

Blunted hemodynamic response to a methylphenidate challenge in regular users of amphetamine: an ASL based pharmacological MRI study

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Introduction Studies in rats and (non-)human primates indicate lasting dopaminergic deficits after amphetamine (AMPH) treatment: i.e. reductions in striatal dopamine (DA) and its membrane transporter (DAT) (Ricaurte 2005, Reneman 2002). It has been demonstrated in non-human primates that a reduction in DAT binding caused by chemical lesioning, imaged by positron emission tomography (PET), correlates with cerebral blood volume changes evoked by an i.v. AMPH challenge (Jenkins 2004). This suggests that pharmacological MRI phMRI is a powerful tool for assessment of normal and dysfunctional DA brain function. In this study, we investigate the response of cerebral blood flow (CBF) as measured by arterial spin labelling (ASL) to an oral DA challenge with the psychostimulant methylphenidate (MPH). MPH is a DAT reuptake inhibitor and thereby increases levels of DA. ASL is a novel and non-invasive technique for quantitative assessment of cerebral blood flow (CBF). We compared the hemodynamic response evoked by MPH in AMPH users with healthy controls. Based upon the literature we hypothesized that we would observe a reduced or blunted hemodynamic response to MPH in AMPH users, presumably reflecting AMPH mediated changes in DA neuronal activity.

Subjects & Methods Seven male AMPH users (use of AMPH > 40 occasions; average age 26.0 y, SD 4.0) and nine healthy male controls (average age 22.0 y, SD 2.9) underwent phMRI. Subjects had to abstain from psychoactive drugs for at least 2 weeks. phMRI was performed on a Philips Intera 3.0T MRI scanner. A 3D-T1 weighted anatomical scan was acquired together with a combined ASL EPI sequence (PULSAR, Golay 2005) of 100 volumes with FOV 240 x 240 mm, TR/TE=3000/14 ms, 17 slices, slice thickness 7 mm. The ASL slab was 80 mm thick with a 1200 ms label delay. Following baseline scanning, subjects ingested 35 mg MPH and were scanned with the same protocol 1.5 hours later, when DAT occupancy by MPH is at its peak.

Analysis Perfusion weighted time series were averaged, creating a mean CBF before and after administration of methylphenidate. Resulting CBF images were registered to 3DT1 anatomical scans. Based on the literature (Ricaurte 2008, Jenkins 2004) and taking into account the spatial resolution of the data we chose the following ROIs: caudate, putamen, thalamus and hippocampus. For individual space registration we segmented the 3DT1 images using FreeSurfer software (<http://surfer.nmr.mgh.harvard.edu>). We then registered the images to the FreeSurfer anatomical brain and smoothed with a 2 mm kernel. For standard space registration we used Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) (Ashburner, 2007), with a gaussian smoothing of 6 mm. Transformations were applied to perfusion images accordingly. ROIs were obtained from both the individual FreeSurfer segmentations and the Harvard-Oxford brain atlas included with FSL 4.1 software. Mean baseline and post challenge CBF values were computed and subsequently analyzed using paired t-tests.

	FS pre (SD)	FS post (SD)	p-value	DL pre (SD)	DL post (SD)	p-value
Caudate control	41.0 (9.0)	37.2 (6.9)	0.116	42.2 (8.1)	38.3 (10.5)	0.127
Caudate amph	39.9 (5.5)	40.5 (8.8)	0.842	40.1 (7.3)	39.1 (12.0)	0.758
Putamen control	51.1 (13.1)	46.9 (8.8)	0.158	53.2 (13.4)	48.9 (9.9)	0.167
Putamen amph	52.7 (7.8)	52.4 (12.9)	0.946	54.4 (8.4)	53.0 (12.5)	0.723
Thalamus control	53.4 (29.7)	34.9 (10.7)	0.049	50.0 (27.5)	32.1 (10.5)	0.043
Thalamus amph	54.3 (23.9)	59.6 (16.3)	0.634	52.4 (23.7)	55.6 (15.1)	0.763
Hippocampus control	69.6 (31.9)	50.8 (13.1)	0.039	62.3 (27.5)	43.8 (10.1)	0.030
Hippocampus amph	71.6 (21.9)	69.1 (26.0)	0.817	71.4 (23.4)	65.1 (27.9)	0.560

Table 1 Group mean CBF (ml/100g/min) before (pre) and after (post) ingestion of 35 mg methylphenidate for healthy controls and regular users of amphetamine (amph) with standard deviations (SD). Note that FreeSurfer (FS) and DARTEL (DL) processing give similar results.

Discussion We report a marked reduction in CBF in response to an oral MPH challenge in specific brain regions involved in the DA brain circuitry of healthy control subjects using ASL based phMRI. In contrast, no CBF changes were seen in AMPH users. Previously, i.v. MPH administration was shown, using PET, to globally decrease CBF (Wang 1994) in healthy subjects. Oral MPH only caused decreases in CBF in several cortical regions and, similar to our findings, failed to affect the striatum (Mehta 2000). It is likely that local CBF changes in response to a MPH challenge are correlated to changes in DA function, as MPH-induced metabolic changes correlated with differences in D2 receptor binding (Volkow 1998). The blunted response in specific DA brain regions of AMPH users most likely reflects AMPH induced changes to the DA circuitry. In conclusion, ASL based phMRI seems a powerful and reliable new tool for assessment of the DA system, with consistent findings using different registration methods. Voxel-based analysis, additional ROI analysis and correlations to behavioural and SPECT data are ongoing

Refs: Ricaurte et al. (2005) J Pharmacol Exp Ther. 2005 Oct;315(1):91-8. Reneman et al. Psychopharmac. (2002)159(3):335-40; Jenkins et al. J Neurosci. (2004) 24(43):9553-60; Golay et al. (2005) MRM 53:15-21; Ashburner et al. (2007) Neuroimage 38:95-113; Wang (1994) Life Sciences 54 (9): 143-146; Volkow et al.(1998) Am J Psychiatry 155:1325-1331

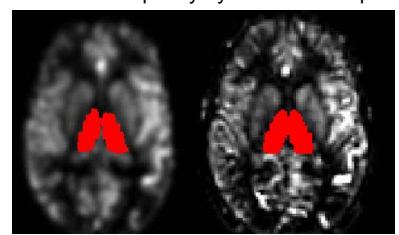


Figure 1 FreeSurfer (left) and DARTEL (right) registered perfusion images with both thalamus ROIs superimposed in red

Results MPH caused a statistically significant decrease in CBF in healthy controls. This effect was, however, only observed in the thalamus and hippocampus, and not the striatum (both with Freesurfer and DARTEL registration). The largest reductions were seen in the thalamus (see Figure and Table). No changes in CBF were observed in any of the brain regions examined in the AMPH users. Findings were consistent using registration to individual and standard space., e.g. a reduction in CBF of 34.6% using Freesurfer and 35.8% using Darte.

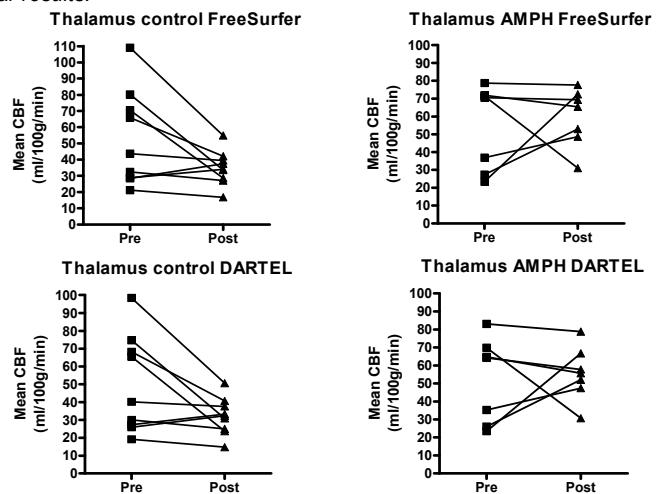


Figure 2 Mean CBF per subject in the thalamus at baseline (Pre) and after 35 mg of MPH (Post) in healthy controls and users of amphetamine, after processing with FreeSurfer (top) and DARTEL data (bottom) respectively.