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Magnetic susceptibility of brain iron is associated with childhood spatial IQ

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ABSTRACT

Iron is an essential micronutrient for healthy brain function and development. Because of the importance of iron in the brain, iron deficiency results in widespread and lasting effects on behavior and cognition. We measured iron in the basal ganglia of young children using a novel MRI method, quantitative susceptibility mapping, and examined the association of brain iron with age and cognitive performance. Participants were a community sample of 39 young children recruited from pediatric primary care who were participating in a 5-year longitudinal study of child brain development and anxiety disorders. The children were ages 7 to 11 years old (mean age: 9.5 years old) at the time of the quantitative susceptibility mapping scan. The differential abilities scale was administered when the children were 6 years old to provide a measure of general intelligence and verbal (receptive and expressive), non-verbal, and spatial performance. Magnetic susceptibility values, which are linearly related to iron concentration in iron-rich areas, were extracted from regions of interest within iron-rich deep gray matter nuclei from the basal ganglia, including the caudate, putamen, substantia nigra, globus pallidus, and thalamus. Controlling for scan age, there was a significant positive association between iron in the basal ganglia and spatial IQ, with this effect being driven by iron in the right caudate We also replicated previous findings of a significant positive association between iron in the bilateral basal ganglia and age. Our finding of a positive association between spatial IQ and mean iron in the basal ganglia, and in the caudate specifically, suggests that iron content in specific regions of the iron-rich deep nuclei of the basal ganglia influences spatial intelligence. This provides a potential neurobiological mechanism linking deficits in spatial abilities reported in children who were severely iron deficient as infants to decreased iron within the caudate.

Introduction

Iron is an essential micronutrient for healthy brain function and development (Beard and Connor, 2003; Lozoff, 2007; Lozoff and Georgieff, 2006). Iron-containing enzymes and iron-dependent proteins are involved in dendrite and synapse development, and iron uptake in oligodendrocytes is essential for proper white matter myelination. Iron is also essential for the metabolism and catabolism of neurotransmitters, including dopamine, norepinephrine, serotonin, and GABA (Beard and Connor, 2003; Lozoff, 2007; Lozoff and Georgieff, 2006). Iron deficiency during infancy results in widespread and persistent effects on many neurophysiologic and regulatory processes, including cognitive, motor, and social–emotional behavior, suggesting that a lack of iron during neurodevelopment has lasting implications for brain function (Beard and Connor, 2003; Lozoff, 2007, 2011; Lozoff and Georgieff, 2006; Sachdev, 1993). Studies of iron deficiency in later childhood and adulthood have demonstrated similar negative consequences of iron deficiency (Beard and Connor, 2003; Sachdev, 1993), although iron repletion can, at least partially, reverse these negative effects (Khedr et al., 2008; Sachdev, 1993). To date, most studies linking

Abbreviations: QSM, Quantitative susceptibility mapping; GRE, Gradient echo; LADB, Learning about the developing brain study; DAS, Differential abilities scale; ME-SPGR, Multi-echo spoiled gradient-echo sequence; V-SHARP, Variable-filter-radius SHARP; ROIs, Regions of Interest.

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iron deficiency to cognitive deficits in children have relied on peripheral measures of iron, which may be poorly correlated with iron in the brain (Li et al., 2015). Furthermore, because nutritional iron is preferentially targeted toward maintaining hemoglobin concentration when iron levels are low, iron in the brain may reach critically low levels that have lasting impact on brain development well before blood samples reflect this critical shortage (Rao and Georgieff, 2002). Thus, in order to understand the neurobiological basis of the cognitive deficits resulting from iron deficiency, we must first explore the relationship between iron measured directly in the brain and the cognitive functions impacted by low iron levels. The current study aims to understand the neurobiological role of brain iron in children's cognitive functioning.

During the process of brain development, iron accumulates at variable rates in different anatomical locations, with the basal ganglia nuclei, including the caudate, putamen, substantia nigra, and the globus pallidus, having higher iron contents than the surrounding tissues (Hallgren and Sourander, 1958; Li et al., 2011, 2014). Animal studies have demonstrated that iron deficiency during early brain development leads to alterations in the neurotransmitter systems of the basal ganglia, including decreased expression of dopaminergic receptors and decreased functioning of both dopaminergic and serotonergic transporters (Beard, 2001; Beard and Connor, 2003; Lozoff, 2007; Lozoff and Georgieff, 2006; Munoz and Humeres, 2012). Furthermore, neonatal iron deficiency results in global hypomyelination, including in the pathways connecting the iron-rich basal ganglia to the rest of the brain (Beard and Connor, 2003; Lozoff, 2007; Lozoff and Georgieff, 2006).

Many of the cognitive and behavioral functions implicated in iron deficiency, including learning, memory, verbal and non-verbal reasoning, and visual–spatial abilities, rely on a prefrontal–subcortical dopaminergic network that includes the iron-rich basal ganglia (Brown et al., 1997; Burgaleta et al., 2014; Khedr et al., 2008; Lozoff, 2007; Lozoff and Georgieff, 2006; Lozoff et al., 2000; MacDonald et al., 2014; Munoz and Humeres, 2012). The caudate and putamen, collectively referred to as the striatum, are the primary points of input for the basal ganglia, receiving projections from all parts of the cortex (Alexander et al., 1986; Grahn et al., 2008; Ring and Serra-Mestres, 2002). The striatum is then reciprocally connected to the substantia nigra through the nigrostriatal tract and sends outputs to both the substantia nigra and the globus pallidus, which then projects information back to the cortex through corticostriatal loops (Alexander et al., 1986; Grahn et al., 2008). Both animal models and studies of humans with early life iron deficiency reveal cognitive deficits in line with the disruption of prefrontal–basal ganglia pathways, suggesting that iron in the basal ganglia may influence cognitive functioning (Lozoff, 2011; Lozoff and Georgieff, 2006; Lukowski et al., 2010).

In this study, we measured brain iron in the basal ganglia of young children using quantitative susceptibility mapping (QSM), which is a novel MRI technique that is highly sensitive to paramagnetic non-heme iron in brain tissue and is linearly proportional to iron contents in certain brain areas (Schweser et al., 2011; Wharton et al., 2010; Wu et al., 2012). It is well known that pediatric brains have much lower iron concentration than the adult brains in the deep brain nuclei regions (Aquino et al., 2009; Hallgren and Sourander, 1958), thus the development of sensitive method or noninvasive assessment of iron deposition is of particular importance in comparison to adult brain imaging studies. While $R2^*$ and $R2'$ from gradient-echo (GRE) MRI have long been used as a quantitative measure of brain iron (Aquino et al., 2009; Haacke et al., 2005), it was increasingly recognized that the GRE phase might provide more sensitivity to the iron deposition (Haacke et al., 2005). However, the GRE signal phase is not quantitative, since it is affected by surrounding tissue magnetic susceptibility distributions and the orientation. To overcome this problem, QSM was developed to deconvolve the phase using the magnetic dipole kernels to convert the nonlocal phase into magnetic susceptibility (de Rochefort et al., 2010; Li et al., 2011; Liu et al., 2009; Schweser et al., 2011; Shmueli et al., 2009; Wharton et al., 2010; Wu et al., 2012). The resultant tissue magnetic susceptibility inherits the high contrast of GRE signal phase, and provides clear contrast between the iron-rich brain nuclei and the surrounding tissues. Magnetic susceptibility is a localized intrinsic property of tissue, and is typically not affected by the blooming artifact. As a result, the contrast and boundary of iron-rich deep brain gray matter nuclei is often better delineated by QSM than GRE magnitude $R2'$ and $R2^*$ (Lim et al., 2013). Furthermore, similar to $R2^*$ ($1/T2^*$), converging evidence suggests that magnetic susceptibility of iron-rich gray matter is linearly proportional to the iron content (Bilgic et al., 2012; Langkammer et al., 2012; Schweser et al., 2011; Shmueli et al., 2009; Wu et al., 2012). Given the excellent contrast and the linearity with iron, QSM is a promising candidate for noninvasive assessment of iron deposition in deep brain nuclei.

Using QSM, we explored, for the first time in children, the relationship between iron content measured directly in the brain and cognitive capabilities, as a step toward understanding the pathophysiology of iron deficiency and developmental sequelae. Although the current study only focuses on a subset of cognitive abilities, it is likely that other domains of behavior are also related to iron in the brain. Based on the literature linking iron deficiency to poor neurocognitive outcomes in children, we hypothesized that there would be an inverse relationship between iron in the basal ganglia and cognitive scores.

Table 1
Sample characteristics.

	QSM pilot ($N = 39$)		Full sample ($N = 183$)	
Race				
African American	20		90	
Not African American	19		93	
Sex				
Female	22		100	
Male	17		83	
Right handed	31		142	
	Mean [SD]	Range	Mean [SD]	Range
Age at scan	9.51 [1.25]	7.25–11.67	–	–
Age at DAS	6.80 [0.71]	6.00–8.25	6.62 [0.54]	5.42–8.50
DAS IQ[a]				
Overall	100.64 [15.17]	61–130	100.02 [14.03]	48–138
Verbal	102.41 [13.80]	81–142	101.83 [13.75]	67–142
Non-verbal	99.26 [16.14]	58–142	100.21 [14.18]	37–140
Spatial	99.69 [13.00]	67–126	98.08 [12.80]	58–142

[a] DAS = differential ability scale.

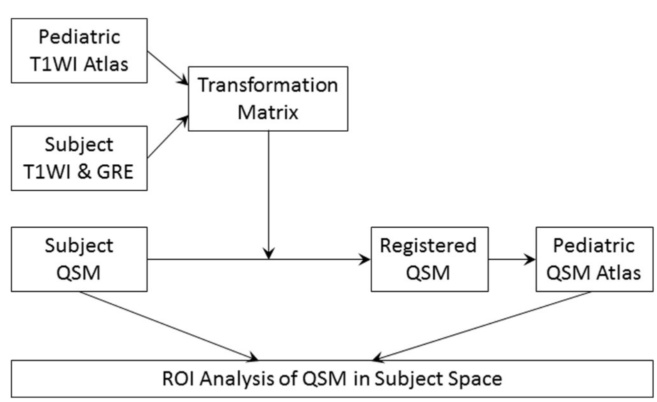

Fig. 1. Summary of ROI analysis pipeline. T1-weighted images (T1WI) and GRE magnitude images (echo 1) were used to calculate the transformation matrix that maps the GRE images to a standard pediatric T1WI atlas. The resulting transformation matrix was then used to register individual subject's susceptibility map to the pediatric atlas. The registered QSM maps from all subjects were then averaged to form a pediatric QSM atlas. ROIs were first defined on the QSM atlas, then inverse transformed back to the individual subject space of the native QSM maps. Finally, the mean susceptibility of each ROI was calculated for each subject on which subsequent statistical analysis was performed. A more detailed flowchart of the pipeline can be found in Supplementary Fig. 1.

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