Manganese-based pharmacological MRI using a low invasive approach: a feasibility study

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Introduction

Pharmacologic MRI is increasingly been recognized as a useful tool to study brain activation and deactivation patterns following pharmacologic challenges (1-3). The parameter used to map brain activation does however reflect the haemodynamic response rather than the underlying neuronal activation. Moreover, the BOLD response may be confounded by systemic haemodynamic or regional vaso-constricitve or –dilatory drug effect (4). An elegant way to map calcium influx associated with neuronal activation upon sensory stimulation or glutamate challenge has been demonstrated using dynamic manganese-enhanced MRI (5,6) . The experimental set-up used was however rather invasive requiring cannulation of the internal carotid artery. In this study, we aimed to combine the advantage of manganese-enhanced phMRI with the low invasiveness required for routine use.

Material and Methods

The rat model used involved a unilateral denervation of the middle forebrain bundle (MFB) with 6-OHDA as described before (7) . The effect of the lesion was tested by assessing the turning behaviour after APO challenge, but no further sensitization protocol was deployed. For phMRI rats were anesthetized with isoflurane (1.7-1.8 %) , mechanically ventilated, continuously monitored and kept warm by a heated water pad. Two i.p. catheters were inserted and Mn (380μM/kg in 74mM solution) was injected prior to placing the animal into the animal holder. MRI was performed at 7T (Biospec Bruker, Germany) using a dedicated receive-only head coil (except for one case where for technical failure the body coil was used). A multislice (7 slices: 1 mm thick, 0.21 gap, FOV: 3.5 cm) T1-weighted gradient-echo sequence (GEFI, TR=200ms, TE= 4.5ms, 2 averages, flip = 50, matrix =128x128) was used. 4 dummy scans were discarded and 70 time points (1 hour scan time) were acquired. To disrupt the blood-brain barrier, mannitol was injected prior to the serial T1 scanning (3-5 ml of a 20% solution). 15' after the start of the phMRI scan, amphetamine (3mg/kg) (AMPH group, n=7) or saline (NACL group, n=7) was injected. All animals were sacrificed at the end of the scan. Signal time courses were averaged over the left dorsolateral striatum as defined by landmarks using Analyze software. The signal time courses were averaged over groups and differences in the mean values over the baseline (image 1-20) and challenge period (images 30-60) were tested for significance using the student's t-test.

Results

The two groups did not differ in body weight (464 g [AMPH] vs. 490 g, [NACL] p=0.41) nor in their turning behaviour (103 [AMPH] vs NACL [94] turns, p=0.66).

In the lesioned dorsolateral striatum, a distinct signal increase was observed in the AMPH group, but no signal increase in the NACL group (1.4% [SD:1.0] vs. -0.13 % [1.1], $p<0.05$, fig). There was no difference between groups in the baseline that did not show any systematic trend either.

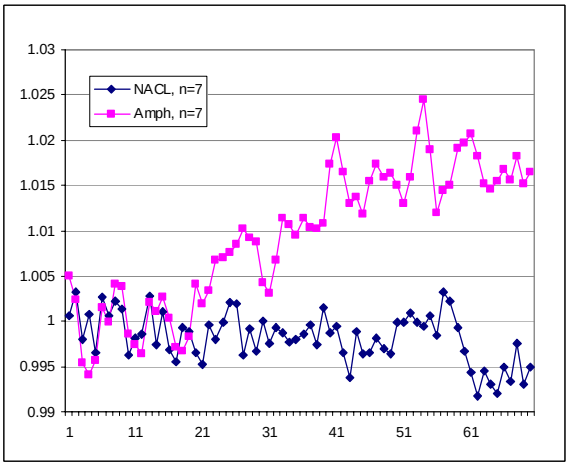

Figure: Group averaged normalized signal time courses in the left dorsolateral striatum. Injection of AMPH or NACL after 15' (image 17).

Conclusion

The results demonstrate the feasibility of a low invasive approach to study manganese-enhanced phMRI. The preliminary region-of-interest analysis also suggests a robust detection of amphetamine effects as no baseline drift was observed. Further comparative studies with BOLD and rCBV based phMRI are warranted to study the respective sensitivity and specificity.

References

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