

Pharmacological Magnetic Resonance Imaging (phMRI) in healthy subjects using an i.v. challenge with d-amphetamine

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Introduction

The dopamine (DA) system is pivotal in the pathology of several neuropsychiatric diseases. Pharmacological MRI (phMRI) can investigate neurotransmitter function by measuring the hemodynamic response to a pharmacological challenge. D-amphetamine (dAMPH), a drug that increases extracellular DA, is frequently used as a challenge. Jenkins et al (2004) have demonstrated in non-human primates that a dAMPH challenge can adequately assess DA function, since the hemodynamic response to dAMPH was blunted following DA lesioning. In addition, D2 receptor agonism has been found to influence regional cerebral blood flow (rCBF) (Chen et al. 2010). The purpose of this current study is to investigate how drug-induced brain hemodynamic changes correlate with D2 receptor availability in the human brain.

Materials & Methods

Twelve healthy male volunteers participated in this study (mean age = 21.0, S.D = 1.47). A 3DT1 anatomical scan was acquired on a Philips 3.0T MRI scanner, followed by a pseudo-continuous ASL sequence: TE/TR: 13.85/4.0 s, matrix size= 80x80, FOV = 240x119x240 mm, slices = 17, slice thickness = 7 mm, labelling duration = 1650 ms, post-labelling delay = 1525 ms, number of dynamics = 300. After the first 75 dynamics (10 minutes) of baseline scanning, 0.3 mg/kg AMPH was administered intravenously over 2 minutes. SPECT imaging took place under continuous infusion of the validated D2-receptor tracer [¹²³I]IBZM, using a 12-headed dedicated brain SPECT camera (SME 810).

ASL images were averaged over 25 dynamics into 12 time-bins. They were registered to 3DT1 scans and standard space using DARTEL (Ashburner, 2007) and smoothed (6 mm). Based on the literature (Jenkins 2004, Udo de Haes 2007) we chose striatum, anterior cingulate cortex (ACC), prefrontal cortex (PFC) and thalamus as ROIs using the WFU Pick Atlas toolbox. To control for general cardiovascular effects, a CBF ratio to whole brain CBF (CBF_{wb}) was calculated (CBF_{ROI} / CBF_{wb}). Mean baseline and post challenge CBF values were computed and subsequently analyzed using repeated measures ANOVA.

Results

Significant effects of dAMPH administration were observed in both striatum ($F(3.30, 36.34) = 2.96, p = 0.041$) and ACC ($F(3.45, 36.8) = 3.63, p = 0.018$), not in the PFC or thalamus. Planned contrasts in striatum showed a significant increase in CBF from baseline to time-bin 1 ($p=0.002$), time-bin 2, ($p<0.0001$), time-bin 3, ($p=0.001$) and time-bin 5 ($p=0.002$). In ACC CBF significantly increased from baseline to time-bin 2, ($p=0.024$), time-bin 4 ($p=0.004$), time-bin 4 ($p=0.027$), time-bin 5 ($p=0.041$), and time-bin 8 ($p=0.028$). SPECT images remain to be analyzed.

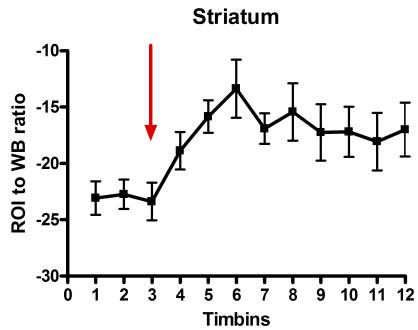


Figure 1 Ratio of Striatal CBF to WM (whole brain) CBF, averaged over 12 subjects with error bars. Red arrow marks start of amphetamine i.v.

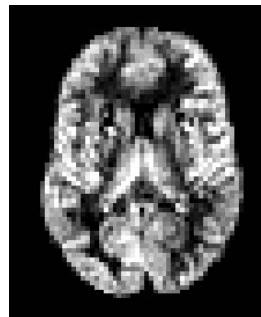


Figure 2 ASL data of a single subject averaged over 25 volumes (3.3 minutes)

Discussion

We report a significant increase in rCBF in response to an i.v. dAMPH challenge in specific brain regions involved in the DA brain circuitry of healthy control subjects. AMPH-induced changes in phMRI signal have previously been shown to correlate strongly with AMPH-induced increases in extracellular DA in rats (Chen et al., 2005). Based on the similarities between these findings and our own results and the fact that this effect was visible despite a conservative cardiovascular correction, the AMPH-induced hemodynamic response is likely to reflect DAergic functioning. Future analysis of SPECT data will determine whether this response is correlated to D2 receptor availability.

Conclusion

ASL based phMRI using i.v. dAMPH as a dopaminergic challenge seems to be a useful tool in imaging DA function.

Refs: Jenkins et al. (2004) J. Neurosci. Vol.24 no.43 pp.9553-9560; Chen et al. (2010) Dev Neurosci 32:125-138; Ashburner et al. (2007) Neuroimage Vol.38 no.1 pp.95-113; Udo de Haes 2007 Human Brain Mapping 28:625-635 (2007); Chen et al., (2005) Synapse 55:80-88