A blunted response to dextro-amphetamine in recreational dextro-amphetamine users assessed using [^{123}I]IBZM SPECT and pCASL based phMRI.

Anouk Schrantee[1], Lena Vaclavu[1], Dennis F R Heijtel[1], Matthan W A Caan[1], Jan Booij[1], Aart J Nederveen[1], and Liesbeth Reneman[1]
[1]*Academic Medical Center, Amsterdam, Netherlands*

Introduction: phMRI is a non-invasive imaging technique that allows us to study the effect of psychotropic drugs on brain neurotransmitter systems, for example the dopamine (DA) system. Dextro-amphetamine (dAMPH) is a psychostimulant that increases extracellular DA and has been shown to increase regional cerebral blood volume (rCBV) in animals, which correlated well with DA release as measured with microdialysis[1]. In addition, phMRI can be used as a tool to assess the integrity of the DA system. For instance, DA-lesioned primates showed reduced rCBV response to a dAMPH challenge compared to controls following MPTP lesioning, which correlated strongly with DA transporter availability[2]. However, it is currently unknown whether phMRI can assess DA (dys)function in humans with presumed altered DA functionality. Preclinical studies have shown that dAMPH damages DA nerve endings in the striatum of adult nonhuman primates[3]. Therefore, the aim of this study was to assess whether ASL-phMRI can detect differences in hemodynamic response to acute dAMPH administration between recreational dAMPH users and healthy controls. This was compared to 'gold standard' SPECT measurements of DA release. In line with the literature, we expected that dAMPH users would not show differences in baseline D2/D3 receptor densities[4], but instead a blunted response to a dAMPH challenge on the SPECT and phMRI scans, indicative of a dysfunctional DA system.

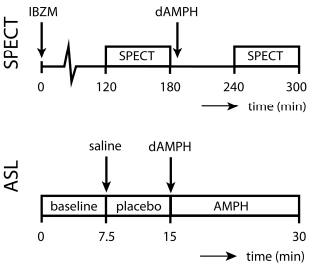

Figure 1 SPECT and ASL protocol

Materials & Methods: 19 male regular dAMPH users (mean age=21.7y) and 19 age and education matched male healthy controls (mean age=21.1y) underwent both MRI and SPECT imaging that were counterbalanced and at least one week apart.

MRI *(fig 1)*: MRI studies were performed on a 3T Philips Ingenia using a 16 channel receive-only head coil. PhMRI data were acquired with a pCASL sequence (TR/TE: 4000/14, resolution: 3x3x7 mm^3, 20 slices, labeling duration: 1650ms, delay: 1525ms, GE-EPI read-out, 240 dynamics). After 60 baseline images subjects received a saline challenge and after 120 images the dAMPH challenge (0.3mg/kg iv). After acquisition, data were realigned, quantified and normalized to common image space with SPM8. Striatal and grey matter (GM) CBF timecourses were extracted and compared between groups. To obtain CBF changes in the striatum specific to DA, effects of dAMPH on cerebral microvasculature were corrected for by calculating the percentage difference between GM and striatal CBF at that specific timepoint (sCBF=striatal CBF – GM CBF)/GM CBF. Statistical significance was assessed by testing post-dAMPH volumes and saline volumes against baseline using paired t-tests. Heart rate (HR) was measured during both the MRI scan and the SPECT dAMPH administration.

SPECT *(fig 1):* Subjects underwent two [^{123}I]IBZM SPECT scans to assess striatal D2/3 receptor availability and striatal dAMPH-induced DA release scan. The images were acquired on a Neurofocus SPECT system (12 detectors, 6mm FWHM) with the following parameters: matrix: 64x64; pixel size: 3.15mm; energy window: 135 – 190 keV; slice thickness: 5 mm, acquisition time per slice: 300 s, number of slices: 12; 80 MBq [123I]IBZM as a bolus followed by continuous infusion for 5 hours (20 MBq/h). dAMPH (0.3mg/kg iv) was administered after the first scan. SPECT images were corrected for attenuation and reconstructed using iterative algorithms. Striatal and occipital ROIs were drawn manually onto each individual scan. The occipital cortex (OCC) was used as a reference region and specific D2/3 binding potential (BP) was calculated as follows: *(mean striatal BP – mean OCC BP)/mean OCC BP*. dAMPH-induced decrease in [^{123}I]IBZM BP was expressed as a % of the pre-dAMPH BP.

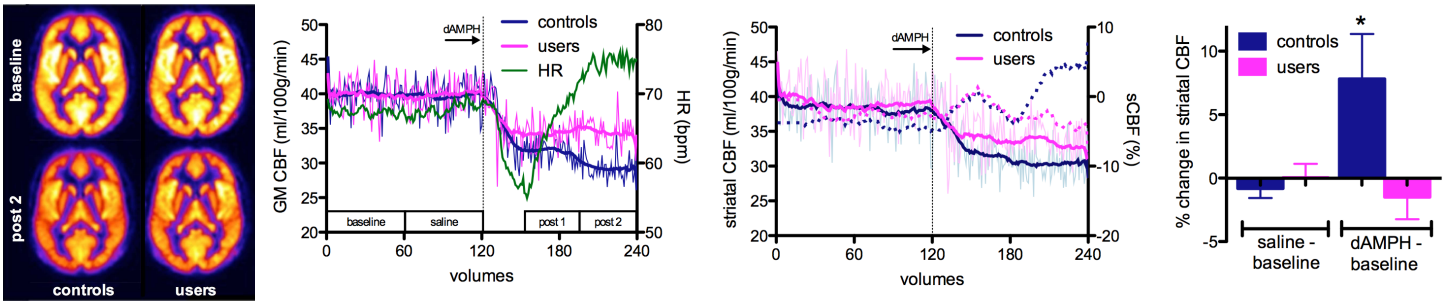

Figure 2 (a) mean CBF image of all controls and users, pre- and post- dAMPH administration (b) mean raw GM CBF timecourses for controls and users and mean HR for all subjects (c) raw and smoothed striatal timecourse in users and controls (solid lines); specific striatal CBF corrected for GM CBF (dashed lines) (d) change in striatal CBF during saline and dAMPH administration (post2) compared to baseline for controls and users (means+SEM are displayed)

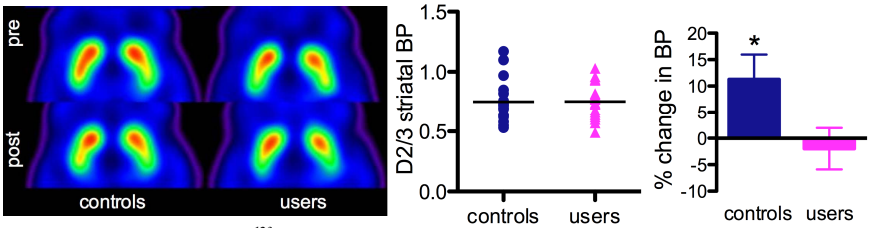

Figure 3 (a) mean image of [^{123}I]IBZM binding in all controls and users pre- and post-dAMPH administration (b) D2/D3 receptor availability in the striatum (c) DA release as measured by % change in [^{123}I]IBZM BP from baseline (means+SEM are displayed)

Results: For the MRI, acute dAMPH administration reduced striatal and GM CBF significantly compared to saline administration (p<0.000). However, dAMPH users showed a blunted dAMPH-induced decrease in striatal and GM CBF (fig 2b,c). Correcting striatal CBF for GM CBF resulted in specific increases in CBF in the healthy controls (p=0.041), but the response in the amphetamine users was blunted for users (p=0.404, fig 2d dAMPH - baseline). Post-dAMPH volumes were divided into two segments, one with a rapid decrease in HR (post1) and one with a stable HR (post2, fig 2b). Although there was a significant effect of acute dAMPH on HR (p<0.000), this followed a different timecourse than that of the CBF response (fig 2b). In addition, no HR differences between users and controls were found (p=0.859). For the SPECT, baseline D2/3 striatal binding did not differ between users and controls (p=0.758, fig 3b). However, striatal dAMPH-induced release of DA was blunted in the users compared to controls on the SPECT scan, reflecting DA release (fig 3c), as controls showed a significant increase in DA release following dAMPH administration (p=0.027), whereas users did not show different BP from baseline (p=0.623).

Discussion and conclusions: Our results of a blunted response to a dAMPH challenge on the SPECT and phMRI data are consistent with earlier studies in non-human primates and rodents and suggest that also in humans, dAMPH affects the DA system. These findings are particularly relevant, not only for users of this popular recreational drug but also for patients treated with this medicine, for instance for attention deficit hyperactivity disorder. The current study also highlights the potential of phMRI to assess changes in DA neurotransmitter function in humans, as the findings on phMRI were in accordance with the SPECT results.

References: [1] Chen (1997) Magn Reson Med, 38:389-98 [2] Jenkins (2004) J Neurosci, 24:9553-60 [3] Ricaurte (2005) JPET 15:91-8 [4] Bonhomme (1995) Brain Res 27:(1-2)