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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/

mm^2. Both DTI has enhanced fat suppression implemented by slice selective gradient reversal for second refocusing RF pulse and conventional spectrally selective fat suppression module. Both DTI sequences were acquired and reconstructed with partial homodyne Fourier transform (number of over-scan lines 16) and SENSE (ASSET™) parallel imaging, acceleration factor R = 2.

Region of interest and tract based analysis

Subcortical iron-rich nuclei, including globus pallidus, caudate nucleus, putamen, red nucleus, substantia nigra, nucleus accumbens, thalamus and ventral tegmental area were selected as regions of interest (ROI) to assess whether the QSM of these ROIs would be significantly associated with working memory performance. All ROIs except from the ventral tegmental area were selected from Talairach and Harvard-Oxford subcortical atlases (Lancaster et al., 2000) in FSL. The ventral tegmental area was selected based on the probabilistic atlas of the mid brain (Murty et al., 2014). Both atlases are in MNI152 standard space. All selected ROIs were combined to make an image with specific labels for each ROI. The labeled image in MNI space was then registered to QSM images using the transformation matrices of affine-registration from MNI152_T1_1mm template to T1-weighted image and then to the magnitude image of QSM data for all individuals. The average QSM value of each subcortical ROI was then computed from all voxels overlapping with the corresponding label and those with QSM > 0 ppm, since the gray matter mainly appears paramagnetic in QSM (Li et al., 2011; Schweser et al., 2011; Shmueli et al., 2009).

To investigate the role of white matter structural properties on working memory performance, the caudo-frontal white matter tract was traced by probabilistic fiber tracking using the probtrackx tool of FDT v2.0, FSL. The masks of caudate nucleus and frontal lobe in MNI space were first selected based on Harvard-Oxford subcortical and cortical atlases, respectively. They were non-linearly registered to FMRIB58_FA standard-space template and then to each individual's FA image. In the next step, the mask of the caudate was used as seed region to trace the caudo-frontal white matter pathway. The default parameters (5000 streamline samples, step length of 0.5 mm, and curvature threshold of 0.2) were used for the probabilistic fiber tracking. The tracts were thresholded and binarized by 10% of the samples to remove the voxels with low probability of connection and the average FA value for each tract was computed across all subjects.

Next, all individual's FA images were separately registered to the QSM images and the same transformation matrix was applied to each individual's caudo-frontal tract. The average of QSM values along the caudo-frontal white matter tract was then computed for all subjects. Due to the diamagnetic property of white matter (Li et al., 2011; Liu et al., 2014), all voxels within the tract with negative QSM value were averaged to measure the mean QSM for the white matter tract.

Assessment of visuo-spatial working memory

Visuo-spatial working memory was assessed for all participants using a task where a number of dots in a four-by-four grid were displayed sequentially and the task was to remember the order and the location of the dots. The task was started at level 2 with presenting two dots in two different positions, and the level of difficulty was automatically adjusted by increasing the number of positions. An algorithm took the participant's performance into account to dynamically adapt the level. The working memory performance was then calculated as the level at which the subject had a 75% probability of giving correct answers. This was done by fitting a logistic regression line to the proportion of correct answers at each level to extract a predicted level for the exact proportion of 75% correct trials.

A similar visuo-spatial working memory task has been used in the previous functional MRI studies of children and adults, and found to activate frontal, parietal and striatal regions (Dumontheil et al., 2011; Klingberg et al., 2002; Olesen et al., 2004).

Results

Magnetic susceptibility was quantitatively mapped for all children and adults. Fig. 1A shows one axial slice of QSM image for one individual from each age group. The contrast difference between these two sample images is clearly visible for both gray and white matters. Mean and standard errors of the QSM values in all subcortical ROIs for both children and adults are plotted in Fig. 1B. All values are the average values of the homologous regions in left and right hemispheres. Children had lower QSM in all subcortical regions compared with adults (*t*-test, $p < 0.002$). Globus pallidus showed the highest QSM in both children and adults (Fig. 1B). The midbrain ROIs had higher QSM compared to striatal regions. The average QSM values measured in adults correlated ($r = 0.85$) with iron distribution values reported in the postmortem study of around 50 subjects aged 30 to 100 years old (Fig. 1C) (Hallgren and Sourander, 1958). Moreover, working memory performance significantly differed between children and adults (working memory in children: 4.47 ± 0.97, in adults: 5.46 ± 0.54, *t*-test: $p < 0.001$).

Next, we performed a partial correlation between QSM values of all subcortical regions and working memory performance, correcting for age and sex, within each age-group (Table 1). There was a significant correlation for caudate nucleus in both children ($r = 0.64$, $p = 0.004$) and adults ($r = 0.46$, $p = 0.04$). Only the correlation between caudate QSM and working memory performance survived the multiple comparison corrections of 9 tests (Bonferroni corrected p-value < 0.0055).

We repeated the correlations between working memory performance and QSM separately for the left and right hemispheres. For children the correlation was mainly driven by the right caudate (right caudate $r = 0.79$, $p = 0.001$; left caudate: $r = 0.40$, $p = 0.09$), while for adults both remained significant (right caudate $r = 0.44$, $p = 0.05$; left caudate: $r = 0.45$, $p = 0.04$). The QSM measures from other subcortical nuclei did not correlate with working memory performance neither in the right nor in the left hemisphere (all p-values >0.15). The positive correlation of right caudate QSM with working memory performance survived the multiple comparisons of 18 tests (Bonferroni corrected p-value <0.0027).

To assess the group-related changes in caudate QSM and its relation to working memory performance, we performed a two-way ANOVA model correcting for age and sex. The main effects of caudate QSM ($F = 20.28$, $p = 7.49 \times 10^{-5}$) and group ($F = 5.31$, $p = 0.03$) were significant. Moreover, the interaction between group and QSM of caudate ($F = 10.99$, $p = 0.002$) was significant which indicates the significant group differences in the relationship between QSM and working memory (Fig. 2).

In contrast to the finding of the aging studies (Daugherty et al., 2015), we did not find any significant relationship between striatal iron level and gray matter density in children and adults ($p > 0.65$). We also assessed the volume and the gray matter density of the subcortical structures. In contrast to the findings from QSM, there was no significant effect of the volume (all $p > 0.54$) or gray matter density (all $p > 0.17$) of the subcortical nuclei on working memory performance in either of the groups, suggesting that QSM imaging could provide some unique information not captured by more traditional structural imaging techniques.

Since caudate nucleus was the only subcortical nucleus that its relevant QSM measure was significantly correlated with working memory performance, white matter pathways connecting caudate to frontal lobe were then traced with probabilistic fiber tracking (Fig. 3). Frontal lobe was chosen because of its well-known importance in working memory performance (Curtis and D'Esposito, 2003). We then assessed whether the QSM of these white matter pathways could explain the variability in working memory capacity. Again, we compared the results

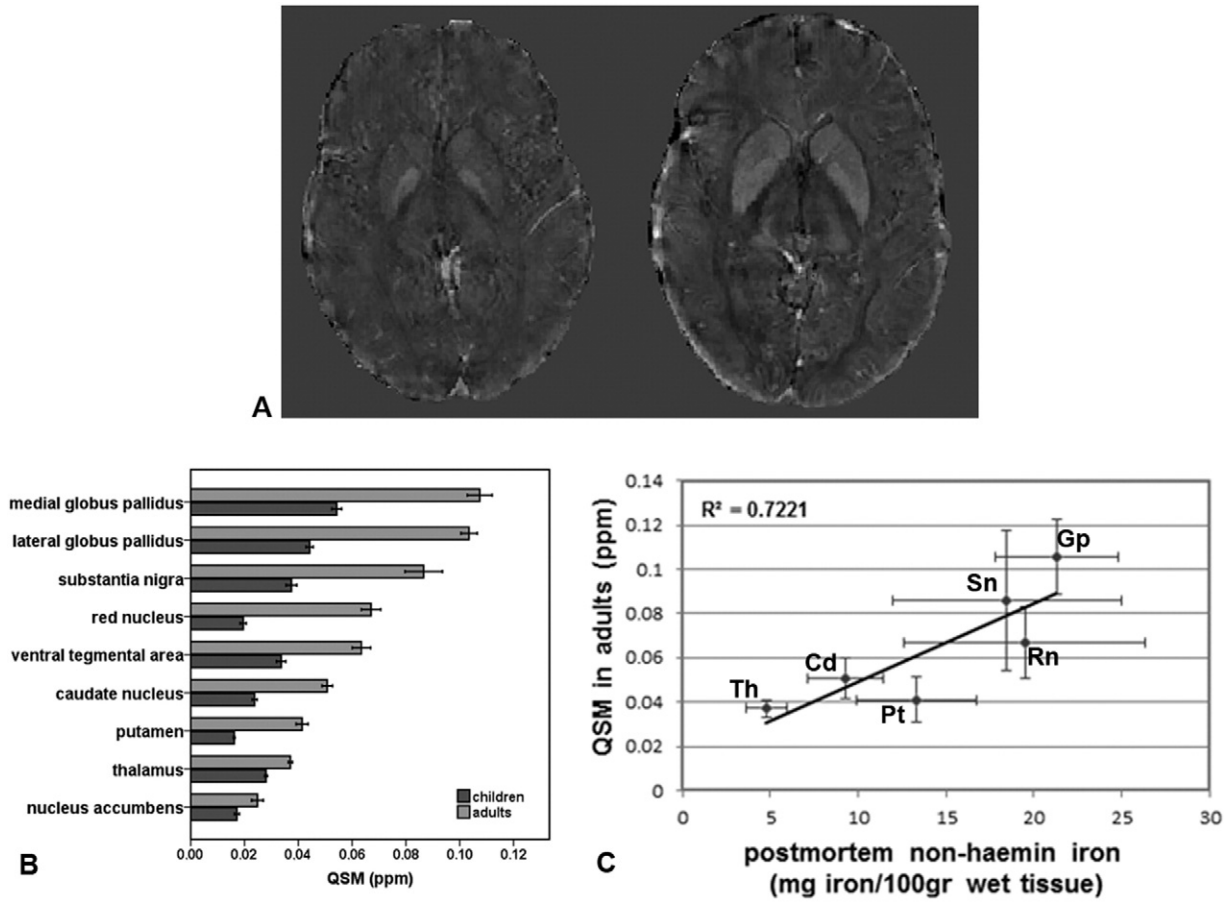

Fig. 1. (A) Axial slice of QSM image for one child at age 6 shown in left and for one adult at age 21 shown in right. (B) QSM in subcortical regions for both children and adults, error bars are ±1 standard error. (C) The relationship between average QSM values of adults' subcortical regions in the present study and iron distribution in postmortem samples from subjects aged 30 to 100 years, reported in (Hallgren and Sourander, 1958) for Gp: globus pallidus, Sn: substantia nigra, Rn: red nucleus, Pt: putamen, Cd: caudate, and Th: thalamus.

with an alternative measure for white matter, the fractional anisotropy (FA). FA in general is related to microstructural properties of white matter such as axonal diameter, density, packing and myelination (Beaulieu, 2002).

The averaged QSM and FA of the caudo-frontal white matter pathway were significantly different between the two age groups (QSM in children: −0.015 ± 0.002 ppm, QSM in adults: −0.019 ± 0.003 ppm, *t*-test: $p < 0.001$; FA in children: 0.39 ± 0.02, FA in adults: 0.43 ± 0.03, *t*-test: $p < 0.001$). QSM and FA measures of the caudo-frontal

Table 1
Correlations between QSM measures in subcortical regions and working memory performance.

Control variables	Subcortical region		Children	Adults
Age and sex	Nucleus accumbens	Correlation	0.05	0.22
		Significance	0.85	0.36
	Caudate nucleus	Correlation	**0.64**	**0.46**
		Significance	**0.004**	**0.04**
	Putamen	Correlation	−0.45	0.32
		Significance	0.06	0.17
	Lateral globus pallidus	Correlation	−0.07	−0.04
		Significance	0.78	0.85
	Medial globus pallidus	Correlation	−0.19	0.02
		Significance	0.45	0.92
	Red nucleus	Correlation	0.25	0.16
		Significance	0.32	0.49
	Substantia nigra	Correlation	0.18	0.11
		Significance	0.67	0.65
	Ventral tegmental area	Correlation	0.33	0.28
		Significance	0.18	0.23
	Thalamus	Correlation	−0.02	0.41
		Significance	0.93	0.07

Bold data indicates the correlation coefficients and the p-values for the correlations with $p < 0.05$.

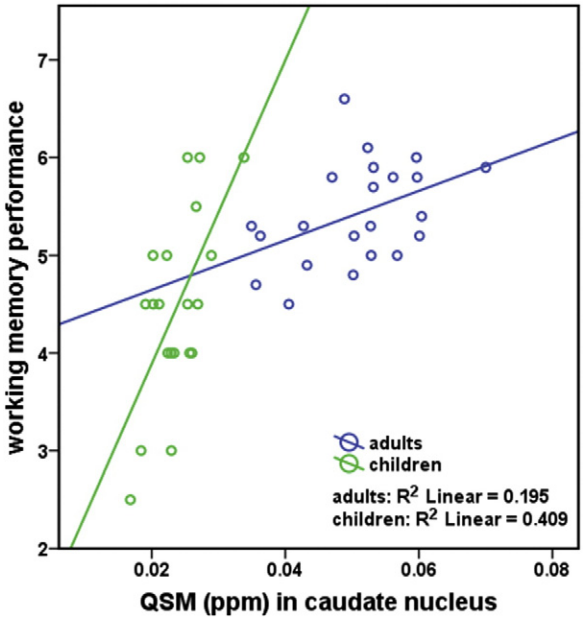

Fig. 2. Scatter plots of the relation between QSM in caudate nucleus and working memory performance in children and adults.

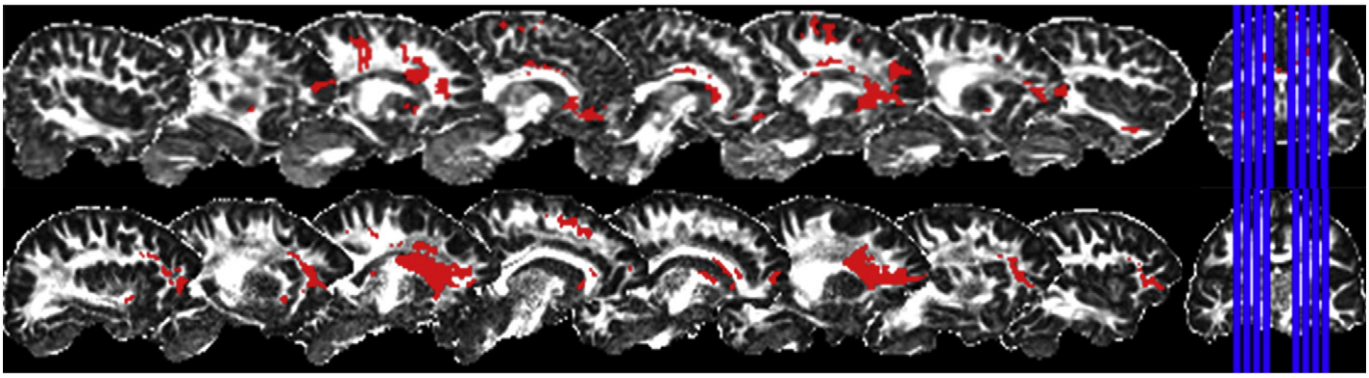

Fig. 3. Probabilistic white matter tracking of caudo-frontal pathway. First row: one random subject at age 6. Second row: one random subject from adults' group at age 21.

tract did not correlate ($p = 0.27$), and there was no significant correlation between working memory performance and white matter QSM or FA for adults or children (children: $p > 0.24$, adults: $p > 0.52$).

Discussion

Here we used QSM to estimate the brain iron and myelin in children and adults. All subcortical nuclei had higher iron content in adults compared to children. The QSM measure in caudate nucleus significantly correlated with working memory scores within both the children and the adult groups. We also found that adults had higher FA and more negative QSM in the caudo-frontal white matter tract, compared to children, which is possibly due to higher amount of myelin. Although the white mater maturation was well-detected by both FA and QSM measures, we could not link these measures with working memory performance in our present study.

Among all subcortical regions, globus pallidus had higher QSM values in comparison to midbrain nuclei including red nucleus, substantia nigra, and the ventral tegmental area. The striatal regions, caudate nucleus and putamen, had the lowest QSM values. These results are consistent with the reports of other processing methods of susceptibility imaging such as R2* (inverse of T2*) and magnetic field correlation (MFC) (Langkammer et al., 2012; Li et al., 2014b; Persson et al., 2015). Moreover, the QSM measures of the adults' iron-rich nuclei in the present study significantly correlated with the distribution of non-heme iron reported in a post-mortem study (Hallgren and Sourander, 1958) with the greatest measure for globus pallidus and lowest level for thalamus. Children had significantly less QSM measure in all subcortical nuclei compared with adults. This confirms the increasing accumulation of brain iron in mid brain and striatum during typical development (de Andraca et al., 1997; Li et al., 2014b).

The QSM of caudate nucleus was the only subcortical brain measure that correlated with working memory performance in both children and adults. Caudate nucleus is active during performance on working memory tasks in nonhuman primates (Levy et al., 1997), children (Klingberg et al., 2002; Ziermans et al., 2012) and adults (Postle et al., 2000). Moreover, dopamine synthesis in the caudate nucleus, measured by positron emission tomography (PET) tracers, has been positively linked to working memory capacity in adults (Cools et al., 2008; Landau et al., 2009). The link between brain iron and dopamine function might be that iron (Fe^{2+}) acts as a cofactor for tyrosine hydroxylase which is a responsible enzyme for dopamine synthesis (Ramsey et al., 1996; Youdim and Green, 1978). Alterations in both brain iron and dopamine have been associated with alterations in attention, cognition and motor control (Beard and Connor, 2003; Egerton et al., 2009; Lozoff, 2011; McCann and Ames, 2007). This may explain the high concentration of iron and dopamine in the same basal ganglia regions (Beard and Connor, 2003), and explain the importance of caudate iron in working memory performance.

Brain iron detected by QSM has been well studied in movement and neurodegenerative disorders such as Parkinson's and Alzheimer's diseases (Acosta-Cabronero et al., 2013; Ide et al., 2015). It also has been assessed in neurodevelopmental disorders such as ADHD (Adisetiyo et al., 2014; Cortese et al., 2012). These studies have reported less magnetic susceptibility in caudate nucleus, putamen and thalamus for ADHD subjects compared with typically developing controls. However, the brain iron estimated by imaging methods has not been linked to cognition in these studies. In a longitudinal study of healthy adults aged 19–77 years old, higher brain iron in caudate was linked to smaller caudate volumes and less improvement in working memory after 2 years (Daugherty et al., 2015). Their finding supports the idea that striatal iron accumulation together with the shrinkage of striatum is a risk factor for cognitive decline in normal aging. In contrast to the aging study of caudate iron (Daugherty et al., 2015), the current study showed a positive correlation between caudate iron content on working memory performance in children and adults and no change in gray matter density. The relation between the QSM measure of caudate nucleus and working memory performance was found to be stronger in children compared to adults (group by QSM interaction in explaining working memory: $p = 0.002$). Our results suggest the positive effect of caudate iron in working memory performance during childhood. During adulthood the link is still positive, but there is a weaker effect of caudate iron on working memory performance. According to the lifespan trajectory of the magnetic susceptibility in caudate nucleus (Li et al., 2014b), the estimated brain iron in caudate increases during childhood and it reaches a plateau around the age of 40. This lifespan trajectory together with our finding during childhood and adulthood suggests an important role of caudate iron in cognitive performance in the studied age range.

At this point, it is unclear why specifically the caudate, but no other subcortical regions, showed a significant correlation with working memory. It is possible that the choice of ROI-based analysis affects the results, and that a voxel-wise analysis, or using smaller ROIs, would show additional significant associations.

The QSM and FA values of the caudo-frontal white matter tract did not correlate in our study. The lack of correlation between FA and QSM measures suggests that these two white matter measures indirectly map different microstructural properties of white matter. FA is influenced by number, thickness and architecture of axons, density of fibers and myelination (Beaulieu, 2002). The negative susceptibility of white matter has been linked to myelin (Liu et al., 2014), however the QSM measure of white matter is partly affected by the paramagnetic property of iron collected in oligodendrocytes (Connor and Menzies, 1996).

In contrast to our previous findings (Darki and Klingberg, 2015), we did not find any significant correlations between white matter measures of caudo-frontal tract and working memory performance. However, our previous study included a longitudinal sample of children and young adults (89 participants, scanned 3 times) between the ages of 6–25 years, in which the significant correlations were driven mostly

from younger subjects aged below 18 years old. In the current study, the lack of significant results could be explained by a small number of subjects in the children's group.

A limitation of our study is that the Harvard-Oxford subcortical atlas has been used for the ROI-based analysis of the both children and adult QSM data, since to our knowledge there is no available pediatric subcortical atlas. The use of an adult subcortical atlas could have introduced greater error in specifying the ROIs for the children compared to the adults. We tried to minimize this problem by doing the analysis in the individual's space and using each subject's T1-weighted image as a reference image. The subcortical atlas was first registered to the T1-weighted image of each subject using the inverse of the affine registration between the single subject's T1-weighted image and the anatomical brain template, and then to each individual's QSM data. However, it is preferable to use a pediatric brain template as well as a pediatric subcortical atlas to reduce the potential errors.

In conclusion, we found that QSM is a feasible technique to measure developmental changes in the striatum, and that inter-individual differences are related to cognitive performance. QSM might thus be used in future studies of regional iron content in the brain and how this relates to normal and abnormal cognitive development during childhood.

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