Improving Visualization of Mouse Brain Nuclei in Manganese-Enhanced MRI using Super-Resolution Reconstruction

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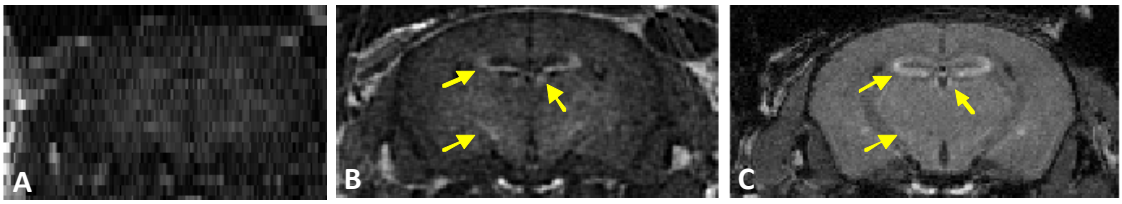
PURPOSE: Manganese-enhanced MRI (MEMRI) is increasingly used in small animal brain imaging, and is of particular interest to study higher brain functions, such as learning, memory, and reward behaviour in awake animals. Often gradient-echo (GE) sequences are used to monitor manganese uptake but inversion recovery spin-echo (IR-SE) offers an enhanced and different contrast as well as the additional benefit of being less susceptible to field inhomogeneities [1]. However, high-resolution (HR) 3D IR-SE imaging is not compatible with in vivo experiments due to very long acquisition times, and instead, anisotropic, low-resolution (LR) 2D slice stacks are acquired. In this study we demonstrate how super-resolution reconstruction (SRR) can be used to overcome the anisotropy issue and produce isotropic HR volumes in acquisition times within one hour. In addition, we demonstrate that IR-SE offers an improved contrast in a number of nuclei, particularly in the limbic system, which are of interest to study higher brain function.

METHODS: Two mice received daily 60mg/kg MnCl2 via a mini-osmotic pump for 5 days. At day 6, the mice were scanned on a 7T Bruker Pharmascan using a IR-SE sequence with a TR/TE/TI of 2700/8/670 ms, Navg = 1, in-plane resolution of 0.1 mm and slice thickness of 0.5 mm. Slice stacks were oriented in the transverse plane. The inversion time was chosen for optimal contrast in the hippocampal formation, based on a pilot experiment in which multiple TI times were acquired. The scan time per stack was 5 minutes. 12 LR slice stacks were acquired by rotating the field-of-view 12 times around the phase encoding direction (inferior-superior) in uniform increments of 180/12 degrees. SRR was performed using these images as described previously. Given the LR IR-SE slice stacks and a model of the acquisition process, SRR solves the so-called *inverse problem* of recovering the underlying HR image. Using additional prior knowledge about the solution, *e.g.* its smoothness, the problem can be formulated as a regularized least squares problem. For the purpose of both effective and efficient reconstruction, the method developed in [2] was chosen. This method employs the L2-norm of the second order derivative of the reconstruction as a regularizing term, and uses an affine transformation scheme that minimizes aliasing and spectral distortions. The system is solved by the conjugate gradient method. For comparison, a T1W GE scan was performed using a 3D flash sequence with a TR/TE of 30/3.6 ms, a flip angle of 30 deg., Navg = 5, and an isotropic resolution of 0.1 mm. The total scan time was 30 minutes. The SRR image and the GE image were rated by a neuro-anatomist for the visibility of a number of nuclei on a 3-point scale (not distinguishable, discernible positive enhancement or clear positive enhancement), as well as a relative rating specifying which of both techniques provided the best contrast for a structure.

RESULTS: The figure shows a corresponding coronal slice of (A) the original LR data, (B) the SRR image and (C) the GE image. The resolution enhancement due to SRR is obvious. It can also be seen, however, that the SRR image does not achieve an SNR as high as the GE image. Nevertheless, the SRR image shows some structures that are more clearly discernable from the surrounding tissues than in the GE image, such as the lateral habenular nucleus and the ventromedial thalamic nucleus (arrows). This examplifies the unique contrast properties of IR-SE MEMRI. In Table 1, a hierarchical overview of part of the rating results is given, demonstrating that SRR reconstruction of IR-SE data enables superior visualization of many (small) nuclei with specific functions e.g. in memory, stress, anxiety and reward behaviour.

CONCLUSION: IR-SE improves image contrast so that brain nuclei involved in higher brain function can be discerned ([1] and this paper), SRR improves the spatial resolution dramatically, so that fully isotropic 3D data can be acquired *in vivo* with a scan protocol of 30-60 minutes.



Level 1	Level 2	Level 3	Function	SRR vs GE
Telencephalon	Cerebral cortex	Motor	Voluntary movement	GE
	Sub-cortical structures	Olfactory tubercle	Reward behaviour	SRR
		Globus pallidus	Movement regul., addiction	SRR
		BSTMA	Anxiety	GE
	Hippocampus	CA1	Memory, spatial coding	GE
		CA2	Memory, spatial coding	SRR
		CA3	Memory, spatial coding	SRR
Diencephalon	Hypothalamus	Suprachiasmatic nucleus	Circadian rhythm	=
	Sub/epithalamus	Habenula	Pain, stress, learning, reward	=
Brain stem	Midbrain	Inferior culliculus	Auditory perception	SRR
	Pons	Nuclei of lateral lemniscus	Auditory processing	SRR
Cerebellum	Cerebellar cortex	Lamination	Motor control, learning	GE

REFERENCES: [1] Tindemans et al, NMR in Biomed., 2006, 19:18-29; [2] Poot *et al. MICCAI* 2010, pp. 615–622;