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***In vivo* characterization of brain iron with magnetic field correlation imaging**

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In adult humans, the brain contains high concentrations of tissue iron relative to most other organs [1,2]. Furthermore, altered brain iron homeostasis has been associated with a variety of pathologies, including Parkinson's, Alzheimer's and Huntington's diseases [3–5]. Owing to its strong magnetic properties, iron can substantially affect MRI contrast and may be regarded as an endogenous contrast agent. For these reasons, iron in the brain has long been considered a potential imaging biomarker for iron-related neuropathologies [1,2].

Tissue iron enhances MRI contrast in the brain primarily by shortening the transverse relaxation times T2 and T2* through increased water proton dephasing. Consequently, regions with larger amounts of iron tend to appear darker on T2- and T2*-weighted images. In order to have a quantitative index of brain iron, several MRI metrics have been proposed, including the relaxation rates R2, R2* and R2' [2,6]. The R2 relaxation rate is simply defined as 1/T2, while the R2* relaxation rate is defined as 1/T2*. The relaxation rate R2' is calculated as the difference R2*–R2. If one constructs parametric maps for these rates, then high iron regions appear bright, reflecting the enhanced transverse relaxation rate caused by the presence of iron.

While relaxation rates have proven useful for brain iron quantification, they have some inherent limitations [6]. First, both R2 and R2* can be significantly affected by relaxation processes unrelated to iron, such as dipole–dipole interactions. As a consequence, neither of these relaxation rates is highly specific to brain iron. The difference rate R2' improves specificity by cancelling out some of the contributions to R2 and R2* from sources other

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than iron. However, iron-related information is also lost in calculating $R2'$, thereby reducing its sensitivity to iron. A second difficulty with using relaxation rates to quantify brain iron is that their values depend somewhat on the details of how they are measured. For example, $R2^*$ can be altered significantly by changing the image resolution, while both $R2$ and $R2^*$ may be affected by the choice of echo times [7,8]. This inherent link to the measurement process makes standardization of relaxation rates challenging.

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To obtain indices that are more robustly defined than relaxation rates, it is natural to consider physical properties of brain iron that can be specified independently of the MRI signal. This is the approach taken in diffusion MRI, where the conventional metrics of mean diffusivity and fractional anisotropy are intrinsic to the sample. In this way, MRI may be regarded solely as a measurement tool and is disentangled from how the metrics are conceived. For brain iron quantification, two such intrinsic tissue metrics have been recently proposed: the magnetic susceptibility [9,10] and the magnetic field correlation (MFC) [11,12]. Below, we focus primarily on the MFC, as it has until this time received less attention than the magnetic susceptibility.

In order to understand the MFC, one should appreciate that iron in brain has a highly nonuniform microscopic spatial distribution [13,14]. In particular, much of the iron is localized within glial cells, which are typically a few microns in size. If a constant external magnetic field is applied, such as that found in an MRI system, these iron-rich glial cells become magnetized and act as microscopic magnetic dipoles that perturb the main magnetic field. This results in a complex magnetic landscape within the tissue that varies on a length scale comparable to the size of the glial cells.

Now consider a water molecule diffusing through such a magnetic landscape. Over time, it experiences a certain average magnetic field, which is approximately equal to the external applied field but shifted slightly due to the bulk magnetic susceptibility of the sample. However, at any particular time, the molecule's local field may be either a bit higher or lower than the average, depending on its position within the magnetic landscape. Let us call the difference between the local field and the average field $\delta B(t)$, where t is the time. By construction, the average of $\delta B(t)$ vanishes over long time intervals.

A macroscopic region of brain tissue contains a large number of such water molecules distributed across the magnetic landscape. The average of $\delta B(t)$ over this full ensemble of water molecules is also zero, as averaging the field difference of a single water molecule over time is equivalent to averaging $\delta B(t)$ for a given time over all of the water molecules. In physics parlance, this property goes by the name of ergodicity. However, the average of the product $\delta B(t) \cdot \delta B(t')$ does not necessarily vanish, and this corresponds precisely to the MFC divided by the square of the proton gyromagnetic ratio γ . Thus, we can formally write $MFC = \gamma^2 \langle \delta B(t) \cdot \delta B(t') \rangle$, where the angle brackets indicate an averaging over the ensemble

of water molecules. The proton gyromagnetic ratio is just included as a convenient normalization factor, which gives the MFC dimensions of inverse time squared.

Note that in defining the MFC we have not made reference to any type of MRI acquisition. The MFC depends only on the intrinsic magnetic properties of the sample, the two times t and t' , and the applied field. Moreover, if the sample is in steady state, as is normally assumed, then the time dependence of the MFC is only through the difference $t-t'$, and if the magnetic properties of the sample are linear, which is also a good approximation in most cases, then the MFC scales trivially with the square of the magnitude of the applied field.

The MFC characterizes the microscopic variability of the magnetic field, which is a direct consequence of the magnetic landscape generated by the iron-rich cells. Conceptually, the MFC is somewhat analogous to the mean diffusivity, which quantifies the variability in molecular diffusion displacements. The connection between MFC and iron is thus akin to the connection between the mean diffusivity and microstructure. An important caveat is that the MFC is sensitive to all sources of magnetic field inhomogeneities, but with iron-rich cells thought to be the dominant source, at least for high iron brain regions, such as the basal ganglia. Other potential sources of microscopic magnetic field inhomogeneities in the brain are deoxyhemoglobin in capillaries and veins, myelin and calcifications [12]. In addition, exogenous paramagnetic contrast agents can also affect the MFC [15].

It is important to distinguish the information provided by the MFC with that provided by the magnetic susceptibility, which is related to the shift in the average field and, in principle, has no definite connection to the microscopic variability. Therefore, MFC and magnetic susceptibility are independent and complementary quantities, as much as are diffusion and flow. Moreover, the complex microscopic spatial distribution of brain iron implies that a single metric is insufficient for its full characterization, suggesting that it can be useful to employ the MFC and magnetic susceptibility in tandem. It should also be emphasized that, while MFC and magnetic susceptibility may, in practice, both be strongly correlated with the bulk iron concentration, neither should be regarded, in general, as a precise and robust measure of this quantity. Rather the MFC and magnetic susceptibility are sensitive to particular aspects of the iron distribution that are potential biomarkers for brain iron homeostasis.

The basis of MFC imaging is that the MFC can be estimated with MRI by using asymmetric spin echo sequences, with the degree of MFC weighting increasing with the degree of asymmetry [11]. More precisely, if t indicates the time shift of the 180° refocussing pulse from the symmetric position of midway between the excitation pulse and the signal readout, then the signal decay can be modeled as a monoexponential in $(t_s)^2$. The decay constant for this monoexponential is simply twice the MFC for the time difference $t-t' = TE/2$, where TE is the echo time for the sequence. Again, there is a close analogy with diffusion MRI, with $(t_s)^2$ playing the role of the b -value and $2 \cdot \text{MFC}$ playing the role of the diffusion coefficient.

Only recently have applications of MFC imaging to neuropathology been explored in some depth. A study of multiple sclerosis revealed elevated MFC values in the deep gray matter of patients relative to controls [16]. Other diseases to which MFC imaging has been applied

include aceruloplasminemia [12], mild traumatic brain injury [17] and Huntington's disease [18]. All these studies demonstrated a significant sensitivity of MFC to pathology, presumably via alterations in iron homeostasis.

To date, there have been few direct comparisons between MFC and other iron-related MRI metrics. However, an investigation of healthy adolescents and adults found that MFC was more consistent than R2 in detecting intraregional differences for deep gray matter areas, where age-related iron changes are known to occur [19]. A separate study of ADHD found significant MFC differences, relative to controls, in the basal ganglia that were not observed with either R2 and R2* [20].

Although still in an early stage of development, the encouraging preliminary results for detecting disease-related alterations of brain iron homeostasis, as well as the fact that it is based on a rigorous physical theory, make MFC imaging a promising tool for assessing tissue iron in brain. Because MFC and magnetic susceptibility provide complementary information, the combined use of these two metrics may be particularly fruitful.

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