ATS use (Table 3 and Fig. 3). Differences between escalating and non-escalating stimulant users in these regions remained stable after including amphetamine as well as MDMA use as separate covariates (Supplementary Table 3). Notably, the extent of the left basolateral amygdala cluster increased substantially after including MDMA use as a covariate (from 15 to 121 voxels). Multiple regression analyses revealed an association between the left basolateral amygdala volume at baseline and subsequent use of amphetamine ($\beta = -0.32$, adjusted $R^2 = 0.09$, $P < 0.05$). Associations remained stable after including subsequent MDMA use, age, gender and study as additional predictors ($\beta = -0.29$, $P < 0.05$), suggesting a specific predictive value of baseline volumetric measures of the left basolateral amygdala and subsequent amphetamine use. Follow-up MDMA use significantly predicted left medial PFC baseline volumes ($\beta = -0.25$, adjusted $R^2 = 0.05$, $P < 0.05$). However, this association failed to reach statistical significance after including subsequent amphetamine use, age, gender and study as additional predictors. In contrast the subsequent cumulative ATS use significantly predicted left basolateral amygdala ($\beta = -0.28$, $P < 0.05$), left medial PFC ($\beta = -0.2$, $P < 0.05$), and the right medial PFC ($\beta = -0.26$, $P < 0.05$) volumes. Associations with the cumulative ATS use remained stable after including age, gender and study as additional predictors.

Table 2 Study 2: socio-demographic and drug use data of escalating (ESU) and non-escalating (NSU) stimulant users

Characteristic at baseline	ESU (n = 14)	NSU (n = 14)	P-value
Socio-demographics			
Age (years)	23.42 (±5.34)	22.14 (±3.30)	0.45
Education (years)	14.94 (±3.33)	14.57 (±1.91)	0.78
Gender distribution (f:m)[a]	5:9	11:3	0.41[a]
ATS use at baseline			
Cumulative ATS use (units)	5.74 (±2.95)	5.41 (±2.95)	0.74
Age of ATS onset (years)	20.42 (±5.76)	17.61 (±2.02)	0.10
ATS use during follow-up			
Cumulative ATS: months 0–12 (units)	27.52 (±20.70)	1.25 (±1.51)	0.001
Cumulative ATS: months 13–24 (units)	25.37 (±23.59)	1.83 (±3.25)	0.002
Other drug use at baseline			
No. of alcoholic drinks per week[b]	8.21 (±2.31)	8.50 (±2.87)	0.73
No. of cigarettes per day[b]	12.11 (±7.64)	6.21 ((±7.82)	0.06
Years of tobacco use	5.12 (±4.47)	3.71 (±4.18)	0.72
Cannabis use duration (months)	43.33 (±32.84)	60.00 (±37.88)	0.31
Cannabis use frequency (days/months)[b]	13.18 (±13.11)	14.64 (±12.08)	0.54
Cannabis use dosage (joints/occasion)[b]	1.76 (±1.54)	2.65 (±1.65)	0.23
Other drug use during follow-up 1			
No. of alcoholic drinks per week[b,d]	7.14 (±2.45)	8.85 (±1.61)	0.23
No. of cigarettes per day[b,d*]	10.07 (±8.48)	5.21 (±5.98)	0.06
Cannabis use frequency (days/months)[b,d]	11.04 (±12.87)	9.57 (±10.08)	0.71
Other drug use during follow-up 2			
No. of alcoholic drinks per week[b,d]	8.36 (±3.04)	7.75 (±1.21)	0.52
No. of cigarettes per day[b,d]	12.17 (±9.71)	7.33 (±6.51)	0.17
Cannabis use frequency (days/months)[b,d]	12.04 (±13.24)	9.33 (±11.13)	0.60

[a]Chi-square test.
[b]During the 12 months before the examination.
[c]lifetime.
[d]based on n = 12 ESU and n = 12 NSU.

Table 3 Regions with lower grey matter volumes at baseline in users who escalated stimulant use (ESUs) compared to users who did not escalate use (NSUs) during the 12-months follow-up

Region of interest (subregion)	t-value	MNI (x/y/z)	Cluster size
Study 1			
Left amygdala (basolateral)	4.00	−24 / −7 / −30	25
Right amygdala (basolateral)	4.95	− 25 / −3 / −27	287
Left medial prefrontal cortex	4.66	−14 / 62 / 1	33
Study 2			
Right basal ganglia (caudate)	5.83	6 / 15 / 1	53
Left medial prefrontal cortex	4.49	−1 / 62 / 22	11
Pooled samples			
Left amygdala (basolateral)	3.63	−35 / −9 / −29	15
Right amygdala (basolateral)	3.60	32 / −10 / −14	10
Left medial prefrontal cortex	5.33	−2 / 50 / 37	294
Right medial prefrontal cortex	4.55	3 / 59 / 22	56

All $P < 0.05$, family-wise error corrected.

Discussion

This first prospective imaging data in occasional ATS users suggest that smaller grey matter volumes in the medial PFC, amygdala and dorsal striatum differentiate between occasional ATS users exhibiting future escalation in ATS use from those who do not. Importantly, at baseline, participants were comparable on a range of potential confounders including sociodemographics, neurocognitive performance, psychological distress and previous substance use, including ATS and cannabis. Regional grey matter volumes in these regions were negatively associated with future cumulative ATS use, suggesting a high predictive value of the observed volumetric variations. Further analyses revealed some evidence of a compound-specific association between left basolateral amygdala volumes at baseline and subsequent amphetamine use. In contrast, we did not observe compound-specific associations between baseline volumes of the right basolateral amygdala or bilateral medial PFC and the subsequent use of MDMA and amphetamine. However, given the moderate correlations between amphetamine and MDMA use the compound-specific associations should be interpreted with caution.

Regions associated with subsequent ATS use

Users who subsequently increased ATS use specifically showed prospectively smaller volumes in the medial PFC, basolateral amygdala and the dorsal striatum. These

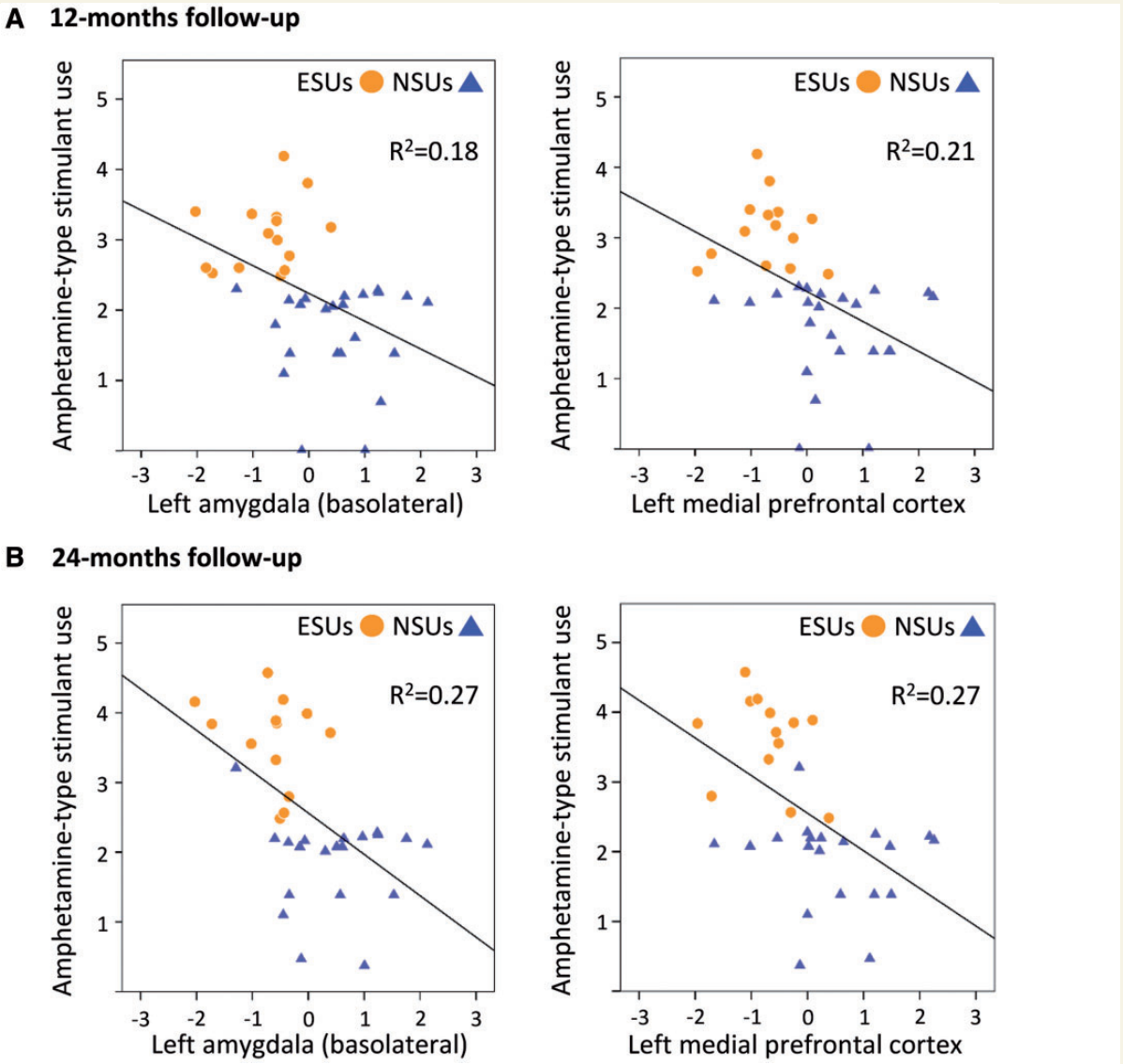

Figure 1 Associations between baseline grey matter volumes and subsequent increasing/decreasing amphetamine-type stimulant use in study 1. Scatterplots show that participants with lower grey matter volumes in the basolateral amygdala and the medial prefrontal cortex at baseline increased use during the subsequent 12 and 24 months. ESU = escalating stimulant users, participants who increased amphetamine-type stimulant use during the subsequent 12 months; NSU = non-escalating stimulant users, participants who decreased or maintained amphetamine-type stimulant use during the subsequent 12 months.

regions have extensive anatomical connections (McDonald *et al.*, 1996; Price, 2003) and represent important nodes in cortico-limbic-striatal circuitry. Previous research has implicated the cortico-limbic-striatal circuitry in functions that critically guide our behaviour, such as salience attribution (Kalivas and Volkow, 2005), inhibitory control (Eagle and Robbins, 2003; Bari and Robbins, 2013), emotion regulation/impulsivity (Ochsner *et al.*, 2012) and decision making. Deficits in these functions and alterations in the underlying prefrontal-limbic-striatal systems have been frequently observed in chronic stimulant users (overview in Aron and Paulus, 2007; Crunelle *et al.*, 2012; Ersche *et al.*, 2013*b*; Mackey and Paulus, 2013). Our data extend these previous cross-sectional findings, suggesting that these alterations are not only the consequences of prolonged stimulant use, but, at least partly, may also have preceded or even promoted the development of problematic stimulant use patterns.

Across both samples of occasional users we observed prospectively smaller medial PFC volumes in those users with future escalating ATS use. The medial PFC has been implicated in functions that critically guide and control our behaviour, including decision-making, forecasting the future consequences of our behaviour and inhibitory control (Noel *et al.*, 2013). However, viewed in isolation alterations in the medial PFC might not sufficiently explain why some occasional users increase their use whereas others do not. In both samples medial PFC deficits were accompanied

Table 4 Pearson correlations between z-standardized extracted brain volumes at baseline and log transformed increasing/decreasing ATS use in the subsequent 12 and 24 months

	ATS use 12 months	ATS use 24 months
Study 1		
Left amygdala (basolateral)	$r = -0.43$ ($P = 0.007$, $n = 38$)	$r = -0.53$ ($P = 0.002$, $n = 33$)
Right amygdala (basolateral)	$r = -0.49$ ($P = 0.002$, $n = 38$)	$r = -0.44$ ($P = 0.010$, $n = 33$)
Left medial prefrontal cortex	$r = -0.46$ ($P = 0.004$, $n = 38$)	$r = -0.52$ ($P = 0.002$, $n = 33$)
Study 2		
Right dorsal striatum (caudate)	$r = -0.69$ ($P < 0.001$, $n = 27$)	$r = -0.60$ ($P = 0.002$, $n = 23$)
Left medial prefrontal cortex	$r = -0.48$ ($P = 0.012$, $n = 27$)	$r = -0.46$ ($P = 0.026$, $n = 23$)

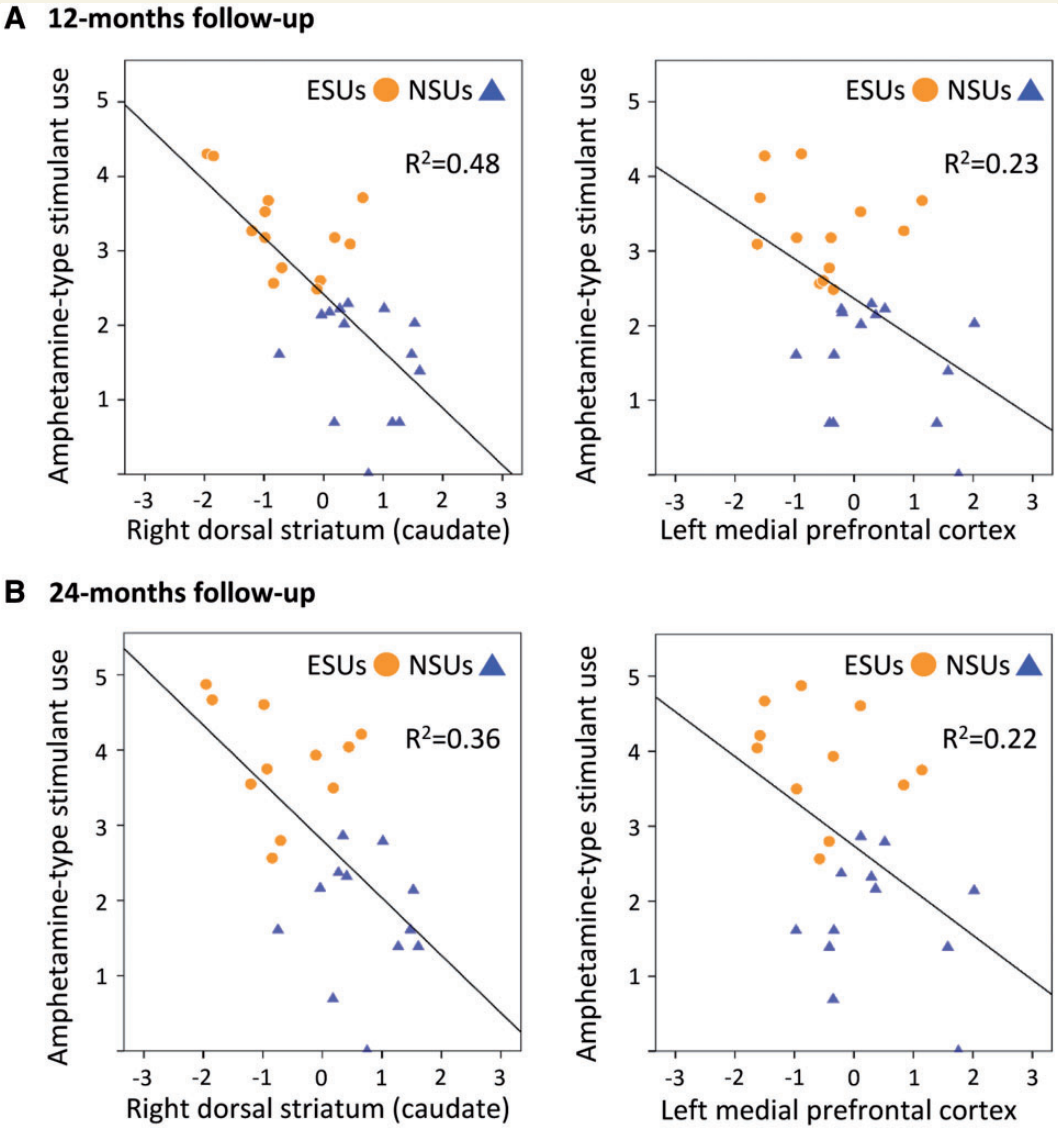

Figure 2 Associations between baseline grey matter volumes and subsequent increasing/decreasing amphetamine-type stimulant use in study 2. Scatterplots show that participants with lower grey matter volumes in the striatum and the medial prefrontal cortex at baseline increased use during the subsequent 12 and 24 months. ESU = escalating stimulant users, participants who increased amphetamine-type stimulant use during the subsequent 12 months; NSU = non-escalating stimulant users, participants who decreased or maintained amphetamine-type stimulant use during the subsequent 12 months.

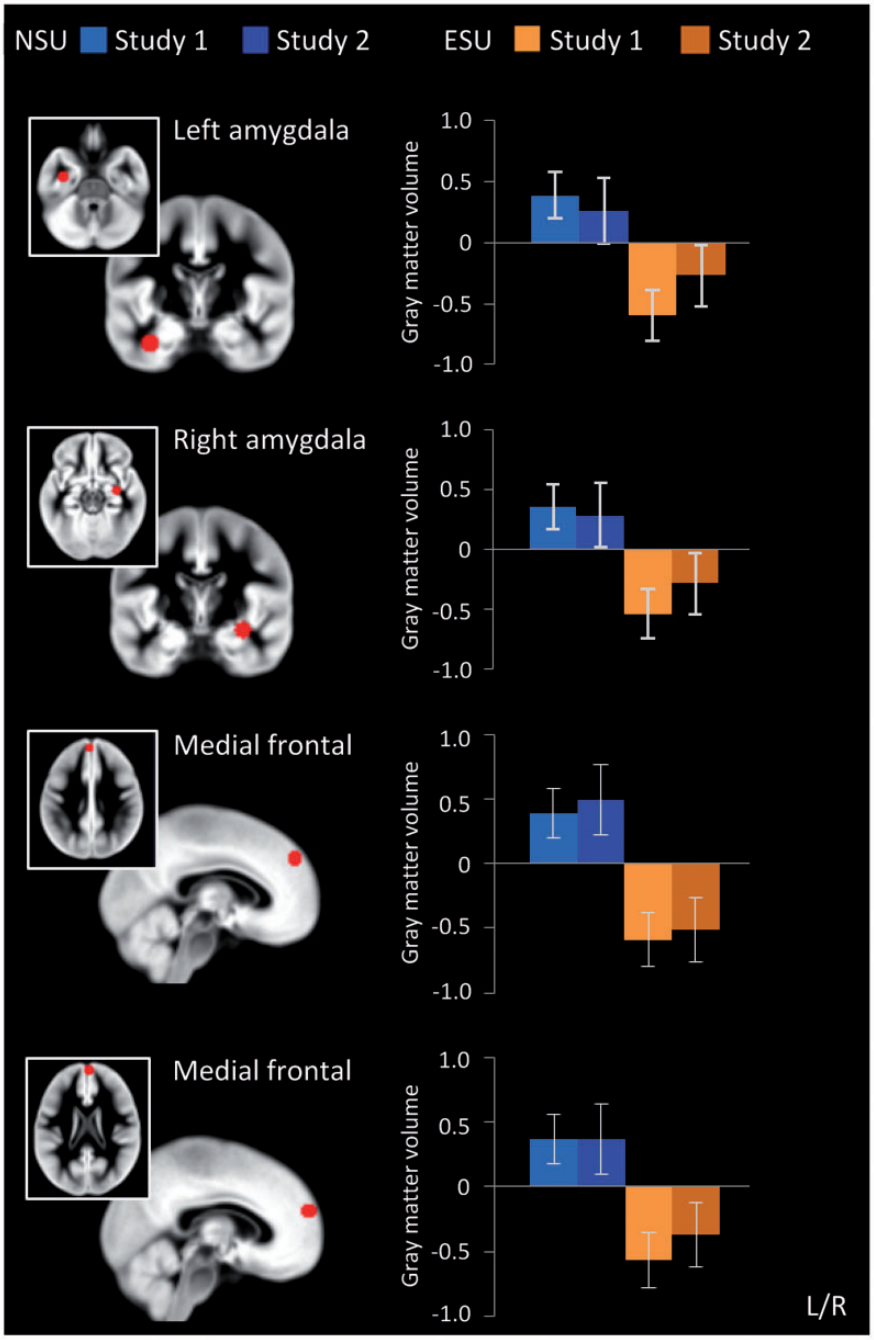

Figure 3 Prospective brain volumetric differences between participants who subsequently escalate use and those who do not. A direct comparison of baseline grey matter volumes of participants who increased amphetamine-type stimulant use during the subsequent 12 months (n = 29) with participants who decreased use after the baseline examination (n = 37) revealed prospectively smaller grey matter volumes in the bilateral medial prefrontal cortex and the bilateral amygdala in the group of users who subsequently increased use (family-wise error-corrected $P < 0.05$). Extracted baseline grey matter volumes from these regions revealed a consistent pattern of smaller baseline volumes in users who subsequently increased use across both samples. ESU = escalating stimulant users, participants who increased amphetamine-type stimulant use during the subsequent 12 months; NSU = non-escalating stimulant users, participants who decreased or maintained amphetamine-type stimulant use during the subsequent 12 months.

by alterations in limbic-striatal regions, specifically the basolateral amygdala and the dorsal striatum.

The basolateral amygdala plays a pivotal role in emotion processing and is involved in attaching emotional valence to specific events by mediating conditioned negative and positive reinforcement (Calder *et al.*, 2001), particularly positive reinforcement (Baxter and Murray, 2002) and reward expectancy (Holland and Gallagher, 2004). Lesion

studies in laboratory animals suggest that the bidirectional crosstalk between the basolateral amygdala region and the medial PFC plays an important role in flexible behavioural control and optimal decision-making. Disruptions in the basolateral amygdala–medial PFC circuitry particularly decrease the ability to flexibly adopt to changing reward values and increase impulsive choices (Ostrander *et al.*, 2011; Zeeb and Winstanley, 2013).

Finally, we observed smaller baseline dorsal striatal volumes in future escalating users in Study 2, which were negatively associated with ATS use during the subsequent 12 and 24 months. As part of the striatum the caudate's role in incentive reward processing is well established. In addition, connections from the striatum convey information to the PFC concerning internal presentation of goals and the means to achieve them (Fuster, 2001; Miller and Cohen, 2001). The caudate, in particular, seems critical for the development of stimulus response mapping and habit formation, which underlie automatic, inflexible behaviour (Grahn *et al.*, 2008). Moreover, disruptions to these fronto-striatal systems have consistently been associated with impulsivity as well as impaired executive control of impulsive behaviour (Feil *et al.*, 2010; Fineberg *et al.*, 2014).

The regions identified in the present study are part of a neural network previously implicated in various form of impulsivity, including deficient emotion regulation, inflexible behaviour and suboptimal decision-making (Jentsch *et al.*, 2014). Findings from preclinical studies suggest that impulsivity represents a key risk factor for the development of addiction (Perry and Carroll, 2008). For example it has been observed that high impulsivity in rats predicts subsequently increasing (Perry *et al.*, 2007), and escalating stimulant intake (Anker *et al.*, 2009). In addition, cross-sectional studies have produced considerable evidence of disrupted processing in impulsivity-related domains in chronic ATS users, such as impaired reinforcement-based decision making (Leland and Paulus, 2005; Tanabe *et al.*, 2009; Koester *et al.*, 2013; Stewart *et al.*, 2013), impulsive choices (Hoffman *et al.*, 2008; Bickel *et al.*, 2011) and deficient inhibitory control (Aron and Paulus, 2007; Feil *et al.*, 2010; Ersche *et al.*, 2012*a*). Initial findings in high-risk populations revealed an association between higher impulsivity and an increased risk for the subsequent development of substance addiction (de Wit, 2009; Ersche *et al.*, 2010; 2012*b*; 2013*a*).

Possible relationship with low dopaminergic functioning

Neuroimaging and genetic studies have identified the dopaminergic system as a likely contributor to different facets of impulsivity in the context of drug addiction (Kreek *et al.*, 2005; Volkow *et al.*, 2009). The dopaminergic system targets the frontal and limbic structures that regulate impulsive behaviour, including the prefrontal cortex, amygdala and dorsal striatum (Volkow *et al.*, 2002*a*, *b*). The concentration of dopaminergic receptors varies positively with grey matter volume, as indicated by a recent study reporting regional-specific voxel-wise associations between dopaminergic D2 receptor availability and grey matter volume (Woodward *et al.*, 2009). Collectively, these data suggest that the smaller grey matter volumes observed in the participants with subsequent escalating ATS use may reflect low dopaminergic receptor, particularly D2 receptor, functioning. Although the present data do not allow direct conclusions regarding dopaminergic functioning in the participants, this interpretation would be in line with converging evidence suggesting that low D2 receptor functioning links different forms of impulsivity to drug addiction vulnerability (Jentsch *et al.*, 2014).

Compound-specific associations with grey matter volume at baseline

Distinct long-term effects of the ATS compounds MDMA and amphetamine, including brain structure and function have been reported (Berman *et al.*, 2008; Gouzoulis-Mayfrank and Daumann, 2009). In contrast, the present study found only limited evidence for compound-specific associations between grey matter volumes and the subsequent use of MDMA and amphetamine. The lack of compound-specific prospective associations might indicate that the identified brain structural differences represent general, rather than compound-specific vulnerability markers for escalating ATS use. Given that MDMA has a relatively low addictive potential in humans compared to other ATS compounds, such as amphetamine and methamphetamine (Gouzoulis-Mayfrank and Daumann, 2009), this might suggest that during the initial stages of ATS addiction vulnerability factors have a greater impact on the development of escalating use than the addictive potential of the drug *per se*. Increased impulsivity and reduced dopaminergic functioning have been particularly associated with a generally increased risk for the initiation of drug use and addiction (Verdejo-Garcia *et al.*, 2008).

It is noteworthy that the only specific association that reached significance was between left basolateral amygdala volume and subsequent amphetamine use. In line with the proposed role of the basolateral amygdala in mediating positive reinforcement, the basolateral amygdala plays a crucial role in aversive and appetitive conditioning. In the context of drug addiction, animal studies emphasize the role of the basolateral amygdala in the acquisition and retrieval of emotional memories (Robbins *et al.*, 2008). Notably, these animal studies found that amphetamine enhanced appetitive conditioning and that this effect was strongly dependent on the basolateral amygdala (Alderson *et al.*, 2000).

Inconsistent findings between the study samples

Whereas differences in the medial PFC were observed across both studies we did not find consistent findings

regarding the basolateral amygdala and the dorsal striatum. Given that both studies used the same inclusion/exclusion criteria and that the samples in both studies were comparable on several potential confounders the divergent findings cannot be ascribed to group differences in these confounders. Given the overlapping anatomical and functional features of the striatum and the basolateral amygdala, the differences might be explained in terms of a common underlying vulnerability factor. Previous studies have revealed extensive reciprocal anatomical connections between the striatum, basolateral amygdala, and prefrontal regions (McDonald *et al.*, 1996; Price, 2003), as well as modulatory effects of dopaminergic neurotransmission in the functional interplay between them (Kobiella *et al.*, 2010). Recent neurocognitive perspectives on drug addiction propose that drug addiction vulnerability is the product of an imbalance between two separate, but interacting, neural systems: an impulse system that signals immediate prospects that comprises dopamine-dependent amygdala-striatal circuits, and a reflective prefrontal system that signals future prospects and controls the impulse system (Bechara, 2005; Noel *et al.*, 2013). In line with these perspectives, grey matter differences in the prefrontal system were accompanied by differences in the amygdala-striatal system across both studies. From a systems perspective it might be hypothesized that disruptions in different nodes of the amygdala-striatal circuits accompanied by deficits in the prefrontal systems lead to deficient top-down control and an increased propensity to use ATS on the behavioural level.

Methodological limitations and summary

First, most participants in the study used both MDMA and amphetamine, and increased use mostly reflected increased use of both compounds. Moreover, changes in amphetamine and MDMA use during follow-up were positively correlated. This might have limited the use of multiple regression models to disentangle compound-specific associations and the corresponding findings should be interpreted with caution. The widespread pattern of polydrug use in ATS users often makes it difficult to relate findings in human users to a specific drug (Gouzoulis-Mayfrank and Daumann, 2006). In addition, the fact that most ATS users combine the use of different drugs makes it virtually impossible to recruit 'pure' users of a specific compound. In addition the extrapolation from findings in a sample of 'pure' users to the general user population where polydrug use is the norm would be problematic. Second, for the present study units of ATS were defined on a pragmatic basis. Because of the different pharmacological profile, administration routes and purity of the compounds it is impossible to calculate equivalent doses with absolute accuracy. We therefore decided to use units that corresponded to the commonly supplied quantities of the drugs. Third, the present study did not find behavioural differences between the groups. The study predominantly aimed to examine brain structural markers of an increased ATS addiction risk and included only a limited number of behavioural measures. The neurocognitive test battery used to screen the subjects included one task that has been related to executive control (Stroop task) and no prospective between-group differences were observed in task performance. Several forms of impulsivity have been described and future studies should include a range of behavioural measures of impulsivity to explore the associations between different forms of impulsivity and subsequent stimulant use. Fourth, although a number of participants significantly increased the use of ATS after the baseline examination, most participants did not fulfil the diagnostic criteria for ATS addiction during the 24-month follow-up period. Longer follow-up periods are needed to determine whether some of the participants will transit to ATS addiction and whether these can be prospectively differentiated from participants who continue ATS use on a recreational basis. In addition, the classification of escalating stimulant users and non-escalating stimulant users in the present studies was based on a data-driven approach and not based on diagnostic criteria. However, results from the correlational and regression analyses in the entire sample confirmed the association between subsequent ATS use and volumetric variations in regions that differentiated between escalating and non-escalating stimulant users. Finally, brain structural data in the two studies were acquired on different MRI systems and at different field strengths. However, all analyses on the pooled sample incorporated 'study' as covariate to statistically control for the effects of the different systems used for data acquisition. Furthermore, in a separate SPM analysis the MRI system was included as an additional between-group variable (data not shown). Although this analysis revealed a main effect of MRI system, no interaction effect between MRI system and the second between-group factor 'Group' (escalating stimulant user versus non-escalating stimulant user) was found. Together, this argues against strong biasing effects of the different MRI systems.

In summary, individual differences in impulsivity and executive control have been proposed to represent risk factors that render an individual vulnerable to drug addiction and depend on intact limbic-striato-frontal crosstalk. The present findings provide the first prospective evidence that regionally-specific smaller volumes in these brain regions, particularly the basolateral amygdala and the medial PFC, might represent predictive risk indices for subsequent escalation of ATS use and potential addiction. The observed differences might reflect variations in dopaminergic functioning.

Acknowledgements

The authors thank Jeany Qiuchen Li and Nicola Kenter for excellent technical assistance, and all volunteers for their participation in the studies.

Funding

This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), grants: Go717/6-1/2 (Dr Gouzoulis-Mayfrank), BE 5465/2-1 (Dr Becker), and HU1302/4-1 (Dr Hurlemann). Dr Hurlemann was supported by the Ministry of Innovation, Science, Research and Technology of the German State of North Rhine-Westphalia (MIWFT), grant: NEMO—Neuromodulation of Emotion. Dr Kendrick was supported by the National Natural Science Foundation of China (NSFC), grant: 91132720.

Supplementary material

Supplementary material is available at *Brain* online.

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