Pharmacological MRI in the assessment of monoaminergic function
Schouw, M.L.J.

Citation for published version (APA):
CHAPTER 7
METHYLPHENIDATE AFFECTS EMOTIONAL BEHAVIOUR IN D-AMPHE TAMINE USERS: IMPLICATIONS FOR ADHD PATIENTS

M.L.J. Schouw*
M.A. Bottelier*
M.B. de Ruiter
H.G. Ruhe
R.J.L. Lindauer
L. Reneman

*These authors contributed equally to the content of this paper

In preparation
ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is hallmarked by dysregulation of the dopaminergic (DA) system. The use of d-Amphetamine (dAMPH) leads to DA dysfunction in non-human primates as damage to DA nerve terminals has been observed.

Links between DAergic functioning and emotional processing have also been made and it has been suggested that DAergic intervention can alter amygdala function.

Therefore, we examined emotional function, focusing on the amygdala, 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 an emotional face processing task (Hariri et al, 2002) 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 ½ hours after receiving an oral dose of 35 mg MPH (approximately 0.5 mg/kg) when peak MPH binding was assumed.

We observed emotional dysfunction in the group of intermittent high-dose dAMPH users, which normalized following oral MPH administration. MPH thus restored amygdala hyperactivity in individuals with DA dysfunction, likewise in children with ADHD.
INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is the most prevalent psychiatric disorder of childhood, and affects 3 to 9% of school-age children and 1 to 5% of adults worldwide (Biederman and Faraone, 2004; Leung and Lemay, 2003; Wilens et al, 2004). For years now, stimulant drugs are the mainstay of ADHD treatment (Greenhill et al., 2002; Fone and Nutt, 2005) and their use worldwide has increased substantially (Olfson et al, 2003; Robison et al, 2004). Side effects may consist of weight loss, and in adult patients dependence may develop, in addition to increased wakefulness and decreased fatigue. (Rapport et al, 2002)

D-Amphetamine (dAMPH) and methylphenidate are the stimulants used in the treatment of ADHD. Both drugs act by blocking the dopamine (DA) transporter (DAT), which prevents the reuptake of DA presynaptically and thus increases DA concentration in the synaptic cleft. In addition, dAMPH also stimulates DA release.

Recently, emotional dysregulation has been described in children with ADHD following stimulant treatment (Molina et al, 2009). In line with this, several preclinical studies have demonstrated that exposing preadolescent rats to a DAergic agent like methylphenidate (MPH) results in profound changes associated with a depression-like state later in life (Bolaños et al, 2003; Carlezon et al, 2003) It has been shown that these emotional deficits can be reversed by antidepressant treatment in adulthood with a serotonine reuptake inhibitor, such as fluoxetine (Bolaños et al, 2008). Bolanos et al. suggested that antidepressant treatment enhanced DA transmission in reward-related brain areas, resulting in a reverse of depression-like behavior induced by early (preadolescent) MPH exposure.

The amygdala is a brain structure critical for emotional processing and activates most strongly during the processing of emotional faces (Hariri et al, 2002). Amygdala function measured with functional Magnetic Resonance Imaging (fMRI) is now a well known biomarker of emotional dysregulation, i.e depression (Tao et al, 2012). For instance, increased amygdala activity assessed with fMRI has been found in patients suffering from major depressive disorder (MDD) which decreased after successful treatment with paroxetine (Ruhé et al, 2011).

Although emotional function is typically thought to involve the serotonergic system, recent experimental studies support the idea of a DA-ergic contribution to an emotional response, as suggested by biochemical, pharmacological and lesion experiments (for review see (Bolaños et al, 2003; Carlezon et al, 2003; Salgado-Pineda et al, 2005). Although much less studied, several clinical studies now also support DA disruption in emotional processing. For instance, in healthy controls it has been shown that dAMPH potentiated the response of the amygdala during the perceptual processing of angry and fearful facial expressions. (Hariri et al, 2002) Nevertheless, in adolescents with ADHD increased activity of the right amygdala was normalised by MPH (Posner et al, 2011).
To further investigate the role of the DA system in emotional processing we examined emotional function in a group of dAMPH users, using task related fMRI before and after oral administration of MPH. We investigated dAMPH users, because there is preliminary evidence that users of this drug suffer from a dysfunctional DA system. We set out to answer the following questions: 1) Does amygdala function differ between recreational dAMPH users and healthy control subjects? 2) Does a DAergic challenge with MPH modulate amygdala function? 3) If so, does it affect amygdala function differently in recreational dAMPH users when compared to control subjects? If indeed DA plays an important role in emotional processing, as suggested in the (preclinical) literature described above, we hypothesized that in recreational dAMPH users we would observe an increased responsiveness of the amygdala to negative or fearful faces, which would normalize following a challenge with MPH, presumably due to enhanced DA transmission.

**METHODS**

This study was approved by the medical ethics committee of the Academic Medical Centre Amsterdam. Written informed consent was obtained from all subjects.

**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. 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 and co-workers (Reneman et al., 2002) who found lower DAT binding in ecstasy users with an 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.
**Procedure**

The tasks were presented in the same order for every subject; first a go-nogo task, then a reward task and then the emotional face recognition task. Results of the go-nogo task (in preparation) and the reward task (Schouw *et al.*, 2012) are 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 1½ hours until peak plasma levels were expected (Demenescu *et al.*, 2011) 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).

**Imaging**

All MR imaging was performed using a 3.0 Tesla 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. The BOLD acquisition imaging parameters were: TR/TE 2300/30 ms; FOV 220x220 mm$^2$; 40 slices; voxel size 3 x 3 x 3 mm; no gap; 80° flip angle, SENSE 2.0.

**Emotion processing task**

The implicit emotion processing 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.

All subjects performed a modified version of the event-related implicit emotion processing task used by (Demenescu *et al.*, 2011). Color photos of afraid, happy and neutral facial expressions were presented. The stimuli were selected from the Karolinska Directed Emotional Faces (KDEF) stimulus set (Lundqvist, D., Flykt, A., & Öhman, A. (1998) and consisted of standardized facial expressions of emotions expressed by amateur actors. Twenty-four stimuli (twelve male and twelve female faces) were presented for each of the three facial expressions. In addition, 2 control stimuli consisting of an arrow pointing to the left or right, overlaid on a scrambled face, were presented. The control stimuli were presented 80 times (40 with an arrow pointing to the left, 40 with an arrow pointing to the right). Each stimulus type was not presented more than twice in a row. Each stimulus was shown on the screen for 2.5 s with an interstimulus interval (black screen) varying between 0.5 and 1.5 s. Participants were instructed to indicate each face’s gender by pressing one of two buttons with the index
finger of the left or right hand on two button boxes (left for a male face and right for a female face). For the control stimuli, participants had to push a button according to the direction the arrow was pointing in (left button for left direction and right button for right direction), the direction of the arrows and correct faces were counterbalanced.

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 were analyzed in SPSS version 18.0 (SPSS Inc, Chicago, Ill) and are presented as mean ± standard deviation unless indicated otherwise. Reaction times were entered into a mixed model ANOVA in SPSS with the factors Group (2 levels: healthy controls and dAMPH), Drug challenge (2 levels: pre and post) and Stimulus type (4 levels: afraid, happy, neutral and baseline).MRI scans were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) implemented in Matlab version 7.13. Images were first manually reoriented to the anterior commissure. Subsequently, fMRI images were realigned to the first volume, corrected for differences in slice acquisition time, co-registered to the anatomical scan, segmented into grey matter, white matter and cerebrospinal fluid, spatially (non-linearly) normalized to the Montreal Neurological Institute (MNI) T1 template, resampled into 2x2x2 mm voxels and spatially smoothed using a 6 mm full width at half maximum Gaussian kernel. Statistical analysis was performed within the framework of the general linear model. To determine BOLD activation in response to different facial expressions, box-car regressors convolved with a canonical hemodynamic response function were used to model responses to each facial expression. Data were high-pass filtered at 128 s and temporal autocorrelation was modeled with an AR(1) process provided within SPM 8. To assure that the faces paradigm elicited reliable activations, a whole brain second level fMRI analysis across groups and sessions was performed for each facial expression (random effects analysis). The resulting statistical parametric maps were initially thresholded at $p < 0.001$. Clusters significant at the $p < 0.05$ level family-wise error (FWE) corrected for multiple comparisons were considered statistically significant. Next, a region of interest (ROI) analysis was performed by extracting mean BOLD activation in the bilateral amygdala using a mask of the bilateral amygdala as defined by the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al, 2002). (figure 2) Because no statistically significant differences were found for the left and right amygdala the mean amygdala response across hemispheres was used. Mean amygdala activations for the left and right amygdala were analysed with mixed models in SPSS with the factors Group (2 levels: healthy controls and dAMPH), Hemisphere (2 levels: left and right), Drug challenge (2 levels: pre and post) and Affective Valence (3 levels: afraid, happy and neutral). The association between the extent of dAMPH use and amygdala reactivity was studied with Pearson product-moment correlation coefficient provided within SPSS (two-tailed).
RESULTS

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) grams/occasion. The mean cumulative lifetime exposure to dAMPH was 352.6 (± 465.3) grams 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.

Task performance
Reaction times are shown in Table 2.
Subjects were faster after dAMPH than before dAMPH ($F(1, 14) = 11.70, p < .01$). Responses to control stimuli (scrambled faces that required a left/right response) were faster than to the emotional stimuli (requiring sex discrimination ($F(3, 12) = 36.27, p < .001$). No statistically significant effects were found involving the factor ‘Group’.

Whole brain analyses across groups and challenge
Whole brain fMRI analyses across groups (AMPH and HC) and challenge (pre and post MPH) were performed to verify whether the facial expressions elicited reliable activation (Table 3 and Figure 2). Presentation of fearful faces was associated with activation of right amygdala extending into anterior hippocampus, left and right fusiform gyrus, right prefrontal cortex.
and right middle temporal cortex. Activation of left amygdala did not survive correction for multiple comparisons. Presentation of happy and neutral faces was generally associated with the same pattern of activation, albeit to a weaker extent. Therefore, activation in most of the above mentioned areas did not survive correction for multiple comparisons.

**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.

<table>
<thead>
<tr>
<th></th>
<th>dAMPH (n=8)</th>
<th>Controls (n=8)</th>
<th>p-val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26.0 (± 4.0)</td>
<td>22.0 (± 3.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>DART-IQ</td>
<td>104.5 (± 3.0)</td>
<td>110.4 (± 4.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Years of education</td>
<td>15.1 (±3.6)</td>
<td>16.4 (±2.9)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**dAMPH**

- Average dAMPH use (occasions/year): 27.8 (±17.1) vs. 0 (p = 0.00)
- Duration of dAMPH use (years): 13.9 (± 8.7) vs. NA vs. NA
- Usual dose (grams/occasion): 0.8 (± 1.2) vs. NA vs. NA
- Total exposure (grams): 352.6 (± 465.3) vs. 0 vs. 0.00
- Time since last exposure (months): 1.1 (± 1.3) vs. NA vs. NA

**Other substances**

- Average tobacco use (cigarettes/month): 261.0 (±279.8) vs. 0 (p = 0.01)
- Average alcohol use (units/month): 103.5 (±146.6) vs. 104.5 (±83.5) vs. 0.49
- Average cannabis use (joints/year): 410.3 (±480.5) vs. 19.4 (±31.8) vs. 0.02
- Average MDMA use (pills/year): 3.8 (±10.6) vs. 0 vs. 0.32
- Average cocaine use (occasions/year): 5.0 (±5.2) vs. 0.1 (±0.4) vs. 0.009

NA = Not applicable

**Table 2** Mean RT (SD)

<table>
<thead>
<tr>
<th></th>
<th>dAMPH pre</th>
<th>dAMPH post</th>
<th>Controls pre</th>
<th>Controls post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear</td>
<td>798 (125)</td>
<td>726 (167)</td>
<td>710 (83)</td>
<td>651 (132)</td>
</tr>
<tr>
<td>Happy</td>
<td>749 (91)</td>
<td>654 (84)</td>
<td>686 (88)</td>
<td>659 (75)</td>
</tr>
<tr>
<td>Neutral</td>
<td>799 (129)</td>
<td>651 (66)</td>
<td>692 (81)</td>
<td>665 (165)</td>
</tr>
<tr>
<td>Baseline</td>
<td>599 (66)</td>
<td>531 (45)</td>
<td>607 (134)</td>
<td>526 (77)</td>
</tr>
</tbody>
</table>
### Table 3. Whole brain fMRI analyses for fearful, happy and neutral faces averaged across all participants and sessions.

<table>
<thead>
<tr>
<th></th>
<th>Fearful</th>
<th></th>
<th>Happy</th>
<th></th>
<th>Neutral</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MNI x y z Z k</td>
<td></td>
<td>MNI x y z Z k</td>
<td></td>
<td>MNI x y z Z k</td>
<td></td>
</tr>
<tr>
<td>Amygdala (l)</td>
<td>-20 -12 -16 3.30 10</td>
<td></td>
<td>-18 -20 -16 3.71 16</td>
<td></td>
<td>-22 2 -14 3.21 3</td>
<td></td>
</tr>
<tr>
<td>Amygdala (r)</td>
<td>20 -10 -10 4.46 118 *</td>
<td></td>
<td>18 -12 -10 4.98 49</td>
<td></td>
<td>18 -10 -10 3.21 5</td>
<td></td>
</tr>
<tr>
<td>Fusiform gyrus (l)</td>
<td>-38 -56 -18 4.88 128 *</td>
<td></td>
<td>-38 -58 -20 4.12 45</td>
<td></td>
<td>-34 -62 -16 4.61 95 *</td>
<td></td>
</tr>
<tr>
<td>PFC BA 44/45 (r)</td>
<td>50 34 24 4.67 320 *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle temp. cortex (r)</td>
<td>50 -74 16 4.21 246 *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*L = left; r = right; MNI = Montreal Neurological Institute Coordinates, Z = statistical Z value; k = number of voxels in cluster. All activations significant at p < .001 uncorrected. * cluster level FWE corrected significant at p < .05*
III. IMAGING THE DOPAMINERGIC SYSTEM USING fMRI

Figure 2 Sagittal view (MNI coordinate x = 27) of BOLD activation in right amygdala to presentation of fearful, happy and neutral faces across groups (AMPH and HC) and challenge (pre and post MPH). Data are shown at p < .005 for display purposes.

ROI analyses

Omnibus ANOVA at amygdala ROIs did not show significant differences between the left and right amygdala so this factor was dropped from the analyses. A significant Valence x Group interaction indicated that only for fearful faces, significant group differences were present (p = .037). A marginally significant Group x Session interaction (p = .073) was found for fearful faces (Figure 3).

Post-hoc analyses showed that before methylphenidate challenge, the two groups differed significantly in amygdala activation (p = .027). This difference disappeared after the challenge (p = .94).

Figure 3 A marginally significant Group x Session interaction (p = .073) was found for fearful faces, indicating that before methylphenidate challenge, the two groups differed significantly in amygdala activation (p = .027), whereas this difference disappeared after the challenge (p = .94).
Correlation analysis

Before the challenge, duration of amphetamine use in years was positively correlated with amygdala reactivity in dAMPH ($r = .76, p = .029$, Figure 4). This correlation disappeared after the challenge ($r = .07$, ns).

**Figure 4** Correlation of years of amphetamine use with amygdala reactivity in dAMPH users. $r = .76, p = .029$

**DISCUSSION**

In this study of amygdala activation before and after MPH challenge in dAMPH users and controls, in line with our hypothesis, we found that presentation of fearful faces was associated with abnormal, increased, activation of the amygdala in recreational dAMPH users, which normalized after acute administration of a DA challenge with MPH. Furthermore, the extent of dAMPH exposure was positively correlated with amygdala reactivity.

Our findings of abnormal amygdala activation in recreational dAMPH users most likely reflect an abnormal DA transmission in this brain region, as dAMPH (in doses used in the treatment of ADHD) has been previously found to damage the DA system. Preclinical studies have shown that even relatively low doses of dAMPH (equivalent to the doses used in clinical practice) induce DA dysfunction in rodents and non-human primates (Ricaurte, 2005). DA dysfunction was -for instance- demonstrated by reductions in DA, the DA transporter (DAT), an increase in DA D1 receptor density and Vesicular Monoamine Transporter (VMAT) (Bonhomme et al, 1995). In line with this, in humans, Reneman and co-workers showed that recreational dAMPH use is linked to lower striatal DA transporter (DAT) availability (Reneman et al, 2001). Because the DAT is a structural component of the DA-axon, loss in DAT likely indicates DAergic dysfunction. In addition, in recreational users of dAMPH, a blunted hemodynamic response to a challenge with MPH (Schouw et al, 2010) has been reported. The dose-response correlation between lifetime exposure of dAMPH
use and amygdala activity in the present study further supports a relationship between dAMPH use and amygdala hyperactivity.

We observed increased amygdala activation after fearful faces in dAMPH users when compared to healthy control subjects. These findings are in line with previous studies which investigated the effect of dAMPH administration on amygdala response, although in healthy volunteers only, and observed similar findings: increased amygdala activity in healthy volunteers after dAMPH challenge (Hariri et al, 2002; Salgado-Pineda et al, 2005). It has recently been shown that DA in the basolateral amygdala is critical for fear-processing (Fadok et al, 2009). Additionally, some midbrain DA neurons increase their firing rates to aversive stimuli and predictive cues (Guarraci et al, 1999; Horvitz, 2000). DA levels in the ventral midbrain increase during aversive events and DA neurons of these brain areas project to limbic brain areas important for fear learning (Kalivas and Duffy, 1995). In these areas, DA facilitates long term potentiation, an important neural correlate of memory (Lemon, 2006). Therefore, DA dysfunction or deficiency most likely explain our observation of the abnormal fear processing in dAMPH users, particularly also because it normalized following MPH administration. Alternatively, our findings may be explained by an increased sensitivity to corticotropin-releasing factor, as chronic amphetamine treatment has been shown to enhance corticotropin-releasing factor-induced serotonin release in the amygdala of rats (Scholl et al, 2010). The corticotropin-releasing factor increases serotonin release in the central nucleus of the amygdala, and this neurochemical circuitry has been shown to mediate fear processing.

The first evidence in humans for a putative role of DA in modulating emotional response was a fMRI study exploring the neural basis of abnormal emotional behavior in Parkinson disease (Tessitore et al, 2002). Parkinsonian patients demonstrated an absent amygdala response without dopaminergic medication. DA repletion was shown to restore this response partially. Interestingly, in rats treated with dAMPH, DAergic modulation of the medial PFC by the basolateral amygdala was disrupted, which was hypothesized to cause impairments in emotional processing as is found in stimulant users (Tse et al, 2011).

What happens in case of dysfunctional DA system? The fact that we observed a significant group x challenge interaction suggests that MPH induced a different (largely opposite) effect in d-AMPH users as it did in healthy volunteers; MPH induced an increase in healthy controls and a non significant decrease in dAMPH users. Interestingly, a previous study also reported a blunted DA release in the amygdala (and hippocampus and striatum) of patients suffering from ADHD. Stimulants had a normalizing effect on the activity of the right amygdala (Posner et al, 2011; Volkow et al, 2007). In our study, we thus provide further evidence that DA plays an important role in emotional processing, as we observed abnormal emotional processing in recreational users of a drug that affects the DA system, and non significant decrease of amygdala activity following acute administration of a DAergic agent,
presumably due to enhanced DA transmission. This increase of amygdala activity in healthy controls after mph administration and the decrease in dAMPH users might find it's origin in an inverted U shape of DA-ergic mediated activity of the amygdala as is found in the prefrontal cortex (Dreher et al., 2002).

These findings may have important clinical implications. Our results suggest that in a dysfunctional DA system like in d-AMPH-users and ADHD, MPH (and likely also other DA-acting agents) will have a normalizing effect on amygdala activity. Other studies reported similar positive effects of DAergic agents in ADHD patients with respect to: cortical thickness (Shaw et al, 2006) and prefrontal functioning (Epstein et al, 2007). But what happens if DA-acting agents are administered to a non-dysfunctional DA system, for instance in healthy subjects (e.g., to improve scholarly achievements), or in ADHD patients that have not been correctly diagnosed as suffering from ADHD? We would like to argue that in these cases, MPH administration has a detrimental effect, as in our study MPH induced an increase in amygdala activity in the healthy subjects. Indeed, in animal studies MPH has been shown to induce anxiety like behavior. Bolaños, for example, found in Wistar rats that prolonged treatment with MPH at adolescence (2.0 mg/kg, 16 days) anxiety related behavior increased, in which the animals were significantly more sensitive to stressful situations and had enhanced levels of corticosterone (Bolaños et al, 2003).

Several potential limitations of the current study should be mentioned. As with all retrospective studies, it is impossible to determine exactly what drug at what dose was taken. Urine screening, however, was performed to detect concealed recent dAMPH use. In future studies, more frequent urine screening previous to the study is needed to assess more appropriately what drug was taken at what time and to ascertain previous use of dAMPH. Second, there is a possibility that pre-existing differences between dAMPH users and healthy controls underlie differences in amygdala function. People with a dysfunctional DA system with low response on an acute DAergic challenge, may be predisposed to use dAMPH. Our relatively small sample size in this explorative study most likely explains why we only observed a near significant trend in the group x session interact did not observe a significant. Therefore, our data need be replicated in using larger sample sizes.

Conclusion

We observed increased amygdala activity in a group of intermittent high-dose dAMPH users, which normalized following oral MPH administration. MPH may thus restore amygdala dysfunction in individuals with DA dysfunction, such as the emotional dysfunction found in children with ADHD.