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Quantitative susceptibility mapping of striatum in children and adults, and its association with working memory performance

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ABSTRACT

Quantitative susceptibility mapping (QSM) is a magnetic resonance imaging (MRI) technique in which the magnetic susceptibility characteristic of molecular and cellular components, including iron and myelin, is quantified. Rapid iron accumulation in subcortical nuclei and myelination of the white matter tracts are two important developmental processes that contribute to cognitive functions. Both also contribute to the magnetic susceptibility of the brain tissues. Here, we used the QSM as indirect measures of iron in subcortical nuclei and myelin in caudofrontal white matter pathways. We included two groups of participants; 21 children aged 6–7 years and 25 adults aged 21–40 years. All subjects also performed tests estimating their visuo-spatial working memory capacity. Adults had higher magnetic susceptibility in all subcortical nuclei, compared to children. The magnetic susceptibility of these nuclei highly correlated with their previously reported iron content. Moreover, working memory performance correlated significantly with the magnetic susceptibility in caudate nucleus in both children and adults, while the correlation was not significant for gray matter density. QSM of white matter in the caudofrontal tract also differed between children and adults, but did not correlate with working memory scores. These results indicate that QSM is a feasible technique to measure developmental aspects of changes in the striatum, possibly related to iron content that is relevant to cognition.

Introduction

Magnetic susceptibility is a physical quantity that indicates the extent to which a material is magnetized in response to an applied magnetic field. Susceptibility in biological tissues is a combination of susceptibilities of their molecular and microstructural content and is positive or negative for paramagnetic or diamagnetic materials, respectively. Paramagnetic characteristic originates from spins of unpaired electrons which tend to align with an applied magnetic field, whereas diamagnetic property originates from the induction currents of paired electrons that induce an internal magnetic field in an opposite direction of an applied magnetic field (Liu et al., 2014).

The magnetic susceptibility of biological tissues can affect the magnetic resonance imaging (MRI) signal, and thereby enhance the image contrast between different tissues. Susceptibility weighted imaging (SWI) is an MRI technique that uses T_2*-weighted gradient echo (GRE) sequence and combines the magnitude and phase of a single- or multi-echo imaging to generate different contrasts for different tissues in the brain. However, a limitation of SWI is that the contrast is influenced by non-local phase effects (Liu et al., 2014). To overcome this limitation, quantitative susceptibility mapping (QSM) has been introduced. This technique uses a linear transform between the local phase-frequency differences and local dipolar magnetic fields, and quantitatively maps the magnetic susceptibility of brain tissues (de Rochefort et al., 2010; Wang and Liu, 2015).

In magnetic susceptibility images, calcium and myelin with diamagnetic properties display low intensity, while paramagnetic compounds such as ferritin (containing Fe^{3+} ions) show high intensity (Schweser et al., 2011). Besides ferritin, there are several other sources of iron in the brain tissue that have a potential to contribute to the QSM contrast such as transferrin, hemosiderin and deoxy-hemoglobin. QSM cannot distinguish between different sources and hereby, in the course of this paper, we use "iron" as a general term for all above mentioned iron stores.

It has been suggested that the paramagnetic susceptibility of subcortical nuclei is primarily related to the amount of iron (Bilgic et al., 2012; Wu et al., 2012). This is consistent with a report of the distribution of iron in the subcortical and cortical brain areas studied postmortem in a Swedish sample of about 50 adults (Hallgren and Sourander, 1958; Persson et al., 2015). In a study evaluating iron susceptibility as a function of age in a sample of healthy subjects aged from 1 to 83 years old, magnetic susceptibility in subcortical nuclei showed a rapid increase

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during childhood and early adulthood and then plateaued around the fifth decade (Li et al., 2014b). This is in line with the findings of the post-mortem study (Hallgren and Sourander, 1958).

Brain iron acts as a cofactor for tyrosine hydroxylase which is an enzyme involved in dopamine metabolism (Yehuda and Youdim, 1989; Youdim and Green, 1978). In the human brain, iron has the highest concentration in the subcortical nuclei, including globus pallidus, caudate nucleus, putamen, substantia nigra and red nucleus (Hill, 1988). These regions are highly influenced by dopamine metabolism and they contribute to motor, cognitive and other behavioral functions. Striatum has been linked to several cognitive functions, including working memory (Klingberg et al., 2002; Postle et al., 2000; Ziermans et al., 2012), working memory training (Dahlin et al., 2008; Olesen et al., 2004) and development of working memory during childhood (Darki and Klingberg, 2015; Ullman et al., 2014). Working memory is dependent on several transmitter substances, but the association to dopamine is particularly well researched, both in non-human primates (Vijayraghavan et al., 2007; Williams and Goldman-Rakic, 1995) and humans (Bäckman et al., 2011; Cools et al., 2008; McNab and Klingberg, 2008). Moreover, working memory is impaired in several developmental neuropsychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD) (Martinussen et al.. 2005). Dopaminergic dysfunctions of the striatum have also been associated to ADHD (Dougherty et al.. 1999; Krause et al.. 2000; Ludolph et al.. 2008).

Furthermore, it has been shown that the diamagnetic susceptibility of white matter on QSM is due to the myelin (Liu et al.. 2014). A study on shiverer mice reported that the susceptibility contrast between gray and white matter was minimal compared to wild type mice, since these transgenic mice did not develop myelin properly (Liu et al.. 2011). Another study showed a decrease in phase contrast for the mice fed with a cuprizone diet that induced demyelination (Lee et al.. 2012). In a human lifespan QSM study of 191 participants (1 to 83 years old), white matter showed diamagnetic characteristics up to adulthood and then it continued to become less diamagnetic for older subjects (Li et al., 2014b). This was consistent with the myelination process during development and demyelination in normal aging.

The rapid iron accumulation in subcortical nuclei and the fast myelination of the white matter tracts are vital developmental processes that could contribute to cognitive development (Beard and Connor, 2003; de Andraca et al., 1997; Lenroot and Giedd, 2006; Lozoff and Georgieff, 2006). Animal studies have reported a reduction in brain iron concentration (Dallman et al., 1975; Dallman and Spirito, 1977), dopamine dysfunction, and consequently affected behavior in iron deficient rats (Youdim, 1988). In humans, a low level of serum iron in children and adolescents with iron deficiency has been linked to less attention, motivation and poor performance on cognitive tasks such as working memory (Grantham-McGregor and Ani, 2001; Lozoff, 2007; McCann and Ames, 2007). These cognitive deficits are similar to the ADHD symptoms, and the same association has been found for this developmental disorder (Cortese et al., 2012). However, recent case-controlled studies found no differences in serum iron levels between children with ADHD and typically developing children (Adisetiyo et al., 2014; Donfrancesco et al., 2013), but significantly lower brain iron in caudate nucleus, putamen and thalamus in children with ADHD. It has been suggested that detection of brain iron could be a biomarker for neurodevelopmental disorders (Adisetiyo and Helpern, 2015).

Brain iron has not been widely assessed for associations to performance in cognitive tasks during development and adulthood. In a recent study, iron in caudate has been positively related to spatial intelligence in children aged 7 to 11 years old (Carpenter et al., 2016). This suggests an important influence of striatal brain iron on visuo-spatial processing in children.

Here, we first aimed to assess the age dependent differences in brain iron measured by a newly developed processing technique of susceptibility imaging, QSM. We also estimated the gray matter density in subcortical regions as an alternative structural measure. Secondly, we assessed the relationship between performance on a visuo-spatial working memory task and brain iron as well as the white matter structural properties in children and adults. We hypothesized that the inter-individual variability in working memory performance correlates with region specific measures of brain iron, gray matter density and white matter myelination, which may be of predictive value for cognitive performance.

Methods

Participants

Twenty-five adults (age: 29.1 ± 4.5 years, male/female: 16/9) and twenty-one 6–7 year old children (age: 6.73 ± 0.27, male/female: 12/8) without any neurological or neuropsychiatric disorders participated in the study. Verbal assent from the children and written informed consent from the adults and the parents of the children were obtained. The study was approved by the local ethics committee of the Karolinska University Hospital.

All brain scanning methods were performed with a 3T GE MRI scanner (model MR750) using a Nova 32 channel brain coil. All participants were scanned with structural MRI, diffusion tensor imaging (DTI) and multi-echo SWI for QSM. Three adults were excluded due to the artifacts in the QSM and DTI data. One child was excluded due to artifacts in the QSM data, and for 6 children no DTI data was collected.

Brain imaging and processing

A three-dimensional high resolution T1-weighted imaging was performed using IR prepared FSPGR sequence with inversion time (TI) = 450 ms, repetition time (TR) = 5.7 ms and echo time (TE) = 2.5 ms, in the sagittal plane with field of view (FOV) = 24 × 24, resolution of 0.94 × 0.94 mm^2 in 180 slices, and acquisition bandwidth of 325 Hz/pixel to anatomically scan the brain structures. In order to compute the gray matter density of the subcortical regions, gray and white matters were segmented using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox, in SPM12. The modulated segmented images were then smoothed with an 8-mm Gaussian kernel, and the gray matter density was computed within defined masks of subcortical regions obtained from Talairach atlas (Lancaster et al., 2000).

For QSM, SWI was carried out with a three-dimensional, flow compensated, multi-echo spoiled GRE sequence (Liu et al., 2012) in axial plane with 6 echos, first TE = 3.872 ms, echo time spacing = 4.384 ms, flip angle/TR = 17°/29.4 ms, FOV of 24 × 24 cm^2, resolution of 0.92 × 0.92 mm^2 and 1.2 mm slice thickness and acquisition bandwidth of 325 Hz/pixel. Imaginary and real pairs of images were acquired from the scanner and were then combined to form a complex data, from which the magnitude and phase images were computed using a Matlab-based software, called STI Suite (Li et al., 2014a). The magnitude image was then fed into the BET tool in FSL to obtain the brain mask. In the next step, a three-dimensional phase unwrapping was performed and background phase was removed. In the final step, QSM images were computed using LSQR method (Li et al., 2011).

Diffusion weighted imaging was performed in a form of multi-shell data acquisition using twice refocused EPI spin echo sequence with TR = 8950 ms, TE = 92.5 ms, isotropic resolution = 2 × 2 × 2 mm^3, three different b-values = 300, 1000 and 2000 s/mm^2 in 6, 30, and 30 directions, respectively. Ten volumes were also collected with b-value = 0. The eddy current and head motions were corrected with affine registration to a reference volume using FSL software. The diffusion weighted images were processed with FDT toolbox in FSL and the fractional anisotropy (FA) images were computed. A slightly shorter DTI sequence was used for children, with TR = 7400 ms, TE = 86 ms, isotropic resolution = 2.3 × 2.3 × 2.3 mm^3 in 32 directions and b-value of 1500 s/