Research Highlights

Highlights from the latest articles in imaging

Validation of techniques for perfusion imaging

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Evaluation of: Henriksen OM, Larsson HB, Hansen AE, Grüner JM, Law I, Rostrup E. Estimation of intersubject variability of cerebral blood flow measurement using MRI and positron emission tomography. *J. Magn. Reson. Imaging* doi:10.1002/jmri.23579 (2012) (Epub ahead of print).

Cerebral blood flow (CBF) is a measure of blood entering a tissue per unit time. It is assumed to be related to neuronal activity and oxygen metabolism and has become an important surrogate marker of tissue viability. Many neurological and neurodegenerative conditions, ranging from epilepsy to Alzheimer's disease, have been associated with hypo-, and occasionally, hyper-perfusion.

Considerable effort has been devoted to developing noninvasive or minimally invasive imaging methods for quantifying regional CBF. PET is often considered the gold standard but necessitates a radiation dose and yields limited anatomical resolution. Several MRI techniques have been developed to measure CBF: dynamic contrast-enhanced (DCE) MRI models the pharmacokinetics of an exogenous contrast agent; arterial spin labeling (ASL) compares the image intensity with, and without, arterial tagging; phase contrast mapping (PCM) encodes the velocity of arterial blood; it yields a single measure of global CBF, but does not measure regional perfusion. Owing in part to complex modeling with multiple assumptions and the large inter-subject variability of baseline CBF, the reliability of these methods is largely unknown.

The present work investigates the inter- and intra-subject accuracy and precision of these quantitative CBF methods. MRI measures were obtained on 17 healthy volunteers; ten of these subjects also received ^{15}O-PET scans. Each technique was conducted twice within the same imaging session. This study design enables assessment of the mean CBF, the within-subject variance, and the between-subject variance of the four methods. Images were coregistered and segmented according to tissue type using FSL.

Significantly higher (~60%) global CBF was measured with PCM than with any other modality. ASL was not significantly different to PET; DCE reported slightly higher gray matter CBF and slightly lower white matter CBF than did ASL and PET. However, the authors note that the "CBF measurements obtained by DCE are in best agreement with CBF values from literature."

Similar intersubject variance was observed among all methods (ranging between 16.2 and 20.0%) on global measures. This large variance is expected given the large range of baseline CBF between individuals. Conversely, the methods demonstrated substantially different intrasubject variances: ASL differed by 4.8%, PCM by 7.4%, PET by 11.9%, and DCE by 15.1%.

This study demonstrates that ASL provides the best reliability for serial perfusion imaging with MRI but may not provide the most accurate quantification. DCE may provide more accurate results but is "limited by only moderate repeatability and its use of intravenous contrast." PCM is of limited utility as it is spatially nonselective.

This study has several limitations and perplexing observations. It is only valid for the acquisition methods investigated; different implementations of ASL or contrast-enhanced imaging (i.e., dynamic susceptibility contrast) may provide substantially different results. Also, the various methods showed no correlations, with the exception of DCE and PCM in global CBF measures. More and stronger correlations are expected among methods measuring the same property and no substantive explanation is given for this observation.

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Ultimately, this work is a very important step toward validation of perfusion methods, which vary drastically in their implementation and modeling. It succinctly separates intra- and inter-subject effects and includes multiple imaging modalities.

The role of myelin as a contrast mechanism in susceptibility phase imaging

Evaluation of: Gregory A, Lodygensky GA, Marques JP *et al. In vivo* assessment of myelination by phase imaging at high magnetic field. *Neuroimage* 59(3), 1979–1987 (2012).

Myelin plays a role in efficient neural conduction, and demyelination and dysmyelination are associated with many neurodegenerative conditions, developmental disorders and mental illnesses. Currently, several imaging methods identify or quantify myelin integrity. Relaxation-weighted (i.e., T_2-weighted, T_1-weighted) images provide qualitative assessments, while diffusion tensor imaging, multicomponent T_2 analysis, and magnetization transfer imaging yield quantitative metrics. Each method has significant acquisition, reconstruction and interpretation limitations; additional complementary methods are desired.

Recently, the phase of gradient echo images has been investigated as an information-bearing contrast mechanism. The phase associated with a voxel is related to the magnetic susceptibility within and surrounding that voxel. The dominant susceptibility sources have yet to be fully identified but evidence suggests that tissue iron, lipids and axonal microstructure contribute significantly while cerebral blood volume plays a minor role.

This study demonstrates that myelin is responsible for the majority of the contrast observed between gray and white matter on phase images and that T_2*-weighted gradient echo has potential for assessing myelination during brain development and in pathological conditions. This study performed *in vivo* and *ex vivo* experiments on healthy developing Wistar rats and on 5-week-old shiverer and control mice using a 9.4 T scanner.

The authors observed an increase in phase contrast between gray and white matter with increasing animal age. Phase measurements in white matter correlated well with optical density on myelin stained samples: approximately 70% of the variation in phase was accounted for by myelin. Further evidence of a dominant myelin contribution was obtained from shiverer versus control mice where reduced phase contrast and optical density with myelin staining were observed in the myelin-deficient mice. Additionally, very little change in contrast was noted between phase images collected before and after extraction of tissue iron, again supporting myelin as the dominant susceptibility mechanism. The authors estimate that "approximately 20% of the contrast between gray and white matter is not myelin related."

Several limitations prevent immediate adoption of this technique for myelin assessment in humans. Firstly, tissue iron substantially alters the phase in the basal ganglia in both healthy human subjects and in those with neurodegenerative diseases, such as multiple sclerosis. No explanation was given for their conflicting observation that iron plays a minor role relative to myelin. Secondly, local phase is the result of nonlocal magnetic susceptibility and is highly dependent on the direction of the main magnetic field. Advanced processing methods, such as susceptibility mapping and complex tissue models are required to elicit information on myelin integrity. Lastly, this work was performed at 9.4 T. A 44 ms echo time is required at 3 T to match the phase contrast reported here; while this is not strictly necessary to obtain some contrast in the phase image, this hinders implementation at clinical field strengths.

In summary, this work provides important *in vivo* and *ex vivo* confirmation of the role of myelin in phase imaging. This imaging technique is notable since a high resolution T_2*-weighted sequence can be acquired rapidly, is free of drastic spatial distortions, the magnitude image is likely to be of value, and quantitative values can be obtained from the phase map. This technique may eventually contribute sufficient information on tissue microstructure to become a clinically standard routine.

Quantitative susceptibility mapping for assessing deep gray matter

Evaluation of: Lotfipour AK, Wharton S, Schwarz ST *et al.* High resolution magnetic susceptibility mapping of the substantia nigra in Parkinson's disease. *J. Magn. Reson. Imaging* 35(1), 48–55 (2012).

As described in the previous highlight, the phase of a gradient echo image contains information regarding tissue microstructure. The phase results from the convolution of a magnetic dipole with the tissue susceptibility and thus the phase of each voxel is dependent on the surrounding tissues. Inverse solutions have been proposed to compute the susceptibility distribution based on image phase. The resulting susceptibility map provides a local assessment of tissue composition.

While myelin plays a major role in modulating contrast, nonheme iron has been observed to provide contrast between deep gray matter nuclei and surrounding tissues

on phase and susceptibility maps. Many neurodegenerative conditions are poorly assessed via MRI and new biomarkers may improve diagnosis. Parkinson's disease results from idiopathic loss of dopaminergic neurons in the substantia nigra (SN). Increased tissue iron has been observed in this region; it is hypothesized to mediate neuronal death and has been proposed as a potential biomarker for Parkinson's disease.

This study imaged the SN of nine patients and eleven controls on a 7 T scanner to determine if susceptibility differences exist between patients with Parkinson's disease and healthy controls. Near-isotropic resolution gradient echo images were acquired with resolutions ranging between 0.4 mm and 0.7 mm in each dimension. The echo time varied between 20 and 25 ms. Susceptibility maps were generated with a previously published method that thresholds the ill-conditioned susceptibility inversion problem. The midbrain was segmented into the red nucleus, the SN, and the pars compacta of the SN.

A significant ($p = 0.042$), ~50%, increase in susceptibility was observed in the pars compacta of patients relative to controls. No significant group difference was observed over the entire SN; however, this is attributed to a significant spatial gradient in susceptibility with caudal regions showing higher values than cranial regions. In each slice, there was a consistently higher susceptibility in the SN of patients than in controls.

This work attributes the increase in susceptibility to increased tissue iron. While likely, this was not proven histologically (for obvious reasons). It is possible that a reduction of negative susceptibility sources, such as myelinated axons, could cause an apparent increase in susceptibility. This effect could potentially be resolved with transverse relaxometry. Additionally, although also unlikely, postural differences between groups could affect the background field distortions and thus bias susceptibility maps, and differences in the orientation of main magnetic field could change the measured susceptibility values, which are orientation dependent.

Despite minor limitations, this work is the first to demonstrate susceptibility abnormalities in a Parkinson's population. It employs novel acquisition and processing methods at high field and provides additional confirmation that iron may serve as a disease biomarker.

Subject-specific mapping of the basal ganglia

Evaluation of: Lenglet C, Abosch A, Yacoub E, De Martino F, Sapiro G, Harel N. Comprehensive *in vivo* mapping of the human basal ganglia and thalamic connectome in individuals using 7T MRI. *PLoS ONE* 7(1), e29153 (2012).

The basal ganglia and thalamus are a collection of deep gray matter nuclei that act as crucial relay stations in the human brain. The nuclei are highly interconnected and, as a system, have afferent and efferent connections throughout the cerebral cortex that mediate motor and sensory systems and effect emotion and cognition. Mapping their structure and neural connections – especially in individual subjects – has been exceptionally challenging with MRI.

The present study employs multiple MRI sequences to characterize the basal ganglia nuclei and their connections. This study demonstrates:"(i) subject-specific *in vivo* visualization and segmentation of basal ganglia and thalamus, (ii) comprehensive reconstructions of white matter pathways connecting these structures, (iii) quantification of the probability of each pathway, and (iv) identification of subdivisions of the basal ganglia and thalamus."

To perform this analysis, they acquired T_1-, T_2-, proton density- and susceptibility-weighted images along with diffusion-encoded images with 128 directions and resting state functional images. Individual nuclei were identified via manual tracing of the multicontrast images. Seven nuclei were initially delineated per hemisphere. Regions were then used as seeds to determine the diffusion streamline probability to all other regions to establish a structural connectivity profile. Resting-state functional connectivity maps were employed to determine functional connectivity between nuclei.

This study demonstrates excellent segmentation of the basal ganglia and thalamus and simultaneously provides several connectivity measures. This approach has tremendous potential for improved clinical diagnosis and for neuroscience research. Measuring the location, volume, diffusion parameters, structural connectivity and functional relations of each nucleus could be applied to diagnose or investigate many neurological conditions, psychiatric disorders and developmental disabilities. For example, the authors note that the nigrostriatal pathway can be reconstructed, which could be used to further investigate Parkinson's disease. With additional processing, susceptibility maps, as employed in the previous article, could be constructed from this same data. Based on fiber projections, this work was also used to delineate certain thalamic sub-nuclei, which are typically difficult to discern.

This paper fails to adequately address the reliability of this imaging and analysis protocol. In particular, its sensitivity to intrascan motion, which can severely degrade high-resolution images, may limit its clinical utility. Additionally, manual segmentation is extremely time consuming and is a source of variability, despite their claims (from a single repeat scan) that intra-observer reliability was very high.

Ultimately this work succinctly demonstrates that MRI has the potential to map the structure and function of the basal ganglia in individual patients. The applications of this method are numerous and diverse.