Repeated T1 mapping in brain following clinical dosage of Teslascan

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Introduction

Manganese enhances MRI is increasingly used for exploring neuronal activity, tracing white matter tracts and for structural delineation of normal and pathological brain anatomy in animals *in vivo* [1]. Manganese is a Ca^{2+} analogue and enters the cells via many different Ca^{2+} channels. Depending on mode of administration different features of brain structure and function can be depicted. Unfortunately manganese has neurotoxic properties. Acute neuronal death is observed in response to high CNS concentrations of manganese, whereas neurodegeneration is found after prolonged intracellular accumulation of manganese. These neurotoxic effects hamper the use manganese enhances MRI in human neuroimaging. Teslascan (mangafodipir trinatrium, Amersham Health, Oslo, Norway) is a manganese based contrast agent clinically approved for diagnosing liver pathology and also used in cardiac MRI of tissue viability [2,3]. In the present study we explored the effect of one standard intravenous dose of Teslascan on T1 relaxation rate in the brain. The aim of the study was to investigate whether Teslascan leads to measurable changes in T1 relaxation and for how long such changes persist. If Teslascan in clinically approved dosage in combination with T1 mapping have sufficient sensitivity to allow detection of subtle differences in manganese enhancement, Teslascan could possibly be used for accurate spatial localization of regions with pathological increased or decreased neuronal activity in humans.

Methods

The study was a substudy performed in connection with a study of manganese enhanced MRI for cardiac imaging. The study was approved by the local ethical committee and adhered to the Helsinki convention. Eight healthy male volunteers were recruited from the university campus and participated in the neuroimaging part of the study. Teslascan was administered intravenously at standard dose of 0.5 ml/kg bodyweight at a rate of 4-6 ml/min.

T1-mapping was performed on a 3T Siemens TIM-TRIO using a sagittal 3D saturation recovery turbo-flash sequence with linear reordering. The following parameters were used: FOV 256x256x192, acquisition matrix 256x256x96 with Grappa = 2 along PE and 6/8 partial fourier in the 3D direction, TR/TE = 7.8/3.84 ms, FA = 5 deg. Multiple saturation delays (TD) were used: 104 ms (nrep = 4), 250 ms (nrep = 3), 500 ms (nrep = 2), 1000 ms (nrep = 1), 2000 ms (nrep = 1) and 4000 ms (nrep = 1). Total scanning time was about 20 minutes for each subject. Each volunteer was scanned using the above protocol four times; Before injection of Teslascan, one day after injection, four days after injection and seven days after the injection. For each volunteer all the MRI volumes were coregistered to a chosen reference volume for that individual using the normalized mutual information method in SPM5.

The signal equation for the applied MRI sequence was derived for the case of arbitrary saturation flip-angle to take into account the possible inhomogeneous B1+ excitation field at 3T. To exclude low signal regions voxels with signal intensity below 100 in at least one of the 12 acquisitions in a dataset were excluded before analyses. For each of the remaining voxels, the best fit between the acquired signal intensities and the signal equation was found using least-squares fitting with T1, S_0 and the saturation flip angle as fitting variables. T1-values were extracted from three different brain regions: Hippocampus, Caudate Nucleus and Corpus Calossum, see figure 1. Paired t-test was used to assess the statistical significance of the change in T1 as compared to the baseline measurement, where $p<0.05$ was considered significant.

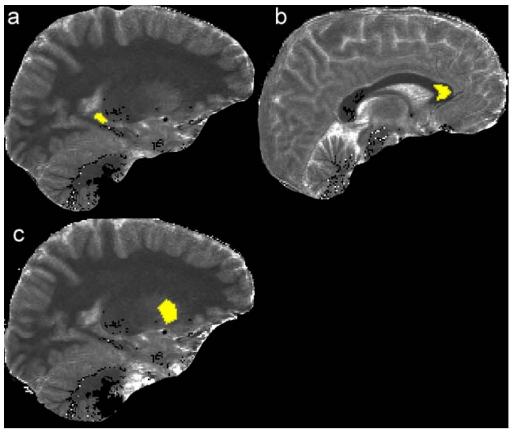

Figure 1. ROI definitions. a) Hippocampus, b) Corpus Callosum, c) Caudate Nucleus.

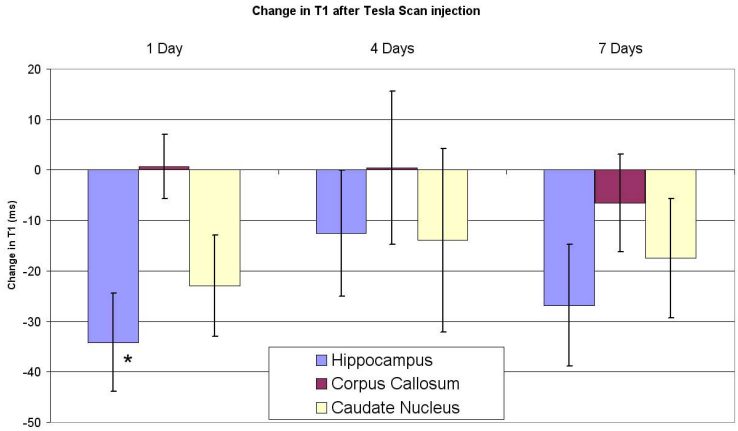

Figure 2. Mean +/- SEM of the change in T1 value at different time points after injection of Teslascan. * $p<0.05$.

Results and Discussion

One subject was excluded due to motion artefacts, resulting in seven subjects included in the analysis. Figure 1 shows the sagittal T1-maps indicating the positioning of the ROIs. The baseline T1 values (mean +/- SEM) in the three different brain regions were: Hippocampus: 1254 +/- 12 ms, Caudate Nucleus: 997 +/- 12 ms, Corpus Callossum: 659 +/- 13 ms. Figure 2 shows the mean and SEM for the change in T1 relative to baseline at the three time points after Teslascan injection. There was a significant reduction in T1 in the hippocampus day one after Teslascan administration. In the caudate there was trend of reduced T1, but not statistically significant. In white matter in the corpus callosum no change in T1 was detected.

In healthy volunteers the amount of free manganese following one clinical dose of intravenous Teslascan was sufficient to induce significant changes in T1 only in the hippocampus at day one after the injection. The accumulation of manganese in the hippocampus can be attributed to two main factors. First, manganese primarily enters into neurons with high activity since uptake is coupled to Ca^{2+} entry into the cells. The hippocampus has very high neuronal activity. Second, the hippocampus is almost enveloped by the cerebrovascular fluid (CSF). At near normal blood concentrations of manganese, brain influx is primarily via CSF. Thus the hippocampus will be exposed to higher manganese concentrations than the other brain regions, although it should be noted that also the head of the caudate nucleus is close to CSF. The lack of T1 changes in white matter is consistent with findings that manganese primarily accumulates in grey matter. Only a trend toward reduced T1 was detected in the caudate nucleus throughout, and in the hippocampus for day four and seven. The amount of free manganese was thus not large enough to produce lasting changes in T1 even in the hippocampus.

References: [1] Pautler et.al MRM 40(5):740 (1998), [2] Young et.al MRM 10(1):1 (1989), [3] Torres et.al Acta Radiol 38:631 (1997).