Validation of susceptibility mapping for quantification of iron in subcortical grey matter in multiple sclerosis

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PURPOSE: Iron accumulation in human brain has been reported in various neurological diseases including multiple sclerosis (MS), where there is increasing interest in subcortical grey matter (GM). Validating MRI measurements of human brain iron requires postmortem study. Using healthy subjects, Langkammer et al. found high correlations for both R2* mapping (1) and quantitative susceptibility mapping (QSM) in postmortem subcortical GM compared to chemical iron analysis (2). However, few studies in patients have been performed using both MRI and histology. Recently, we examined subcortical GM in postmortem MS subjects, comparing Perls’ ferric iron stain to in situ MRI measurements of R2 and R2* transverse relaxometry and phase imaging, finding the highest correlations with R2* mapping (3). Here, we extend this work to QSM, a promising alternative method for brain iron mapping, and compare QSM performed in situ in postmortem MS subjects to Perls’ iron stain.

METHODS: MRI: Three-dimensional multiple gradient-echo acquisitions were collected at 4.7T (Varian, Palo Alto, CA) from two postmortem MS patients 28hrs after death (male, age: 60 and 63 yrs) and four healthy male subjects (age: 47 ± 0.6) to Perls’ iron stain, have significant linear correlations (4). To Perls’ iron stain (5). To Perls’ iron stain, we had significant linear correlations (6). To Perls’ iron stain, we had significant linear correlations (7). To Perls’ iron stain, we had significant linear correlations (8).

RESULTS: Example postmortem images are shown in Fig 1. Subcortical GM is well depicted with all methods; hypointense in FSE (Fig. 1b) and hyperintense in R2* and QSM (Fig. 1c,d) with good correspondence to the Perls’ iron photograph (Fig. 1a). The R2* and QSM maps show very consistent patterns in terms of strong susceptibility sources from non-heme iron in deep GM and heme iron in deoxygenated vessels. Both QSM and R2* mapping have significant linear correlations (R² > 0.6) to Perls’ iron stain (optical density) (Fig. 2). The R2* and susceptibility maps also exhibit significant linear correlations with each other (Fig. 2c,f). Example in vivo images are shown in Fig 3 where the pulvinar thalamus in particular shows high susceptibility contrast in QSM. R2* and QSM have a high linear correlation to each other with R² = 0.827, including measurements from four individuals.

CONCLUSION: In situ postmortem imaging is free of confounding effects from formalin fixation and retains air-tissue interfaces, but is limited by full blood deoxygenation. Nevertheless R2* mapping and QSM had significant linear correlations to ferric iron staining in both postmortem MS subjects. These correlations suggest both MRI methods could be used to indicate iron status of subcortical GM in MS.