# BRAIN IRON LEVELS AS MEASURED BY QUANTITATIVE SUSCEPTIBILITY MAPPING (QSM) ARE NOT SIGNIFICANTLY DIFFERENT BETWEEN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT (MCI) AND CONTROLS

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**Introduction:** Iron accumulation has been implicated in advanced stages of Alzheimer's disease (AD) both in post-mortem studies [1,2] and in vivo using MRI techniques [3]. Although iron is in general associated with oxidative stress in neurodegenerative disease, its effect in AD is still largely unknown. In order to develop effective treatment or preventative strategies the role of iron needs to be elucidated. It is also unknown at what stage of the disease the accumulation of iron starts, since strong clinical symptoms often occur only after severe neurodegeneration has already taken place. Recent developments in the field of quantitative susceptibility mapping (QSM) have made it possible to directly map brain tissue magnetic susceptibility, which has been shown to correlate well with tissue iron concentration in most brain gray matters [4,5]. In the present study QSM was used to assess the difference in iron levels between healthy elderly controls and subjects with mild cognitive impairment (MCI), in cortical and deep grey matter. Although MCI can be caused by other pathologies, in general subjects with MCI develop AD in later stages [6] and can thus be used to investigate pre-AD markers.

**Methods:** Eighteen subjects with MCI (11 male, 7 female; mean age 75.0 ± 7.2) and twenty-two healthy elderly controls (14 male, 8 female; mean age 72.0 ± 5.3) were studied using a 7T Philips MR system with a 32-channel NovaMedical head coil. All participants received psychiatric examination and were screened for cognitive impairment (Mini Mental State Examination [7] and Montreal Cognitive Assessment [8]) followed by specific assessment of cognitive subdomains with several other tests. Subjects were categorized either as cognitively normal or MCI according to established criteria for diagnosis of MCI [9]. A T1-weighted MP2RAGE image (TR/TE=6.9ms/2.0ms; 0.75x0.75x0.75 $mm^3$) was acquired for anatomical referencing and automated image segmentation. Phase data for susceptibility measurements was acquired using a multi-echo 3D GRE scans with 3 echoes (TR/TE/ΔTE=23/6/6ms, flip angle=10°, 0.5x0.5x0.5$mm^3$). Phase datasets acquired with an echo time in the range of 12-18ms were used. Phase unwrapping was performed using Laplacian based phase unwrapping [10]. Subsequently, background field were eliminated with sophisticated harmonic artifact reduction for phase data (SHARP) [11] using a variable spherical kernel size with a maximum radius of 4mm and a regularization parameter of 0.05 [12]. After removal of background field, the resulting images of the two echoes were averaged to obtain a higher signal to noise ratio as compared to single echo reconstruction [13]. Inverse dipole calculations to obtain the susceptibility maps were performed using a LSQR based minimization [10]. The T1-weighted image was co-registered to the GRE magnitude image using FSL FLIRT [14] and used for segmentation in a multi-atlas matching approach [5,15]. The frontal cerebral spinal fluid region (CSF) in the lateral ventricles region showed least inter and intra subject variability and was selected as a reference region for the final susceptibility quantification. All reported susceptibility values are relative to this reference region. The volume of brain structures, an indicator of AD pathology [16], was calculated based on the automated segmentation.

**Results:** From the automatically segmented regions of interest (**Fig. 1**) basal ganglia structures and cortical grey matter known to be affected in AD were selected. There was no significant difference between susceptibility values in the MCI group and the controls when controlling for age, in both basal ganglia (**Fig. 2**, top) or cortical regions (**Fig. 2**, bottom). When comparing brain volume for these regions a significant difference ($p<0.05$) was observed in the hippocampus, in all the other regions there was no significant difference. In about 40% of the subjects (**Table 1**) susceptibility was correlated with volume on a per-subject basis when including all regions. However, no correlations where found in any subject when only cortical regions or basal ganglia structures were compared per-subject. Comparing susceptibility and volume per ROI for all subjects, only controls or only MCI subjects did not result in significant correlations.

**Discussion and Conclusion:** Subjects having MCI do not show increased iron levels, as measured by QSM, when compared to controls. Although hippocampal volumes are significantly different there is no evidence of a strong correlation between susceptibility and volume in any ROI. This preliminary study on a small group of subjects indicates that magnetic susceptibility as a single measure may not be sufficent for clinical use as biomarker for brain dysfunction as reflected by cognitive impairment.

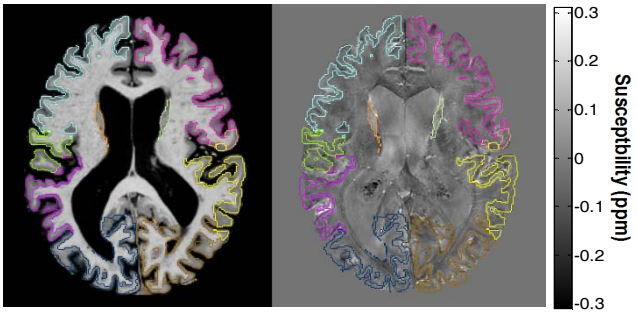


**Fig. 1:** *Example automatically generated ROI's on T1 and QSM images of 79y old MCI patient.*

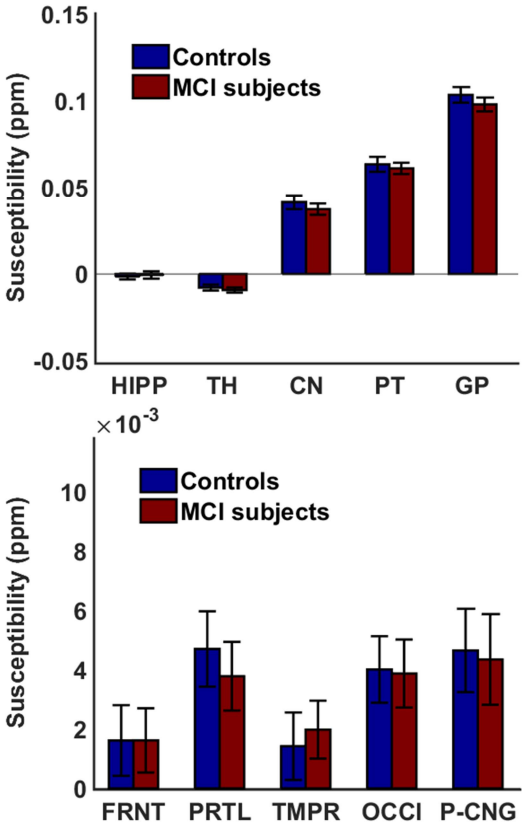


**Fig. 2:** *Group comparison top: Hippocampus, Thalamus, Caudate Nucleus, Putamen and Globus Pallidus. Bottom comparisons for: Frontal, Parietal, Temporal and Occipital cortices and posterior Cingulate Gyrus.*

| | Controls | MCI |
|---|---|---|
| Total # subjects | 22 | 18 |
| # of p<0.05 in QSM vs. Vol **per Subject** | 9 *(41%)* | 7 *(38%)* |
| # of p<0.05 in QSM vs. Vol **per ROI** | 0 | 0 |

**Table 1:** *Overview of significant correlations*

**References:** [1] House MJ, et al. Magn Reson Med 2007;57:172. [2] Connor JR, et al. J Neurosci Res 1992;31:75. [3] Bartzokis G, et al. Cell Mol Biol 2000;46:821. [4] Langkammer C, et al. Neuroimage 2012;62:1593. [5] Lim IAL, et al. Neuroimage 2013;82:449. [6] Sperling RA, et al. Alzheimers Dement 2011;7:280. [7] Folstein MF, et al. J Psychiatr Res 1975;12:189. [8] Nasreddine ZS, et al. J Am Geriatr Soc 2005;53:695. [9] Albert MS, et al. Alzheimers Dement 2011;7:270. [10] Li W, et al. Neuroimage 2011;55:1645. [11] Schweser F,et al. Neuroimage 2011;54:2789. [12] Wu B, et al. Magn Reson Med 2012;67:137. [13] Wu B, et al. Neuroimage 2012;59:297. [14] Jenkinson M, et al. Neuroimage 2002;17:825. [15] Tang X, et al. PLoS One 2013;8:e65591. [16] Silbert LC, et al. Neurology 2003;61:487.