Drug and Alcohol Dependence 130 (2013) 52–60

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Dopaminergic dysfunction in abstinent dexamphetamine users: Results from a pharmacological fMRI study using a reward anticipation task and a methylphenidate challenge☆

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ARTICLE INFO

Article history:
Received 8 May 2012
Received in revised form 10 October 2012
Accepted 15 October 2012
Available online 9 November 2012

Keywords:
Reward
Dopamine
Dextro-amphetamine
Dopamine
Methylphenidate
fMRI

ABSTRACT

Background: Dopamine (DA) is involved in systems governing motor actions, motivational processes and cognitive functions. Preclinical studies have shown that even relatively low doses of D-amphetamine (dAMPH) (equivalent to doses used in clinical Practice) can lead to DA neurotoxicity in rodents and non-human primates (Ricaurte et al., 2005).
Methods: Therefore, we investigated the DAergic function in eight male recreational users of dAMPH and eight male healthy controls using functional magnetic resonance imaging (fMRI). We compared brain activation between both groups during a monetary incentive delay task (Knutson et al., 2001) with and without an oral methylphenidate (MPH) challenge. All subjects were abstinent for at least 2 weeks during the baseline scan. The second scan was performed on the same day 1.5 h after receiving an oral dose of 35 mg MPH (approximately 0.5 mg/kg) when peak MPH binding was assumed.
Results: When anticipating reward, dAMPH users showed lower striatal activation in comparison to control subjects. In addition, MPH induced a reduction in the striatal activation during reward anticipation in healthy controls, whereas no such effect was observed in dAMPH users.
Conclusion: The combination of these findings provides further evidence for frontostriatal DAergic dysfunction in recreational dAMPH users and is consistent with preclinical data suggesting neurotoxic effects of chronic dAMPH use. The findings of this explorative study could have important implications for humans in need for treatment with dAMPH, such as patients suffering from ADHD and therefore this study needs replication in a larger sample.

1. Introduction

Dopamine (DA) is involved in several key physiological systems governing motor actions as well as motivational processes and cognitive functions. Subsequently, abnormalities of dopaminergic cells have been linked to both Parkinson-like motor deficits, attenuated reward processing, and impaired impulse control (Van den Heuvel and Pasterkamp, 2008; Stoy et al., 2011; Vaidya et al., 1998.

In humans, DAergic dysfunction can occur as a consequence of endogenous disease processes (e.g., Parkinson's disease, schizophrenia and attention deficit/hyperactivity disorder (ADHD)), resulting in alterations in frontostriatal DAergic signaling (Van den Heuvel and Pasterkamp, 2008). DAergic dysfunction can also be caused by exogenous influences on the brain, such as the use of dextro-amphetamine (dAMPH) or methamphetamine. Preclinical studies have shown that even relatively low doses of dAMPH (equivalent to the doses used in clinical practice) can lead to striatal DA neurotoxicity in rodents and non-human primates (Ricaurte et al., 2005), as evidenced for instance by reductions in striatal DA concentrations and DA transporter (DAT) binding sites. PET studies in dAMPH treated monkeys have shown reductions in striatal [^{18}F]fluoro-L-dopa uptake in vervet monkeys (Melega et al., 1996, 1997). In line with this, in humans, a study by Reneman et al. (2002) has shown that recreational dAMPH use is linked to lower striatal DAT availability. Because the DAT is a structural component of the DA-axon, loss in DAT has been used as a marker for DAergic damage (Reneman et al., 2002). Because dAMPH is frequently prescribed in the treatment of ADHD it is a drug that is relatively easy to obtain for illicit purposes and in fact is misused by subjects both with and without ADHD (Wilens et al., 2008). Therefore it is important to

☆ Supplementary materials for this article can be found by accessing the online version of this paper at http://dx.doi.org/10.1016/j.drugalcdep.2012.10.010. Please see Appendix A for more information.

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0376-8716
http://dx.doi.org/10.1016/j.drugalcdep.2012.10.010

further investigate DA dysfunction in recreational users of dAMPH. Recreational users, i.e., subjects not being treated for substance abuse, tend to use less frequently and lower dosages than subjects with a substance use disorder. To the best of our knowledge, no other studies have yet investigated the DA system in recreational users of this drug.

Studies in abstinent dAMPH users have demonstrated sustained deficits in several behavioral paradigms, including decision-making (Ersche et al., 2005), memory (Rapeli et al., 2005) and set-shifting (Ornstein et al., 2000). Although functional MRI (fMRI) measures changes in blood oxygenation rather than neurochemistry, it has been suggested that striatal activation during anticipation of reward as measured with fMRI might partially index DAergic function (Schultz, 2002). In addition, fMRI can give region-specific neurovascular responses to a DAergic challenge (Knutson et al., 2004); Willson et al., 2004). In view of this, it is of interest to investigate anticipation of reward in recreational users of dAMPH and their reaction to a DA challenge. The combination of a DA challenge with fMRI (pharmacological MRI; phMRI) enables a more direct assessment of DA functions, because brain activity during striatal activation is investigated in addition to the modulating effect of a DA agent (Honey and Bullmore, 2004).

A drug that is well known to activate the DA system is methylphenidate (MPH), commonly used in the treatment of ADHD. MPH acts by blocking the DAT, which prevents the reuptake of DA by the presynaptic neuron and thus increases DA concentration in the synaptic cleft. Oral MPH challenges have been used in fMRI investigations involving both healthy and ADHD populations (Shafritz et al., 2004; Bush et al., 2008; Schlosser et al., 2009; Rubia et al., 2009), but not dAMPH users. MPH normalized brain responses in ADHD patients on inhibitory tasks (Vaidya et al., 1998; Liddle et al., 2011) as well as reward-related tasks (Wilkison et al., 1995; Rubia et al., 2009).

In this study, we investigated DAergic function in recreational users of dAMPH and healthy controls using fMRI with and without a DA challenge to determine whether dAMPH use can be linked to DAergic dysfunction in humans. We set out to answer the following questions: (1) Does striatal function differ between recreational dAMPH users and control subjects? (2) Does a DAergic challenge modulate striatal function differently in recreational dAMPH users versus control subjects? To that purpose, we investigated the response to an oral MPH challenge during a DAergic task: anticipation of reward using a monetary incentive delay task (Knutson et al., 2001). In view of the fact that anticipation of reward is linked in a large part to striatal response systems, which may be disrupted in dAMPH users, we hypothesized that recreational dAMPH use is associated with impaired anticipation of reward and that this abnormality is (partially) restored by increased extracellular levels of DA following oral MPH.

2. Methods

2.1. Subjects

Subjects were recruited by posting advertisements around the medical campus, on websites and in regional newspapers. A total of eight male, recreational amphetamine users and eight male, healthy control subjects were recruited. Written informed consent was obtained from all subjects. The eligibility criterion for the dAMPH group was previous use of dAMPH on more than 40 occasions. This threshold was chosen based on the work of Reneman et al. (2002) who found lower DAT binding in ecstasy users with average dAMPH use on more than 45 occasions. The eight control subjects were healthy subjects with no self-reported use of amphetamines.

Subjects were asked to refrain from using caffeinated products on assessment days. Both controls and dAMPH users agreed to abstain from all psychoactive drugs for at least two weeks before scanning and therefore dAMPH dependence was reason for exclusion. All subjects indicated being able to abstain without external help during this two week period and were asked to comply with urine drug screening on the day they were scanned (with an enzyme-multiplied immunoassay for amphetamines, cocaine, cannabis, alcohol, opiates and benzodiazepines). Exclusion criteria for all participants were: any neuropsychiatric diagnosis or history of brain disease or injury, use of medication with affinity for DA (e.g., MPH), a positive urine-screen for any DAergic drugs or any contra-indication to MRI such as metallic implants or claustrophobia. Subjects received a small financial compensation for their participation.

This study was approved by the medical ethics committee of the Academic Medical Center Amsterdam.

2.2. Procedure

The tasks were presented in the same order for every subject; first a go–nogo task, then the reward task and then an emotional face recognition task. Results of the go–nogo task and the face recognition task will be reported elsewhere. To minimize learning effects, a practice run for each task was presented outside of the scanner. After the first scanning session, subjects received 35 mg MPH (approximately 0.5 mg per kg body weight) to be taken orally with water. Subjects were then free to relax for 1.5 h until peek plasma levels were expected (Swanson and Volkow, 2003) and then re-entered the MRI scanner for the second session that was identical to the first. MPH was obtained from Sandoz B.V. (Weesp, the Netherlands).

2.3. Imaging

All MR imaging was performed using a 3.0 T Philips MR scanner equipped with an SENSE 8-channel head coil and body coil transmission (Philips Medical Systems, Best, The Netherlands). The session protocol consisted of a high resolution 3D T1-weighted anatomical scan for registration and segmentation purposes and a fast single shot echo planar image (EPI) sequence for BOLD analysis. For the BOLD acquisition imaging parameters were: TR/TE 2300/30 ms; FOV 220 mm × 220 mm; 40 slices; voxel size 3 mm × 3 mm × 3 mm; no gap; 80° flip angle, SENSE 2.0.

2.4. fMRI

The reward anticipation task was presented by a video projection system onto a white screen using E-prime software (Psychological Software Tools, USA). Subjects saw the screen via a mirror attached to the head coil. Responses were logged via a response box attached to the computer presenting the stimuli. Subjects were asked to imagine actually receiving the amounts displayed in the task, but did not receive any additional reward apart from their financial compensation for participation. We chose this option because playing for points or real money has led to similar results in reward response (Cole et al., 2012; Peters et al., 2011).

All subjects performed a modified version of the monetary incentive delay task as described in Knutson et al. (2001). In the task the response to anticipation of gaining or losing money and a neutral condition was determined. Three graded positive cue stimuli signaled that, if the subjects responded on the subsequent target presentation, he would gain a monetary reward (36 trials), three graded negative stimuli signaled that, if the subject would not respond to the target presentation, he would loose money (36 trials). One neutral cue, finally, signaled no incentive outcome

(18 trials). An indication on the stimulus signaled the size of the reward or loss (€0.00, €0.20, €1.00 or €5.00). Stimuli (presented for 250 ms) were presented in a pseudorandom order. Each cue was replaced by a cross-hair with variable delay during the anticipation period (2000–2500 ms). Thereafter, the target was presented for a variable length of time (160–260 ms) and subjects were instructed to respond as fast as possible to the target by pressing a button with their right index finger. Responding in time to the target would result in monetary gain or avoidance of loss. Next, again with a variable delay of 1240–1840 ms after target presentation, feedback of the trial result and the accumulated result of all previous trials was provided for a fixed period of 1750 ms after which a new cue was presented

2.5. Analysis

Continuous variables of group characteristics were analyzed using unpaired two-tailed Student's *t*-tests (log transformed if necessary) and Mann–Whitney tests for drug history variables. All demographic and behavioral data was analyzed in SPSS version 18.0 (SPSS Inc, Chicago, IL) and are presented as mean ± standard deviation unless otherwise indicated.

Behavioral responses to the anticipation of reward task were analyzed for percentage correct response and mean response time with MANOVA for group and MPH interaction. MRI scans were analyzed using FSL 5.1 (FMRIB-Software-Library, Functional Magnetic Resonance Imaging of the Brain Center, Dept. of Clinical Neurology, University of Oxford, Oxford, UK, http://www.fmrib.ox.ac.uk). Non-brain structures were removed from 3D T1 anatomical scans using the Brain Extraction Tool (BET; Smith, 2002). Scans were analyzed using FSL's fMRI Expert Analysis Tool (FEAT; Beckmann et al., 2003) and Motion Correction using FMRIB's Linear Image Registration Tool (MCFLIRT; Jenkinson et al., 2002), BET brain extraction, spatial smoothing set at 5 mm FWHM, high-pass filter cut-off at 100 s. Scans were registered to the high resolution structural image and to standard MNI space (MNI152_T1_2 mm_brain from the FSL atlas library).

The general linear model (GLM) used for first-level analysis was adapted from Knutson et al. (2001), with contrasts set to reward versus neutral, loss versus neutral, reward versus loss and large reward (€5.00) versus small reward (€0.20). The obtained first-level analysis was entered into a second-level (group effect) analysis. Main task effect was determined by examining first level effects for all scans available, both baseline and post-challenge scans were used for this analysis. Next a mask of the corpus striatum based on the Harvard–Oxford brain atlas, including putamen, caudate, nucleus accumbens and globus pallidus, was applied to the data, to determine ROI specific activation. Because cocaine also influences the DA system and cocaine use was common in dAMPH we decided to incorporate cocaine in the analysis. Cocaine use in the last 12 months was demeaned and added as a covariate to the higher-level analysis. In order to keep covariate use as low as possible in this explorative study we decided against correcting for age and IQ, seeing as we do not consider these to have a significant influence on DAergic function in this relatively young population.

For illustrative purposes we determined striatal task-activation for both groups and conditions separately, uncorrected with $p < 0.01$. Baseline group differences, in addition to the effect of the challenge per group were calculated. The interaction effect of group × drug challenge was calculated. For these comparisons (baseline effect, challenge effect and interaction) statistical threshold was set at $p = 0.05$, $Z = 2.3$, with cluster-correction to correct for multiple comparisons. Finally, voxels that showed a significant interaction effect were used to create a mask in order to determine mean percentage signal change in these voxels.

3. Results

3.1. Sample characteristics

The dAMPH group used dAMPH for a mean of 13.9 (±8.7) years on a mean of 27.8 (±17.1) occasions/year and a usual dose of 0.8 (±1.2) g/occasion. The mean cumulative lifetime exposure to dAMPH was 352.6 (±465.3) g and mean time since the last dose was 1.1 (±1.3) months. Table 1 shows that the dAMPH group was slightly older and had a normal but slightly lower pre-morbid IQ than the control group although years of education did not differ significantly. In addition, dAMPH users had used significantly more tobacco, cannabis and cocaine.

3.2. Behavioral effects of reward anticipation

Hit rate for reward anticipation (i.e., proportion of successful button presses during target presentation) and response times for hits, did not significantly differ between controls and dAMPH users at baseline (hit rate 56.5 ± 13.6% vs. 54.5 ± 7.4%, $p = 0.71$; reaction time 197.4 ± 18.8 ms vs. 197.6 ± 27.9 ms, $p = 0.99$) or with MPH challenge (60.7 ± 15.0% vs. 59.5 ± 10.1%, $p = 0.85$; 202.8 ± 17.9 ms vs. 193.1 ± 26.1 ms, $p = 0.4$), nor was there an interaction effect of group × challenge (hit rate $p = 0.93$; reaction time $p = 0.75$).

Table 1
Demographics for dAMPH users and controls with standard deviation (±) and *p*-values for *t*-test (Age, IQ and Years of education) or Mann–Whitney test.

	dAMPH *n*=8	Controls *n*=8	*p*-value
Age	26.0 (±4.0)	22.0 (±3.0)	0.04
DART-IQ	104.5 (±3.0)	110.4 (±4.2)	0.007
Years of education	15.1 (±3.6)	16.4 (±2.9)	0.46
dAMPH			
Average dAMPH use (occasions/year)	27.8 (±17.1)	0	0.00
Duration of dAMPH use (years)	13.9 (±8.7)	NA	NA
Usual dose (g/occasion)	0.8 (±1.2)	NA	NA
Total exposure (g)	352.6 (±465.3)	0	0.00
Time since last exposure (months)	1.1 (±1.3)	NA	NA
Other substances			
Average tobacco use (cigarettes/month)	261.0 (±279.8)	0	0.01
Average alcohol use (units/month)	103.5 (±146.6)	104.5(±83.5)	0.49
Average cannabis use (joints/year)	410.3(±480.5)	19.4(±31.8)	0.02
Average MDMA use (pills/year)	3.8(±10.6)	0	0.32
Average cocaine use (occasions/year)	5.0(±5.2)	0.1(±0.4)	0.009

NA, not applicable

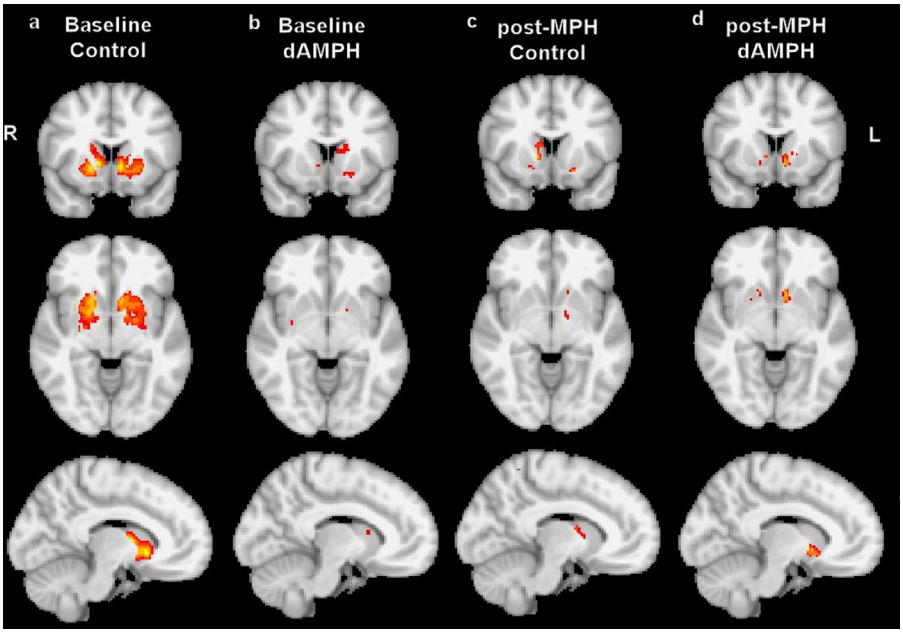

Fig. 1. Activation during anticipation of reward vs. anticipation of the neutral condition. The different panels show the activations during the anticipation of reward in an ROI of the corpus striatum in healthy controls at baseline (a), dAMPH users at baseline (b), healthy controls after challenge with 0.5 mg/kg oral MPH (c) and dAMPH users after challenge with MPH (d). Activated voxels are uncorrected at $p < 0.01$.

3.3. Analysis of reward anticipation

Anticipation of reward vs. anticipation of the neutral condition showed activation in the ventral striatum, thalamus, parietal, frontal and occipital cortex, brainstem, cerebellum, anterior cingulate and the insular cortex (see Figure S1 available in Supplementary Material).

When the two groups and drug conditions were analyzed separately for anticipation of reward vs. anticipation of the neutral condition in the corpus striatum ROI, significant activation was observed in both groups in either drug condition (without and with MPH; Fig. 1). For the control group, widespread and strong activation was seen in the corpus striatum before the MPH challenge. After the MPH challenge this effect became weaker and more focal. In the dAMPH users, anticipation of reward was associated with a weak pattern of striatal activation at baseline that did not seem to be altered by the MPH challenge. Locations and maximum *Z*-scores for these and the following analysis are reported in Table 2. Statistical comparison of the two groups at baseline (without MPH) confirmed that anticipation of reward vs. anticipation of the neutral condition induced a significantly weaker activation pattern across the striatum of recreational dAMPH users compared to healthy controls (Fig. 2, panel A). Following the MPH challenge, anticipation of reward vs. anticipation of the neutral condition induced a statistically significant reduction in striatal activation (Fig. 2, panel B) only in control subjects. Significant clusters (Table 2) were found in the left caudate, right putamen and right pallidum. In the dAMPH group, no statistically significant effect of the MPH challenge was found.

No baseline activation or baseline differences were observed when analyzing loss versus neutral, reward versus loss or large reward versus small reward.

3.4. Interaction of group × challenge in striatum during reward anticipation

A significant group × drug challenge interaction was found in the left putamen for the anticipation of reward vs. anticipation of a neutral condition contrast (Fig. 2, panel C). The mean percentage signal change as shown for the striatum in Fig. 3 during reward anticipation confirms the different effects induced by reward anticipation in both groups, and the effect of MPH there upon: under activation in the dAMPH users at baseline (without MPH) and reduced brain activation after the MPH challenge in the controls. Moreover, in the dAMPH users, the left putamen became more strongly activated during anticipation of reward after the MPH challenge.

No interaction effects for the other contrasts (loss versus neutral, reward versus loss, large reward versus small reward) were observed.

4. Discussion

We observed a different striatal response following a monetary incentive delay task in recreational dAMPH users compared to healthy controls. This task has been found to robustly activate the nucleus accumbens and the caudate when anticipating reward, where receiving the actual reward mainly elicits a response in the medial PFC (Knutson et al., 2001; Haber and Knutson, 2010). When anticipating reward, dAMPH users showed diminished striatal activation in comparison to control subjects. We also observed a statistically different effect of a DA challenge in which MPH induced a decrease in striatal activation during reward anticipation in healthy controls, whereas no effect in dAMPH users was found. No effects of group or challenge were observed on anticipation of loss and size of the reward.

4.1. Group differences on anticipation of reward before MPH challenge

One of the explanations for the lower reward anticipation found in recreational dAMPH users may be an innate hypofunction of the DAergic system, which, in turn, may reflect increased sensitivity toward dAMPH (ab)use and or addiction. A leading theory about addiction states that reduced sensitivity for natural reinforcers underlies the development of addiction (also referred to

Table 2
Location of the *Z*-max cluster, with amount of voxels in the cluster, maximum *Z*-value, *p*-value and MNI coordinates for the maximum voxel. Analysis given for healthy controls (HC) and dAMPH users (dAMPH) both before (pre) and after (post) administration of 35 mg of MPH.

Region	Voxels	Z_{max}	*p*-value	Talairach		
				x	*y*	*z*
Baseline						
HC						
Left caudate/accumbens	1244	5.37	<000	−6	8	−2
Right caudate/accumbens	1015	5.64	<000	10	12	0
dAMPH	Empty	–	–	–	–	–
HC > dAMPH						
Left putamen	470	3.6	<001	−22	2	8
Right putamen	455	3.43	<001	24	4	12
dAMPH > HC	Empty	–	–	–	–	–
Post-MPH						
HC	Empty	–	–	–	–	–
dAMPH	Empty	–	–	–	–	–
HC > dAMPH	131	4.26	0.026	10	0	12
dAMPH > HC	Empty	–	–	–	–	–
Interaction						
HC pre > post						
Left caudate	221	5.6	0.003	−14	16	6
Right putamen/pallidum	123	4.89	0.023	28	−10	−2
Right putamen/caudate	93	4.62	0.049	18	18	−4
dAMPH pre > post	Empty	–	–	–	–	–
HC > dAMPH						
Left putamen/pallidum	105	4.88	0.036	−18	2	6
dAMPH > HC	Empty	–	–	–	–	–

as the reward deficiency hypothesis; Comings and Blum, 2000). According to this theory, the dAMPH group may have an innate DAergic hypofunction, which, in turn, has predisposed them to developing a penchant for stimulant use. Indeed, even after prolonged abstinence, lower D2 receptor availability in a wide variety of addicted individuals has been reported (for review see Volkow et al., 2009). In addition, lower D2 receptor availability has been linked to increased impulsivity measures (Buckholtz et al., 2010), which in itself has been put forward as a component cause for the development of addiction (for review see Hommer et al., 2011).

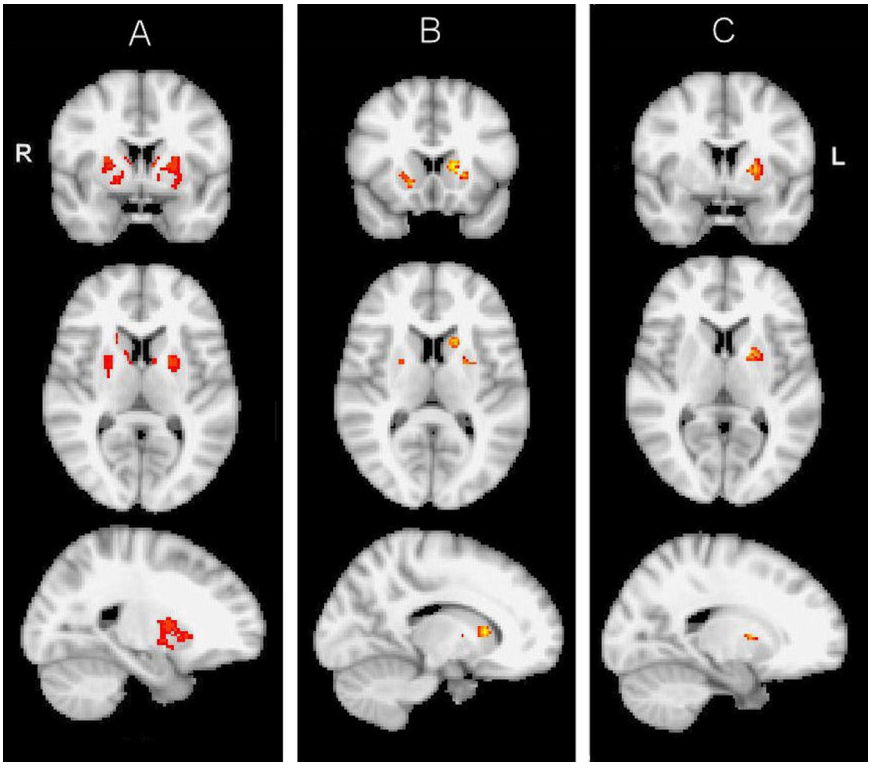

Fig. 2. Interaction of group × challenge in the striatum during reward anticipation. Panel A: Axial, transverse and sagittal views of the difference in response to anticipation of reward between healthy controls and dAMPH users at baseline. Activated voxels indicate areas in which healthy controls had a significantly larger response to reward anticipation than dAMPH users corrected for cocaine use ($Z > 2.3$, $p < 0.05$, cluster-corrected). Panel B: Activated voxels represent the areas within the corpus striatum ROI where a significant decrease in activation during reward anticipation was observed in healthy controls after challenge with 0.5 mg/kg oral MPH ($Z > 2.3$, $p < 0.05$, cluster-corrected). Recreational dAMPH users did not have a significant response to MPH (positive or negative). Panel C: Activated voxels represent areas within the corpus striatum ROI where a significant interaction of group × challenge was observed ($Z > 2.3$, $p < 0.05$, cluster-corrected).

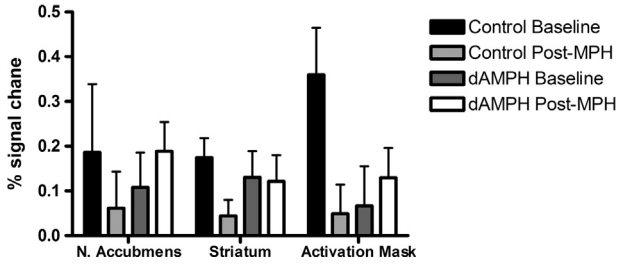

Fig. 3. Mean percentage signal change in nucleus accumbens, striatum and the area of significant interaction (activation mask) during reward anticipation for controls and dAMPH users at baseline and after MPH challenge. Bars represent the percentage signal change within the ROI from the Harvard–Oxford brain atlas and voxels that showed a significant interaction effect in the voxel-based analysis (activation mask) for both healthy controls and dAMPH users at baseline and after challenge with 0.5 mg/kg oral MPH. Error bars represent standard deviation.

Thus, it is possible that our findings may not relate to dAMPH use, but rather increased impulsivity due to low D2 receptor availability. However, we cannot exclude the possibility that selection bias or confounding by factors that were not included in the current study are responsible for the observed differences in this explorative study. Only a large-scale prospective study, as we previously conducted for MDMA (de Win et al., 2008), will be able to show the causal nature of our findings, and exclude that pre-existing differences (such as low D2 receptor availability) underlie our findings.

Addiction has also long been associated with aberrant reward-related responses (for a review see Volkow et al., 2011). It has been demonstrated that alcoholics show reduced ventral striatum activation during the anticipation of monetary gain (Wrase et al., 2007) and a correlation between this response and impulsivity measures has also been reported (Beck et al., 2009). However, cocaine dependent were not different from healthy controls in the anticipation of reward (Asensio et al., 2010). Therefore addiction alone cannot be held exclusively responsible for the changes in reward-related behavior. Although we cannot exclude that the participants in our study were addicted, they clearly stated that they were recreational dAMPH users and not diagnosed with addiction or substance abuse in the past. Moreover, they used dAMPH "only" 28 times per year, which is about once every two weeks and this can hardly be called addictive use of dAMPH with loss of control. Therefore, it is unlikely that addiction-related changes in the mesolimbic DA pathway involved in drug-reward are the predominant mechanism underlying our results.

Another explanation for the reduced sensitivity for reward in the recreational dAMPH users is that this is caused by neurotoxic changes induced by chronic dAMPH use. This interpretation is based on a large body of preclinical studies, such as that from Ricaurte et al. (2005) who observed a reduction in the number of both DAT and vesicular monoamine transporter (VMAT) in non-human primates treated with a dAMPH in a regimen similar to the one used in the treatment of patients with ADHD (Ricaurte et al., 2005). In addition, PET studies in amphetamine treated vervet monkeys have shown reductions in striatal [^{18}F]fluoro-L-dopa uptake (Melega et al., 1996, 1997) and reductions in DAT have been observed in combined dAMPH and MDMA users using [^{123}I]β-CIT SPECT (Reneman et al., 2002). Furthermore, studies on the striatal DAergic system in rats have shown that chronic dAMPH exposure results in neurotoxicity characterized by decreases in DA levels and DAT densities, swollen nerve terminals and degenerated axons (Ricaurte et al., 1984). Given the large body of evidence directly documenting the DAergic neurotoxic potential of dAMPH in rodents and nonhuman primates, and because reward functions are strongly connected to the DA system, our data provide further evidence that recreational use of dAMPH is associated with DAergic dysfunction, as evidenced by a reduced activation during reward anticipation.

4.2. MPH challenge effect

Our findings of diminished brain activation of the ventral striatum of healthy controls following an acute challenge with MPH are in line with the literature. Knutson et al. (2004) investigated the effects of 0.25 mg/kg oral dAMPH in healthy volunteers, using a similar monetary incentive delay task to the one used here, and found that dAMPH blunted the response in the ventral striatum during reward anticipation. However, since dAMPH not only blocks the DAT (similar to MPH), but also enhances DA release, it is expected that higher synaptic DA concentrations were obtained in the study by Knutson than in the current study. It is thought that the magnitude of phasic DA release in the ventral striatum is reduced by a challenge with a DA agent such as dAMPH or MPH during anticipation of reward (Knutson et al., 2004), thereby diminishing brain activation. In dAMPH users we did not observe such a response, providing further evidence for striatal dysfunction.

This dysfunction may also be linked to the phenomenon of drug tolerance. It has been shown that repeated dosing with dAMPH leads to a greater behavioral response and can cause an increased DA release in response to a subsequent challenge which can still be observed one year later (Boileau et al., 2006; Strakowski et al., 1996). After continued exposure this increased sensitivity disappears and DA release is smaller in response to a similar dose (Jacobs et al., 1981; Segal and Kuczenski, 1997). One theory states that this is due to depleted DA stores or alterations in D2 auto-receptor function (Kuczenski and Segal, 1997). Using D1 or D2 receptor specific agonists or antagonists, phMRI studies in rats, combined with microdialysis have demonstrated that specific receptor types are responsible for different aspects of the hemodynamic response to a DAergic challenge (Chen et al., 2005, 2010; Dixon et al., 2005). Where the D1 receptor is only present post-synaptically, the D2 receptor is expressed both pre- and post-synaptically and can inhibit DA release when located on the pre-synaptic neuron (for review see Missale et al., 1998). A lower level of D2 expression may lead to a larger relative percentage of D2 occupation by DA following a challenge, leading to a blunted hemodynamic response to the MPH administration. This mechanism could be responsible for the blunted response we observed in individuals that used dAMPH on a regular basis. In line with this, a reduction in D2 receptors has been found in non-human primates following chronic dAMPH treatment (Ginovart et al., 1999). Reduced levels of D2 expression may therefore also explain the blunted hemodynamic response observed and this may also be a result of the dAMPH use in our group of dAMPH users. However, a lower D2 expression (linked to increased impulsivity as stated above) could also have been pre-existent to the dAMPH use and causative for the start of psychostimulant use in these subjects.

Another explanation for the blunted hemodynamic response could lie in the reduction in DAT availability noted previously in preclinical studies and possibly other parts of the DAergic system (Ricaurte et al., 2005). Interference with MPH's ability to bind to DAT has been shown to fail to produce conditioned place preference behavior, which is related to reward processing (Tilley and Gu, 2008).

In line with this, recent studies revealed a lower response in the ventral striatum during anticipation of monetary rewards in adolescents (Scheres et al., 2008) and adults with ADHD (Plichta et al., 2009). This is of interest to the current study, because ADHD has also been associated with DAergic dysfunction and alterations in DAT availability have been observed previously (Spencer et al., 2005; Strohle et al., 2008). In fact, MPH treatment at (pre)adolescence seems to reduce this risk of developing addictive disorders in

individuals with ADHD (Katusic et al., 2005; Wilens, 2004). Several animal and behavioral studies have suggested that the increased risk for developing addiction may be due to aberrant reward sensitivity in individuals diagnosed with ADHD (Luman et al., 2005; Shiels et al., 2009; Wilkison et al., 1995). It would be interesting to use phMRI with a DAergic challenge to investigate reward sensitivity individuals suffering from ADHD as well as evaluating effects of treatment on the hemodynamic response profile.

4.3. Limitations

First, the number of participants in this study was rather small. The study was designed as explorative involving a limited number of subjects, because predominant dAMPH users are very difficult to find in the Amsterdam region. However, even with this relatively small sample size, effects were considerable and significant even when using strict statistical thresholding.

Second, it cannot be excluded that the observed DAergic dysfunction is due to other drugs than dAMPH since AMPH users had more experience with tobacco, cannabis and cocaine then controls. However, other than cocaine, none of these drugs is known to affect the integrity of the DAergic system. For that reason we performed post hoc analyses adjusting for cocaine use. It is therefore unlikely that the findings of the present study are caused by substances other than dAMPH. Furthermore, because subjects had to abstain for 2 weeks from psychoactive drugs, it is unlikely that the present findings of DAergic dysfunction are due to the acute pharmacological effects of dAMPH or other drugs (other than MPH administered during the study). Urine screening was performed to detect concealed recent dAMPH use. Other than self-report, we were not able to ensure abstention from dAMPH in the two weeks before the scanning sessions. However, a survey in The Netherlands investigated the validity of the drug-history questionnaire that was used in this study. It was found that in 93% of the cases ($n = 594$) the reported drug use was in agreement with the drug-urine test (Addiction Research Institute, 1998). In future studies, hair sample analysis would be a useful way to ascertain previous use of dAMPH.

Age and IQ also differed between the groups. Therefore, additional or supplementary statistical analyses to the analyses involving the primary objective of the study were conducted with age and IQ as covariates (Figures S2 and S3 in Supplementary Material). However, these covariates did not substantially change our findings: we again observed larger activation in healthy controls when compared to dAMPH users at baseline, along with an interaction effect of the MPH challenge. This observation strengthens the hypothesis that our findings are related to stimulant use and not to mismatched characteristics.

Thirdly, because we did not include a placebo challenge we cannot completely rule out the possibility that differences between the groups in expectation of drug effect may have affected our results. However, none of the groups had previous experience with MPH and did not know (exactly) what to expect. Moreover, a previous study only found a small expectancy effect on brain hemodynamics with i.v. administration of MPH, whereas in the current study MPH was given orally (probably resulting in an even smaller expectancy effect; Volkow et al., 2006). In addition, this expectancy effect during i.v. MPH administration was observed only on resting state MRI and not on task-related brain hemodynamics. These observations suggest that in the current study drug expectancy may have affected the results only minimally, if at all.

Fourth, we did not use an actual monetary reward. However, our results on whole brain activation to the anticipation of gain are very similar to earlier results obtained with this task. This task itself has been applied with modified rewards in previous studies as well (points with which subject could purchase snacks (Peters et al., 2011), monetary reward with a maximum thresholds or globally linking performance to size of compensation for study participation (Jia et al., 2011)). Hahn et al. (2011) and Stoy et al. (2011) do not specify whether or not actual money was used. Interestingly, similar results were obtained in all these modified reward studies. Because the Knutson group who designed our task found robust activation of reward related systems in the anticipation of interactive game playing, involving no other reward than playing the game itself (Cole et al., 2012), we feel that our results are trustworthy even with only the fictitious winning of money.

5. Conclusion

To our knowledge, this is the first study investigating DAergic dysfunction in recreational users of dAMPH using a monetary incentive delay task with fMRI. We not only observed a blunted brain activation response during anticipation of reward in dAMPH users, but we also following a DAergic challenge with MPH. These findings provide further evidence for frontostriatal DA dysfunction in recreational dAMPH users and in our opinion are consistent with preclinical data suggesting neurotoxic effects of chronic dAMPH use. It should be noted, however, that no performance deficits were present in this relatively small study. Our findings should, therefore, be replicated in a larger sample. When replicated, our findings could also be used to further investigate the effects of chronic low dose dAMPH in a clinical setting, for example in the treatment of ADHD.

Role of funding source

This work was funded by a Research Fellowship from the Academic Medical Center, Amsterdam the Netherlands, awarded to L. Reneman; the funding organization had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Liesbeth Reneman designed the study and wrote the protocol. Marieke Schouw collected the data, performed the fMRI analysis and wrote the first draft of the article. Michiel de Ruiter advised on the fMRI analysis. Anne Marije Kaag helped with fMRI analysis and processed all demographic and behavioral data. Wim van de Brink and Ramon Lindauer provided valuable input on data handling and the writing of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors report no conflict of interest.

Acknowledgements

The authors would like to sincerely thank Brian Knutson for providing his fMRI task for our use. In addition we would like to thank all participants of our study and the funding organizations for making the entire process possible.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2012.10.010.

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