Repeated acute cocaine challenges modulate the spatial pattern of rCBV response to cocaine in the rat

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Introduction

Acute cocaine challenge induces activation of the dopaminergic system in the rat that can be mapped with MRI methods [1,2]. This approach can be used to study the effects of dopamine antagonists by comparing the response to an acute cocaine challenge in treated and untreated animals. However, the sensitivity of the method is limited by inter-animal variability in the response to the challenge. As a possible alternative to unpaired group statistical comparisons, we investigated the reproducibility of repetitive cocaine stimuli in rats.

Methods

Twelve male Sprague-Dawley rats (250-350g) were anaesthetised using 2% Halothane in N_2/O_2 2:1 and the left femoral artery and vein were surgically prepared for blood pressure monitoring and venous administration of contrast agent and cocaine. The animals were scanned under halothane anaesthesia (maintenance level 0.8%) and artificially ventilated. MRI data were acquired using a Bruker Avance 4.7T system, a 72mm birdcage resonator for RF transmit and a quadrature surface receive coil (Bruker, Ettlingen, Germany). 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, 40s/ image. A 2.67 ml/kg dose of Endorem contrast agent (Guerbet, France) 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 three injections of either cocaine (0.5mg/kg) or 1.4ml isotonic saline were made at least 45 minutes apart from each other. High-resolution T2-weighted (RARE) and T1-weighted images (gradient echo) were acquired to facilitate the alignment and segmentation of images from different animals. Inter-subject co-registration and pixel-wise group comparisons were performed using AFNI. Signal alterations following the injection of cocaine were converted to rCBV values on a pixel by pixel basis [2]. Following in-plane spatial smoothing (0.6mm FWHM) the response readout was calculated pixel-wise as the difference between a 6-minute window (1min20-7min20) post-cocaine challenge and a 6min40s baseline window prior to an individual challenge. The rCBV activation maps of the first and second injections were grouped and subjected to a paired t-test on a pixel by pixel basis.

Results and Discussion

Figure 1 shows the paired t-test maps from a group of n=12 animals, revealing the difference between the first and second acute cocaine challenge. The response upon the second challenge is attenuated in regions including the mPFC, infralimbic, cingulate, retrosplenial and temporal cortices (blue colour). Potentiated responses occur at symmetric foci in the anterior motor cortex (orange-red colour). Other brain areas show less significant and scattered differences. Since the vascular alterations return to baseline around 20-30 minutes following the first cocaine injection, in parallel to extracellular dopamine and cocaine concentrations as observed by microdialysis, a direct vascular effect underlying the modulation of the second challenge can be excluded. The spatial localisation of the difference in response points towards cocaine-induced alterations in the excitability of specific brain regions by subsequent challenges. It should be noted that this phenomenon is quite different from the long-term neuroadaptation to chronic exposure to cocaine [3], and may be interesting for the understanding of the acute effects of cocaine on brain activity.

Conclusion

Repeated cocaine challenges induce significantly different spatial patterns of brain activity in the rat. Fast neuroadaptive “carry-over” effects from a previous challenge would represent a confounding factor in agonist-antagonist studies with repeated cocaine administration. This effect should be taken into account for the design of future fMRI studies in man and animal.

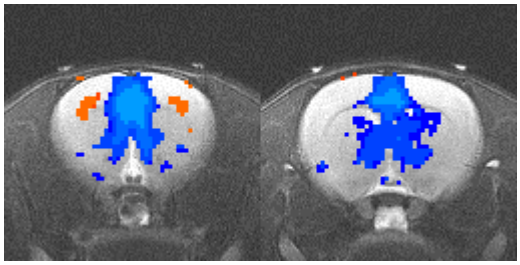

Figure 1: Map of the differences in the response between the 1st and 2nd acute cocaine injection in 2 slices, ~ z_{bregma}+3mm and z_{bregma}+1mm. (Note that *blue* colours reflect a *lower* response to the second injection, *red/yellow* colours a *higher* response to the second injection.)

References:

[1] Marota JJA *et al*. (2000) NeuroImage **11** 13-23. [2] Mandeville JB *et al*. (2001) Magnetic Resonance in Medicine **45** 443-447.
[3] Trantham H *et al*. (2002) Neuroscience. **113** 749-53.