Functional Magnetic Resonance Imaging detects spatio-temporal differences between drug-naive and amphetamine-sensitised rats

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Introduction: Repeated exposure to psychostimulants such as cocaine and amphetamine is known to produce behavioural sensitisation, a long lasting effect expressed as an augmented motor-stimulant response [1]. The expression of sensitisation is thought to occur in the projection fields of mesocorticolimbic dopaminergic neurons. However the functional changes underlying to the development of this phenomenon remain elusive. We have investigated the neuroadaptations that accompany psychomotor sensitisation induced by chronic exposure to amphetamine by using functional magnetic resonance imaging [2] following an acute amphetamine challenge.

Material and methods: Male Sprague-Dawley rats (n=60) were randomly assigned to either saline (1 ml/kg, i.p) or amphetamine (1.5 mg/kg in saline, i.p.) sensitised groups. Animals were treated once daily (9:00 – 11:00 h) for five consecutive days. The MRI experiments were performed ~ 72 h after the last administration (Fig 1). The rats (250-350g) were anaesthetised using 2% Halothane in N_2/O_2 2:1, artificially ventilated and surgically prepared for blood pressure monitoring and venous administration of contrast agent and amphetamine. MRI data were acquired using a Bruker Avance 4.7T system, a 72mm birdcage resonator for RF transmit and a quadrature surface receive coil. The time series experiment comprised 256 time points using the RARE sequence: matrix 128x128; FOV 40mm; slice thickness 2mm; 8 contiguous coronal slices; TE_{eff}=110ms; TR=2700ms; NA=4, 10s/ image. A 2.67 ml/kg dose of Endorem contrast agent was administered i.v. following 5 reference image frames, to sensitise the acquisition to changes in CBV. Subsequently, at least 50 baseline images were acquired and sensitised and non-sensitised animals were given 0.1, 0.3 or 1mg/kg Amphetamine intravenously over a duration of 1 minute.

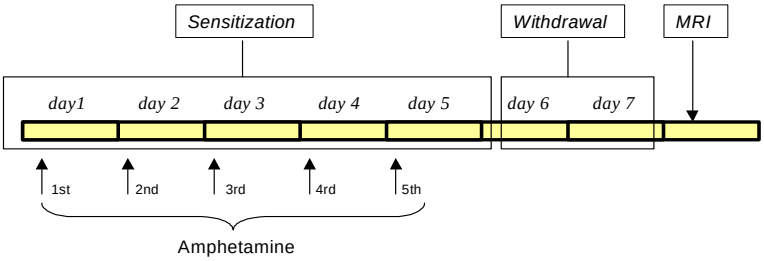

Figure 1: Standard sensitisation protocol with five daily injections of amphetamine 1.5 mg/kg i.p.

Results and discussion: The readout parameter for each rCBV time-course was the difference between 1-4 minute period post-amphetamine injection and a 4-minute baseline period prior to the amphetamine challenge. Figure 2 reports the thresholded group difference (at 1mg/kg challenge dose) following a 2-sample t-test (sensitised vs. unsensitised) at each pixel in spatially smoothed images. Blue areas represent regions where the rCBV change in the sensitised group was *lower* than that in the control group. Comparison between sensitised and control groups for animals challenged with 0.3 and 0.1 mg/kg of amphetamine showed little significant difference (data not shown). An alternative data analysis comparing the number of activated pixels in selected brain regions between sensitised and naive groups, yielded similar results. The acute dopaminergic challenge highlights a reduced cortical rCBV change in amphetamine-sensitised rats. This finding is consistent with the results of previous neurochemistry studies [3], where a decreased dopamine release in the medial prefrontal cortex of amphetamine-sensitised rats was reported. The reduction in the cortical dopaminergic response was statistically significant only at the highest challenge dose. Other authors also reported an augmented dopamine release in the nucleus accumbens core of sensitised animals [4]. Our study, however, did not evidence modulation of the accumbal response, at any of the challenge doses tested. In conclusion, this study demonstrates that functional MRI is capable of detecting functional neuroadaptations following a chronic drug exposure and will remain a valuable tool investigating the development and evolution of the mechanism of drug induced sensitisation and tolerance.

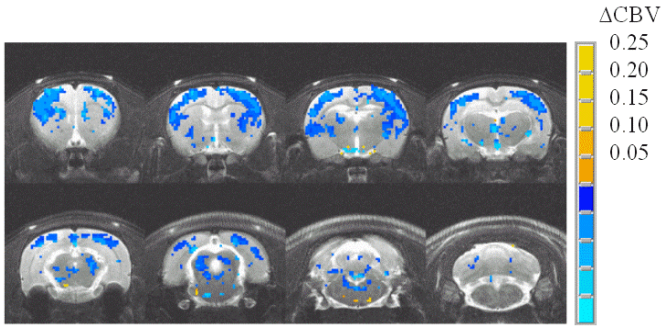

Figure 2: Group comparison maps at 1 mg/kg challenge dose. Blue regions reflect *lower* rCBV changes ($p_u < 0.05$) in the treated group.

References

[1] Steketee JD *et al.* (2003) Brain Research reviews **41** 203-228. [2] Chen *et al.*, (1997) Magn Reson Med. Sep;**38(3)** 389-98. [3] Hedou G *et al.* (2001) Neuropharmacology **40** 366-382. [4] Cadoni *et al.* European Journal of Pharmacology **388** 69-76.