MEMRI and Single Pellet Reaching in Rats

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Introduction

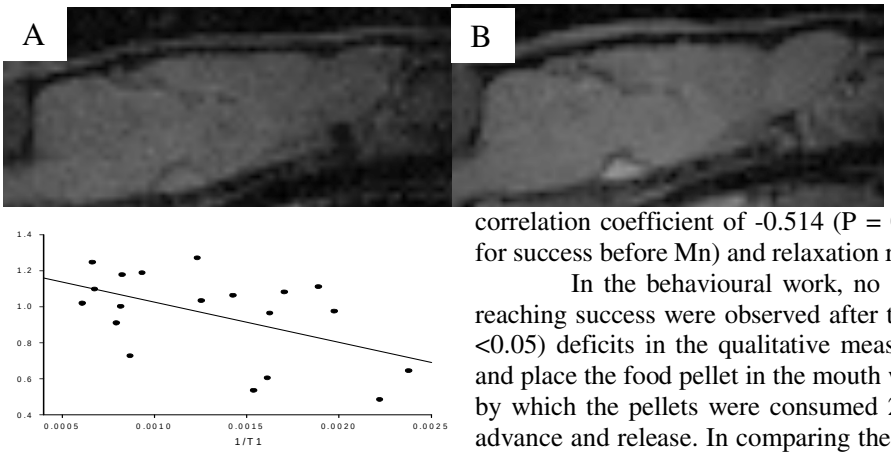
In 1997, it was demonstrated that MRI signal enhancement due to the accumulation of manganese (Mn) ions in regions of the brain that has increased activity could be achieved. Activation induced MEMRI has the potential to be a functional imaging method that is independent of the hemodynamics and can be performed on free ranging animals. Although Mn is an important trace element, it is toxic in high (>90 mg/kg for rats) concentrations[2,3] and is known to produce motor impairments associated with skilled movements (Parkinson's like condition). Single pellet reaching task[4] is widely used to study deficits in skilled motor movements after various brain injuries in rats and other mammals. We have used single pellet reaching to assess the possible adverse effects of Mn on the motor skills in rats. This is an important first step in combining MEMRI with widely used behavioural tests. In addition, we have performed T_1 mapping to assess if global and regional Mn distribution correlations can be related to the behavioural training.

Methods

Twenty-six adult female Long-Evans rats were trained in the single pellet reaching task. One group (n=11) received a 75 mg/kg dose of $MnCl_2$ (120 mM buffered in Bicine pH 7.4) infused through the tail vein at a rate of 1.06 ml/hr. Control groups were either naive (n=6) or received an equivalent volume of saline (n=9). All groups were tested and filmed for reaching behaviour 24 hrs after infusion. As well spontaneous activity was assessed with an activity box (Accuscan Instruments Inc., Ohio). The rats were then imaged (24 hrs after infusions) with a MRI scanner consisting of a 4.7 T 330 mm bore Oxford magnet and a SMIS console. The imaging coil was a homebuilt quadrature bird cage design that was 52 mm ID and 54 mm in length. A MRI compatible Stereotaxi (Kopf, CA) was used to position the animals. The imaging protocol for each rat consisted of a localizer image followed by a saturation recovery T_1 measurement (Saturation delay = 3000, 2000, 1200, 900, 700, 500, 300, 150; TE = 22 ms) in the coronal and sagital directions and a 3D T_1 weighted gradient echo (TR 100ms, TE 7ms 70°). The total imaging protocol took about 1 hr. Reference samples contain 0.5 mM $MnCl_2$ were placed above the brain for standardization. Gas anesthesia (Isoflurane) was used during the infusions and during the imaging sessions. Signal intensity from ROIs were extracted from the T_1 images with Analyze 8.1 (BIR, USA) and T_1 values were calculated using home written software written in IDL. Behavioral testing continued daily for 7 days. Some animals were also imaged on day 3, 5 and 7.

Results and Discussion

The two images below are from the T_1 measurement acquisition. These images depict A) a saline infused and B) a manganese infused rat. The saturation delay is 1200ms and clearly shows enhancement in the pituitary gland. ROI's were drawn in regions corresponding roughly to cortex, cerebellum, hippocampus and olfactory bulbs. Significant ($p < 0.05$) enhancement in the relaxation rat was observed in all regions with the greatest enhancement occurring as expected in the pituitary gland. Using the relaxation rate as a measure of the Mn concentration reaching the brain, we found a correlation coefficient of -0.514 ($P = 0.012$) between reaching success index (accounts for success before Mn) and relaxation rate (ms-1) as seen in the plot below.



In the behavioural work, no significant changes in the end point measures of reaching success were observed after the Mn dose (75 mg/kg), however, significant ($P < 0.05$) deficits in the qualitative measurements of movement components to reach for and place the food pellet in the mouth were observed. A striking indicator that the means by which the pellets were consumed 24 hrs after Mn administration is the time of the advance and release. In comparing the same animal before and after Mn administration, while the time of advance was virtually unchanged (2.16 ± 0.8 s and 1.92 ± 0.2 s respectively), the time of withdrawal was increased by a remarkable factor of 2.90 with Mn administration. This strong asymmetry of the forward and backward movement of the reaching paw was only observed on the first day. As well, the spontaneous activity (eg. rearing) was found to be reduced ($P<.05$) at 1 day and 3 days after Mn infusion. Our results suggest that observable behavioral effects of the manganese may last longer than the literature reports (24 hrs). All observed motor deficits returned to normal levels after 3-4 days.

Reference

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