# Dose dependence of $T_1$ and phase contrast following $Mn^{2+}$ systemic administration at 14.1T

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**Introduction:** Manganese Enhanced MRI (MEMRI) has been increasingly used in animal neuroimaging thanks to the signal enhancement of regions rich (or with active) voltage gated calcium channels when using $T_1$-weighted images [1,2]. Recently it was shown that at higher magnetic field strength, MEMRI can be also exploited by using manganese's susceptibility induced frequency shift [3]. MEMRI protocols need to consider the toxicity of $Mn^{2+}$ [1,4] and it is therefore important to evaluate the potential contrast enhancements obtainable with lower $Mn^{2+}$ doses.
The present work investigates the contrast enhancement after i.v administration of manganese as a function of the dose to assess the sensitivity of $T_1$-W and phase imaging at 14.1T.

**Methods:** All scans were performed on a 14.1 T/26 cm scanner (Varian/Magnex Scientific) using a home built quadrature surface coil as RF transceiver. $T_1$ mapping was obtained using a multi-slice inversion-recovery Look-Locker Segmented Echo Planar Imaging sequence [5] with 20 inversion times (50ms to 4050ms), TR/TE=24.5s/5.7ms, FA=20°, FOV=22*13mm$^2$, resolution =172*172*1000 µm$^3$, acquisition time of 14mins. For Nyquist ghost correction, a readout polarity reversal scheme was used. $T_1$ was calculated using a Nelder-Mead fitting algorithm. $T_1$-, $T_2$*-weighted and phase images with in-plane resolutions of 66µm were obtained using a gradient echo sequence with respiration gating (TR~1s), TE=5ms($T_1$-w)/16ms($T_2$*-w), FA=90°($T_1$-w)/50° ($T_2$*-w), FOV=17*17mm$^2$, resolution = 66*66*400 µm$^3$ and total acquisition time of 8mins. Phase images were unwrapped and large scale phase variations were removed using a dipole fitting algorithm [6].

Experiments were carried out using seven adult rats (Sprague–Dawley) weighting 250-300g. The manganese solution was infused via the tail vein (1.0mL/h) with a concentration of 120mM under 2% isoflurane anesthesia. The different doses were administered as follows: 2 rats with 175mg/kg, 3 rats with 125mg/kg and 2 rats with 75mg/kg. All scans were obtained on the same animal prior and 24h post $Mn^{2+}$ systemic administration under 2% isoflurane anesthesia and animal temperature maintained at ±37.5°C.
Phase images, $T_1$ and $T_2$* weighted images were acquired in different regions of the brain rich in voltage gated calcium channels such as the hippocampus, cortex, and olfactory bulb.

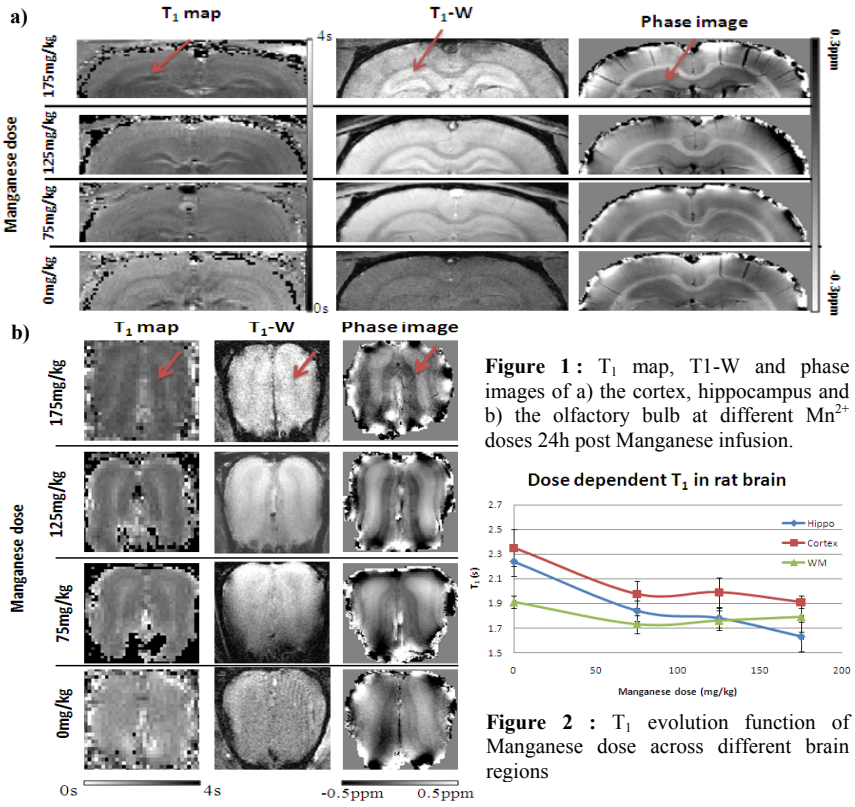


**Figure 1 :** $T_1$ map, T1-W and phase images of a) the cortex, hippocampus and b) the olfactory bulb at different $Mn^{2+}$ doses 24h post Manganese infusion.




**Figure 2 :** $T_1$ evolution function of Manganese dose across different brain regions

**Results:** 24h post manganese infusion for doses of 75, 125, and 175mg/kg, a $T_1$ decrease was observed in the cortex and hippocampus in the corresponding $T_1$ maps (fig. 1a). The effect was stronger at the highest dose of 175mg/kg as confirmed by the quantification of $T_1$ values in these regions (see Figure 2). As expected, the $T_1$ values in the corpus callosum remained constant demonstrating the absence of voltage gated calcium channels in that region. In figure 1.a) and b), the $T_1$ decrease in the cortex and hippocampus (fig. 1a) and in the olfactory bulb (fig. 1b) was accompanied by an SNR increase in the $T_1$-weighted images and phase images for all $Mn^{2+}$ doses. In comparison with pre $Mn^{2+}$ images, the phase images show increased contrast in the hippocampus and in the olfactory bulb with clear depiction of the CA1, CA3 and dentate gyrus and olfactory bulb layers for all $Mn^{2+}$ doses which is in good agreement with the regions enhanced in the $T_1$-weighted images. Qualitatively we can observe that in the phase images from the lowest dose, the contrast of the CA of the hippocampus and olfactory bulb layers was already enhanced and the anatomical depiction was comparable to the 125 and 175mg/kg doses.

**Discussion:** At high magnetic field, phase imaging is a potential candidate to explore MEMRI as the contrast observed is not only improved by the SNR increase from the $T_1$ reduction but also by the frequency shift increase between tissues with different $Mn^{2+}$ uptake. At lower doses, even though the $T_1$ reduction and thus the manganese uptake in different brain regions was reduced, the contrast observed in the phase image remains strong with clear depiction of various anatomical structures further supporting the notion of phase imaging's high sensitivity to magnetic susceptibilities and thus [$Mn^{2+}$]. Furthermore, as these results show that the phase contrast is not significantly hampered by reducing the $Mn^{2+}$ dose by 30%, the toxicity and mortality rate can be reduced. Further work will be followed to quantify the manganese uptake by computing magnetic susceptibility maps [6, 7].

**References and Acknowledgements :** [1] Silva, A. et al., NMR in Biomed. 2004; [2] Jason Tucciarone et al., NeuroImage 44 (2009) [3] Maddage et al., ISMRM, 2010/4550; [4] Grunecker et al., NMR Biomed 2010; [5] Gowland, P. et al., MRM, 1993; [6] Wharton et al., MRM 2010; [7] Shmueli et al. MRM 2009. This study was supported by the EPFL-Merck Serono Alliance award, by CIBM of the UNIL, UNIGE, HUG,CHUV, EPFL and the Leenaards and Jeantet Foundations.