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Determinants of iron accumulation in the normal aging brain

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ABSTRACT

In a recent postmortem study, R_2^* relaxometry in gray matter (GM) of the brain has been validated as a noninvasive measure for iron content in brain tissue. Iron accumulation in the normal aging brain is a common finding and relates to brain maturation and degeneration. The goal of this study was to assess the determinants of iron accumulation during brain aging. The study cohort consisted of 314 healthy community-dwelling participants of the Austrian Stroke Prevention Study. Their age ranged from 38–82 years. Quantitative magnetic resonance imaging was performed on 3T and included R_2^* mapping, based on a 3D multi-echo gradient echo sequence. The median of R_2^* values was measured in all GM regions, which were segmented automatically using FreeSurfer. We investigated 25 possible determinants for cerebral iron deposition. These included demographics, brain volume, lifestyle factors, cerebrovascular risk factors, serum levels of iron, and single nucleotide polymorphisms related to iron regulating genes (rs1800562, rs3811647, rs1799945, and rs1049296). The body mass index (BMI) was significantly related to R_2^* in 15/32 analyzed brain regions with the strongest correlations found in the amygdala ($p = 0.0091$), medial temporal lobe ($p = 0.0002$), and hippocampus ($p \leq 0.0001$). Further associations to R_2^* values were found in deep GM for age and smoking. No significant associations were found for gender, GM volume, serum levels of iron, or iron-associated genetic polymorphisms. In conclusion, besides age, the BMI and smoking are the only significant determinants of brain iron accumulation in normally aging subjects. Smoking relates to iron deposition in the basal ganglia, whereas higher BMI is associated with iron content in the neocortex following an Alzheimer-like distribution.

1. Introduction

Iron is the most abundant trace element in the brain where it is essential for normal brain development and function (Ward et al., 2014). It plays a crucial role for many processes including oxygen transport, the synthesis of DNA and RNA, and the formation of myelin and development of the neuronal dendritic tree (Lieu et al., 2001). Most iron can be found in ferritin (Crichton, 2001), which is a globular storage protein that keeps iron readily available in a nontoxic way (Connor et al., 2001; Quintana and Gutiérrez, 2010). Although there is literally no ferritin in the brain after birth, iron accumulates in different brain structures and at different rates as a consequence of normal aging with highest concentrations being found in deep gray matter (GM), especially in the globus pallidus (Hallgren and Sourander, 1958; Ramos et al., 2014). Postmortem and in vivo magnetic resonance imaging (MRI) studies have shown that iron accumulation follows an exponential saturation function with only little changes after the fourth to fifth decade (Aquino et al., 2009; Connor et al., 1990; Hallgren and Sourander, 1958; Ramos et al., 2014; Rodrigue et al., 2011; Ropele et al., 2014). Iron deposition has also been associated with inflammatory, neurodegenerative, and cerebral small vessel disease (Liem et al., 2012; Sadrzadeh and Saffari, 2004; Ward et al., 2014; Zecca et al., 2004). Even in normal elderly persons, elevated levels of iron relate to worse cognitive performance (Ghadery et al., 2015). However, the determinants of iron deposition during normal brain aging are widely unknown.

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In this work, we assessed possible determinants of iron accumulation in the cortical GM and in deep GM in a large community-dwelling cohort of normal elderly persons. The iron content in the brain was measured by the transverse relaxation rate R_2^* ($1/T_2^*$) which, according to a recent studies, determines the regional iron content with high accuracy (Langkammer et al., 2010; Uddin et al., 2016).

2. Subjects and methods

2.1. Participants

Data for the present study were taken from the Austrian Stroke Prevention Family Study (ASPS-Fam), which is a prospective single-center, community-based study on the cerebral effects of vascular risk factors in a normal aging population of the city of Graz, Austria. ASPS-Fam represents an extension of the Austrian Stroke Prevention Study, which was established in 1991 (Schmidt et al., 1994, 1999). Between 2006 and 2013, study participants of the ASPS and their first grade relatives were invited to enter ASPS-Fam. Inclusion criteria were no history of stroke or dementia and a normal neurologic examination.

A total of 381 individuals from 169 families were included into the study with 2–6 family members. The entire cohort underwent a thorough diagnostic work-up including clinical history, laboratory evaluation, cognitive testing, and an extended vascular risk factor assessment. MRI data were available from 378 participants. A total of 64 subjects were excluded because of incomplete scans after scan abortion or because of image artefacts.

The final data set consisted of 314 participants, and the age ranged from 38–82 years with a mean age of 65.4 ± 10.4 years.

The study protocol was approved by the ethics committee of the Medical University of Graz, Austria, and written informed consent was obtained from all participants.

2.2. Magnetic resonance imaging

Magnetic resonance imaging was performed on a 3T whole-body MR system (TimTrio; Siemens Healthcare, Erlangen, Germany) with a 12 channel head coil. The study protocol included a high-resolution T1–weighted 3D sequence with magnetization prepared rapid gradient echo with whole brain coverage (repetition-time = 1900 ms, echo-time = 2.19 ms, inversion-time = 900 ms, flip angle = 9°, and isotropic resolution of 1 mm) for assessing brain volume and for tissue segmentation. For R_2^* mapping, a spoiled 3D multi-echo gradient echo sequence (fast low angle shot) was used (field of view of 256 × 256 × 128 mm^3, matrix = 256 × 256px, bandwidth = 190 Hz/px, echo-time of first echo = 4.92 ms, echo spacing = 4.92 ms, repetition-time = 35 ms, slice thickness = 2 mm, number of slices = 64, and number of echoes = 6).

2.3. R_2^* relaxometry

R_2^* mapping was performed by fitting a mono-exponential decay function into the signal intensities from the individual echoes. The voxel-wise fitting algorithm was implemented in MATLAB with an efficient and stable Levenberg-Marquard-Fletcher method (Balda, 2008) that considered the noise level for each echo. To prevent fitting errors affecting the regional analyses, highly noisy voxels exceeding a standard deviation of 20% were excluded.

2.4. Regional segmentation and brain volume assessment

For regional assessment of R_2^*, the cortex and deep GM structures were segmented fully automatic using the structural imaging stream "recon-all" from FreeSurfer (version 5.1.0), a tool set for analysis and visualization of structural and functional brain imaging data (documented and freely available for download online http://surfer.nmr.mgh.harvard.edu). The technical details of these procedures are described elsewhere (Dale et al., 1999; Reuter et al., 2010). The processing includes the segmentation of the subcortical white matter and deep GM volumetric structures and parcellation of the cerebral cortex into regions, based on gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004).

The automatic subcortical segmentation (Fischl et al., 2002) divides the brain into 49 regions. The parcellation of the cortical gray and white matter (WMPARC) consists of 34 regions for each hemisphere as well as for gray and white matter. A visual quality check was done for each case using an automated script based tool, which provides a graphical summary of the segmentations, overlaid on the T1-weighted image.

The normalized GM volume was obtained using SIENAX (freely available from: http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA), which extracts brain and skull information from a single whole-head input data set and is not biased by possible registration issues, which might be the case for the FreeSurfer provided "estimated Total Intracranial Volume" (Sargolzaei et al., 2015).

For selection of specific GM regions, we took all 64 regions from the cortical parcellation (the left and right side was considered separately) and the GM regions from the automatic subcortical segmentation (accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus; N = 82). To overcome measurements errors due to motion and elevated noise, we included for each (cortical/brain) region only those participants, who had a standard deviation of less than 10 Hz in that region. We have set the threshold of 10 Hz a priori based on previous results obtained by our group in the cohort under investigation (Ghadery et al., 2015). In the previous analyses, we observed a mean R_2^* signal of around 30 Hz in global GM. Based on the general definition of the signal detection limit noise (the standard deviation of signal in a given region) should not be higher than one third of the detected signal. Therefore, the number of cases for each region differed, and regions with less than 50 cases were excluded from the analysis for the left and right side. Hereby, following regions were affected: entorhinal cortex, frontal pole, fusiform gyrus, inferior temporal, lateral occipital, lateral orbitofrontal, medial orbitofrontal, parahippocampal gyrus, and the temporal pole. The reason for the larger standard deviation in these regions could be their position close to brain-air interfaces, which can cause large susceptibility gradients. The final number of analyzed regions was 64.

2.5. Determinants of regional iron accumulation

Overall, the effect of 25 potential determinants of regional iron accumulation was assessed. As demographical factors, we included age and sex. Life-style related factors consisted of body weight, waist-hip ratio, body mass index (BMI), smoking, and alcohol. Smoking was measured in recent pack-years, where in contrast to the pack-year definition only current (now or quitting within last 5 years) or recent smoking periods with no break longer than 3 years were considered. We also considered major cerebrovascular risk factors, as previously described (Schmidt et al., 1997), including hypertension, hypercholesterolemia, cholesterol, low- and high-density lipid protein, mean diastolic and systolic blood pressure, embolic and cardiac disease, diabetes, and glycated hemoglobin (HBA1C).

The genetic determinants included iron metabolism–associated single nuclear polymorphisms (SNPs): rs1800562, rs3811647, rs1799945, and rs1049296. The SNP rs1800562 (risk allele A) can cause a severe form of Hemochromatosis, in which 85% of all