Establishing MRI phase, abnormal MRI phase, and volume behavior in the subcortical deep gray matter of healthy individuals

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TARGET AUDIENCE: Researchers in the field of iron imaging, brain aging, and considering the present work concerns healthy subjects, the general population.

PURPOSE: For decades, increases in brain iron levels have been known to occur in neurodegenerative disorders such as Alzheimer's and Parkinson's disease. These disorders are associated with advanced age. Coincidentally, *post-mortem*[1] and more recently, magnetic resonance imaging[2] (MRI) studies, have described brain iron concentration increases in healthy individuals, and reported on gender and hemisphere differences. Even though there is an established connection between brain iron levels and aging, it remains unclear whether overall brain iron and local iron levels of tissues with very high iron concentration increase linearly with age and whether increased iron concentrations are related to atrophy. In order to evaluate brain iron concentrations *in vivo* and tackle these remaining questions, several MRI techniques have been proposed. In this study we investigated brain iron levels in a large cohort of healthy individuals using susceptibility weighted imaging (SWI) filtered phase

METHODS: 210 healthy individuals (males: N=89, females: N=121), mean age 39.8 years (SD=15.5, range: 6-76 years), were imaged using a 3D flow-compensated gradient echo (GRE) sequence on a 3T GE scanner. Phase images were high-pass filtered by applying a 2D inverse Hanning window (filter size: 64x64) in Fourier domain. Phase is presented in radians, with paramagnetic substances corresponding to lower mean phase values. Mean MRI phase, mean phase of the abnormal phase tissue (MP-APT) and normalized volumes were determined for total subcortical deep gray matter (SDGM), caudate, putamen, globus pallidus, thalamus, pulvinar nucleus, hippocampus, amygdala, nucleus accumbens, red nucleus, and substantia nigra. MP-APT is a measure of the extent of iron deposition in tissues with very high (>2SD from the mean) concentrations of iron[3]. To assess the relationship between brain structures and aging, both linear regression and non-linear curve estimation adjusted for the effects of gender and hemisphere were carried out. Moreover, separate gender and hemisphere effects were investigated using group-wise comparisons

RESULTS: Significantly lower phase values, indicative of greater iron concentration, were detected in the left hemisphere compared to the right hemisphere and in females compared to males ($p<0.001$). Figure 1 shows the relationship between mean phase, MP-APT and normalized volume with age in the thalamus. In this structure (Figure 1, top), as well as in the total deep gray matter, caudate and pulvinar nucleus (not shown), the mean phase values showed a non-linear relationship, with individuals in late middle-age (40-50) having the lowest mean phase values, followed by a reversal of this trend ($p<0.001$) in the elderly. In contrast, MP-APT, indicative of very high iron deposition, showed strong negative linear relationships with aging (middle; $p<0.001$). Normalized volume measurements were also linearly related to aging (bottom; $p<0.001$). In addition, lower MP-ATP was related to decreased gross brain volumes ($p<0.05$), with an especially strong association between lower MP-APT and gray matter volume reduction ($p<0.001$).

DISCUSSION AND CONCLUSIONS: A strong association between phase (quadratic) and abnormal phase (linear) with increasing age was observed. Increases of brain iron concentrations, as observed in this study, are in line with previous findings[1,2]. Using a sizeable sample of subjects scanned with SWI, it was demonstrated that likely deep gray matter iron increases are strongly related to aging, and that this association is non-linear when assessing overall MRI phase, but is linear when assessing abnormal phase tissue, a measure of high iron content. Furthermore, MP-APT was correlated with brain atrophy suggesting that high iron concentration, aging and possibly pathology in neurodegenerative disorders are intricately associated. SWI filtered phase is a useful tool in monitoring *in vivo* brain iron concentrations.

References:
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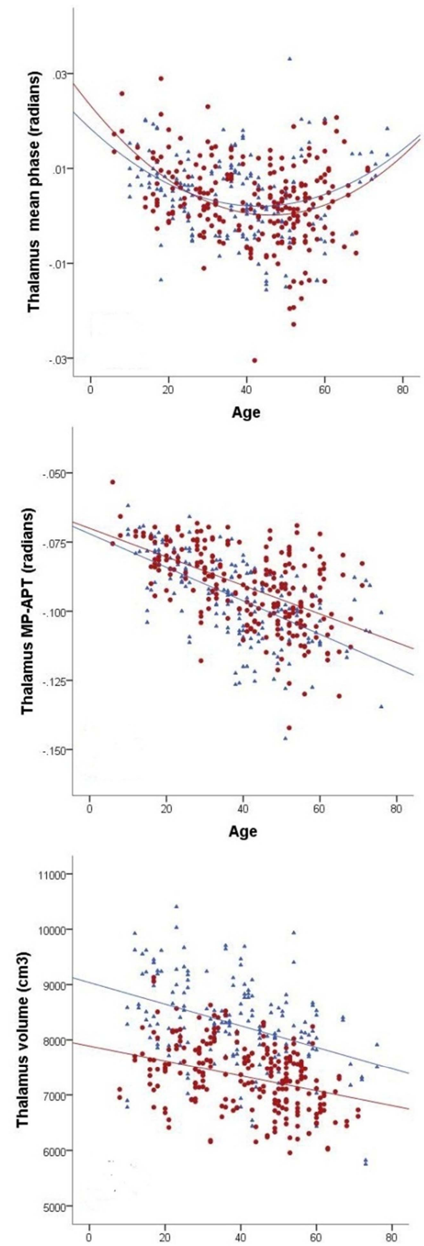

Figure 1. Relationships between age and thalamic mean phase (top; quadratic fit p<.001), mean phase of abnormal phase tissue (MP-APT ; middle, linear fit p<.001), and normalized volume (bottom; linear fit p<.001). Mean phase and MP-APT measures in radians. Red dots designate females and blue triangles males.