Inference at the cluster level from the relationship between QSM and age

Julio Acosta-Cabronero[1], Arturo Cardenas-Blanco[1], and Peter J Nestor[1]
[1]*German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Saxony-Anhalt, Germany*

Target Audience. Researchers and clinicians interested in quantitative susceptibility mapping (QSM).

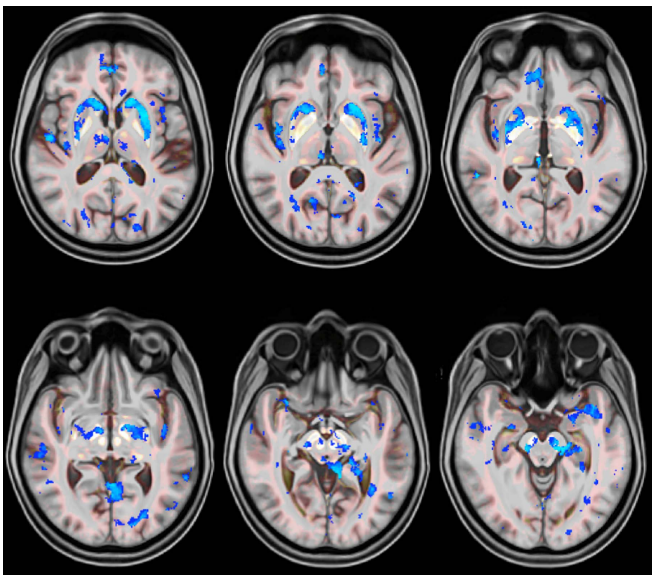
Purpose. Explore the QSM relationship with age in the whole brain.

Introduction. It is thought that, in the course of ageing, iron homeostasis gets disrupted causing iron levels to increase, hence promoting oxidative damage (Zecca et al. Nat Rev Neurosci 2004). Some understanding about this mechanism would be beneficial, not only for the study of aging but also of neurodegenerative brain diseases, for which there are predictions (e.g. iron or copper accumulation) that might be, in part, also a function of normal aging (Ke & Qian, Lancet Neurol 2003). This work aims to identify QSM effects (for the first time at the cluster level) that co-vary with age, with a view to inform our understanding of disease-related phenomena.

Methods. N=34 healthy volunteers (51-77 yrs.) were recruited for this study. Susceptibility weighted datasets were acquired in a Siemens Verio 3T system (32-channel head coil) using a single-echo 3D flow-compensated GRE sequence: TR/TE/α/BW=28ms/20ms/17°/100 Hz/px; matrix, 256×224 (R>L phase encoding); 80 (+16 for oversampling) axial slices (slab-selective excitation) with voxel resolution of 1×1×2 mm^3; GRAPPA factor of 2; for a total scan time of 5:32 minutes. Post-processing methods were optimised; in short, individual complex channel data were combined with an adaptive approach (Yang et al., ISMRM 2009). Combined phases were unwrapped with the Laplacian method (Schofield & Zhu, Opt Lett 2003). The external (background) field was extracted using the PDF algorithm (Liu et al. NMR Biomed 2011, http://weill.cornell.edu/mri/pages/qsm.html). Finally, noise-matched MEDIN-QSM inversions (Liu et al., MRM 2013, http://weill.cornell.edu/mri/pages/qsm.html)—normalised to a posterior white matter region of low variance—were spatially standardised to a study-specific space using an ANTs-based routine (http://stnava.github.io/ANTs). These were then median filtered (in 3D by a 7×7×7-mm^3 convolving window) to minimise the effects of imperfect registration and to cancel out the effects of narrow hyper-/hypo-intense structures (mostly vein suppression as we focus here on storage iron). Finally, cluster-wise non-parametric inferences from the relationship between age at imaging and QSM were carried out using FSL-randomise v2.9 (Nichols & Holmes, HBM 2002) with 5,000 permutations of the data and threshold-free cluster enhancement (TFCE; Smith & Nichols, Neuroimage 2009). Statistical maps were thresholded at $P_{TFCE}<0.01$.

Results. QSM clusters of strong positive correlation with age were identified focally in the striatum (see whole brain results and median/interquartile plot for bilateral putamen ROI extraction as a function of age; $R^2=0.41$, P<1e-4), and more scattered in cortical and white matter areas. A superior nuclear thalamic subregion and mesencephalic structures (substantia nigra and red nucleus) were also strongly involved. The reverse contrast, i.e. negative correlation, was completely negative at $P_{TFCE}<0.01$.

Discussion. A number of studies to date have demonstrated that QSM holds a close relationship with age in deep grey matter nuclei (Bilgic et al., Neuroimage 2012; Wu et al., MRM 2012). In this correlation study, we explored this further by way of a *state-of-the-art* standardisation strategy, followed by 3D median filtering and non-parametric permutation statistics. The results confirmed predominant striatal, mesencephalic and diencephalic involvement; then more scattered, cortical and white matter changes. The latter effects, though thus far unreported, lacked sufficient spatial confluence to make clear observations about their spatial distribution; they therefore warrant a more detailed investigation on a larger group. Interestingly, QSM in the globus pallidus did not co-vary with age with the same strength than in its basal ganglia neighbours (*e.g.* the striatum); this result also warrants further investigation.



Conclusion. A previous study identified *in vivo* QSM alterations in the Alzheimer's disease striatum—chiefly the putamen (Acosta-Cabronero et al., Plos One 2013)—over and above that seen in aged-matched controls. This study suggests that such alterations may be caused by specific vulnerability, i.e., they may represent the exacerbation of pre-initiated age-related metal deposition.