REGIONAL CEREBRAL IRON CONCENTRATIONS AS INDICATED BY MAGNETIC SUSCEPTIBILITIES MEASURED WITH QUANTITATIVE SUSCEPTIBILITY MAPPING (QSM) AT 7 TESLA CORRELATE WITH BRAIN AB PLAQUE DENSITY AS MEASURED BY 11-C-PITTSBURGH COMPOUND B POSITRON-EMISSION-TOMOGRAPHY (PIB-PET) IN ELDERLY SUBJECTS AT RISK FOR ALZHEIMER'S DISEASE (AD)

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Introduction: Aging of the human brain is associated with increased accumulation of extracellular Amyloid beta (Aβ), which can be non-invasively measured by positron emission tomography using radioactively labeled stains such as 11-C Pittsburgh Compound-B (PiB-PET) [1]. While Aβ deposits are a risk factor for age-related cognitive decline and a pathological hallmark of Alzheimer Disease (AD), Aβ related brain change may take place decades before manifestation of AD, involving a prodromal stage characterized by mild cognitive impairment (MCI) [2]. Moreover, postmortem pathological studies have shown that significant Aβ accumulation may also occur in elderly individuals without major cognitive impairments. Cerebral accumulation of iron is a neuropathological feature of several neurodegenerative diseases and also has been demonstrated for AD both in post-mortem studies [3,4] and in vivo by using MRI techniques [5]. The 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 [6,7]. While age is the major risk factor for incidence of AD, genetic liability for late onset AD is conferred by presence of the e4 allele of the Apolipoprotein E (ApoE) gene [8]. The main objective of the current study was to test whether the application of state of the art neuroimaging techniques capable of measuring both cerebral Aβ plaque density as well as iron accumulation may increase specificity for identifying AD-related brain pathology in subjects with MCI. Therefore, in the present study potential relations between cerebral Aβ plaque density and magnetic susceptibility changes were investigated regarding effects on brain dysfunction, as reflected by cognitive impairment. Moreover, ApoE-e4 carrier status was included in the analysis as a genetic risk factor, potentially associated with accelerated disease course.

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 [9] and Montreal Cognitive Assessment [10]) 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 [11]. Isoforms of the ApoE gene were assessed in all subjects. 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°, 0.5x0.5x0.5mm^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 [12]. Subsequently, background field were eliminated with sophisticated harmonic artifact reduction for phase data (SHARP) [13] using a variable spherical kernel size with a maximum radius of 4mm and a regularization parameter of 0.05 [14]. 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 [15]. Inverse dipole calculations to obtain the susceptibility maps were performed using a LSQR based minimization [12]. The T1-weighted image was co-registered to the GRE magnitude image using FSL FLIRT [16] and used for segmentation in a multi-atlas matching approach [7,17]. 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. For all subjects PiB-PET based estimation of individual brain Aβ load [1] utilizing a GE PET/CT Discovery scanner was acquired. Standard quantitative filtered back projection algorithm including necessary corrections was applied. Late frame (minutes 50-70) values were standardized by the cerebellar gray matter value, resulting in 3D-volumes of PiB-PET retention (matrix: 128x128x47, voxel size: 2.34x2.34x3.27 mm^3) which were co-registered to the GRE magnitude image using FSL FLIRT.

Results: In healthy controls none of the basal ganglia or cortical regions showed any correlation between susceptibility and PiB-PET ratio. In subjects with MCI there were strong correlations *($p < 0.01$, $r > 0.65$)* for the caudate nucleus, frontal cortex, temporal cortex, parietal cortex and occipital cortex (***Fig. 1***). Among all the MCI subjects, carriers of the ApoE-e4 allele show stronger increases in susceptibility and PiB-PET ratio. Based on proportionality of gray matter susceptibility with iron content [6,7], this indicates higher iron concentrations in cortical regions that have more Aβ depositions. However, in the controls only the Aβ depositions increased with carriers of the ApoE-e4 allele, but not the iron levels.

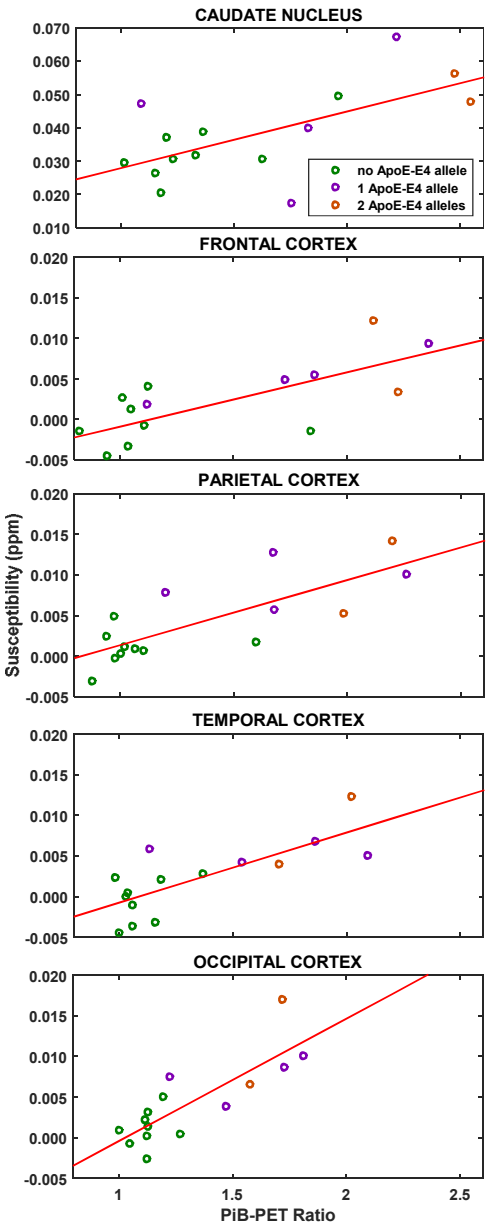

Fig. 1: *PiB-PET ratio and susceptibility values correlate in many cortical gray matter regions and the caudate nucleus in MCI subjects.*

Discussion and Conclusion: Our data indicate significant regional correlations between Aβ plaque density and iron load for the caudate nucleaus, as well as frontal, temporal, parietal and occipital cortex in subjects with MCI. These regions have been implicated as signature regions for neurodegenerative brain change in AD. Relevance of our findings for AD pathology is further supported by the observation that ApoE-e4 carrier-status drives the correlation. Overall, our findings suggest that cerebral iron accumulation may reflect Aβ associated brain dysfunction in subjects at increased risk for late onset AD. Additional longitudinal studies are needed to validate its potential use as biomarker in prospective Aβ targeted clinical trials for early intervention in elderly populations at increased risk for AD.

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