T1-Mapped Acute Cocaine-Induced Brain Activation with Systemic Administrated Manganese-Enhanced MRI

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Introduction:

Cocaine-induced brain activation has been one of the most intriguing topics in man's endeavor to explore addiction mechanisms. Regular BOLD-based fMRI and laser Doppler flowmetry not only suffer from hemodynamic confounding caused by the potent cardiovascular activity of cocaine itself, but also reveal no animal responses under physiological conditions[1, 2]. Systemic administrated Manganese-enhanced MRI (MEMRI), with the capacity to reveal neuronal activity that happens outside of scanner and even farther[3], indicates a promising way to trace actual cocaine-induced neuronal response. In this study, we were the first to find more localized cocaine-induced activation at 24 h after systemic administration of $MnCl_2$.

Materials and Methods:

Twelve naive male Sprague-Dawley rats (250-350 g) received 25% D-mannitol at bolus dose of 5mg/kg through the tail vein under 1.5% isoflurane anesthesia (in 3:7 mixture of O_2 and air) to temporarily break the blood-brain-barrier (BBB). Animals quickly recovered from anesthesia and were set free to move. Fifteen minutes after mannitol injection, 50 mM $MnCl_2$ was intraperitoneally (I.P.) injected at two even doses of 50 mg/kg with injection interval of 20 minutes. One hour after the first $MnCl_2$ injection, either 5 mg/kg cocaine (study group, n=6) or same amount of saline (control group, n=6) was I.P. injected into the animals. Right before mannitol injection and at the 24th hour after cocaine/saline administration, all animals underwent two identical MRI scan sessions. With a Biospec 9.4T/31 cm scanner, rat gradient and birdcage RF coils (Bruker, Germany), as well as 0.2 ml medetomidine I.M. anesthesia, high-resolution images were first taken with multi-slice spin-echo sequence TR/ TE= 400/ 8 ms; FOV=3.5x3.5 cm^2; Matrix size= 256x 256; Slice thickness= 1 mm, 27 continuous slices, NEX=4. Then T1 measurements were acquired using the same sequence but six different TRs varying from 300 ms to 9000 ms. The same geometry was applied with a lower matrix size of 128x128 and NEX=1. Animal ECG, respiratory, and anal temperature were monitored during every scan. Water-bath warming pad was applied to maintain core temperature within 36±1 ℃. Respiratory gating was also performed. AFNI software was used for image motion correction, spatial and frequency smoothing, T1 curve fitting, and statistical comparisons. Twelve brain regions of interest (ROI) of all animal brains were segmented with MIVA software (University of Massachusetts Medical School, Boston, USA, Fig 2). Regional T1 change ratios compared with baseline values were analyzed with student *t*-test between the study and control groups.

Results:

Baseline brain T1 relaxation time of all rats at 9.4 T varies from 1761 ms to 2209 ms. All animals showed globally increased signal intensity and shortened T1 relaxation values at the 24th hour after $MnCl_2$ administration. T1 change ratios in the brain were in the range of 1.3% ~ 21.9% in the control group and 12.2% ~ 36.0% in the study group. In grouped *t*-test, significant differences ($P<0.05$) were found in the prefrontal cortex (PFC), nucleus accumbens (NAc), thalamus, and hypothalamus (Table 1, Fig 1).

Discussion:

D-mannitol was used to disrupt the BBB so that manganese can get into activated brain regions as much as possible. No infusion via the carotid artery was involved as used in regular activity mapping MEMRI, which not only simplified the whole procedure tremendously, but also enabled repetitive MRI scans and manipulations, capture of cocaine-induced brain responses under physiological conditions, and future longitudinal studies. Two identical doses of $MnCl_2$ of 50 mg/kg were separated with 20 minutes to minimize systemic side effect of manganese in combination with the following cocaine administration. After cocaine injection and before the second MRI scan, all animals experienced no anesthesia treatment but were allowed to move freely in the cage as usual, which further maintained the physiological environment and minimized stress-induced brain responses. Systemic administration of $MnCl_2$ has been proved to have the best enhance effect at 24th hour after its administration [x, y, z]. Compared with MEMRI taken simultaneously with BBB disruption and $MnCl_2$ infusion, our protocol is less subject to variations of BBB disruption rates among individual rats, as we allowed 24 hours to balance this effect. Given fast BBB disruption during instant MRI measurement, even saline may cause a higher signal increase than cocaine infusion as the transient increase of $MnCl_2$ in blood is higher. But this transient signal increase may not reveal much information on neuronal activity. T1 change ratios instead of direct signal intensity changes were analyzed, considering the consistent accuracy of T1 measurements in contrast to large variations of signal intensity among different scan sessions. No direct T1 change mapping was taken due to its critical reliance on accurate registration of the baseline and 24th hour images. Baseline rat brain T1 values we found were comparable with previous study[3]. Our results did indicate acute cocaine injection can induce rat brain activation of the dopaminergic system, specifically the NAc and PFC. Less cortical activation was found compared with the other study[2], which may be due to more transient perfusion increase in the cortical area, but may also be the result of insufficient dose injection of $MnCl_2$ for cortical delineation. This calls for robust flow measurement of those cortical regions. Application of mannitol may complicate the peak enhance time of systemic administrated MEMRI, which can be resolved with multiple measurements within the 24th hour after $MnCl_2$ injection. Future study with a larger sample size and dose variations is always more desirable.

Table 1 Regional baseline (Bas) T1 values (msec) and T1 average change ratio (Δ) in the Cocaine (Coc) and saline (Sal) groups

ROI	Amygda	Pit	M1,M2	Thalamus	Cpu	Hypothal	Somat	PFC	NAc	Hippo	Aud	Orb
Bas T1	2053±25	1968±18	2053±21	1871±13	1958±32	2063±28	2209±19	1838±27	1761±16	1985±24	2085±31	1959±22
Coc ΔT1	0.184	0.241	0.100	0.219	0.078	0.207	0.217	0.141	0.117	0.166	0.137	0.161
Sal ΔT1	0.109	0.1409	0.030	0.062	0.020	0.092	0.150	0.051	0.015	0.050	0.049	0.087
P value	0.117	0.108	0.105	0.029	0.250	0.034	0.095	0.028	0.042	0.080	0.114	0.080

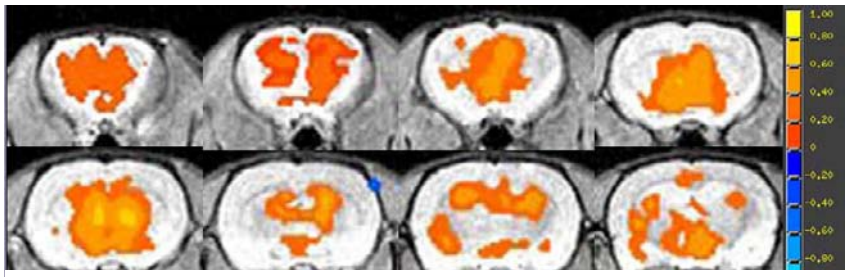

Fig 1. Maps of T1 relaxation change ratio from one rat in the study (cocaine) group at the 24th hour after $MnCl_2$ administration. PFC, NAc, thalamus, and hypothalamus were activated.

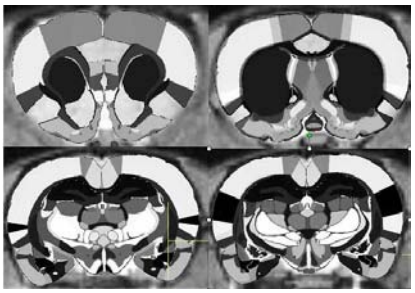

Fig 2. ROI segmentation with MIVA software, not all ROIs were selected.

1. Koretsky AP, Silva AC. NMR Biomed. 2004 Dec; 17(8):527-31.
2. Aoki I, et al. Neuroimage. 2004 Jul; 22(3):1046-59.
3. Lee JH, et al. Magn Reson Med. 2005 Mar; 53(3):640-8.