Weekday Educational Course
Everything You Wanted to Know About Magnetic Susceptibility & Why It Is Important:
Major Sources of Phase Contrast in the Brain
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Highlights

- Gradient-echo MRI phase contrast depends on the underlying tissue magnetic susceptibility but is orientation-dependent and non-local.
- Calculating tissue magnetic susceptibility maps overcomes the orientation-dependent and non-local nature of phase contrast.
- Phase and susceptibility are primarily affected by tissue composition. For example, tissues rich in ferritin (stored iron) are relatively paramagnetic and show strong contrast in phase images and susceptibility maps.
- Tissue structure is also a major source of phase and susceptibility contrast, with orientation-dependent effects arising at several different scales from macroscopic to microscopic and anisotropic susceptibility originating from ordered molecular structure.
- Susceptibility is not the whole story: chemical exchange-induced frequency shifts have been observed in brain tissue with lipids and proteins postulated as contributors.
- Different contrast sources dominate in different brain regions and in different pathologies

Major Sources of Phase Contrast in Brain Tissue

TARGET AUDIENCE – Scientists and clinicians interested in understanding phase, frequency and susceptibility contrast and in developing improved techniques and clinical applications.

OBJECTIVES – Gain an overview and understanding of the dominant contributions to contrast in gradient-echo phase images and magnetic susceptibility maps of the brain.

PURPOSE – Previous research has aimed to elucidate the sources of contrast in phase images and susceptibility maps to facilitate their interpretation by scientists and radiologists and thereby accelerate translation of these imaging techniques into the clinic.

METHODS – Contributions to phase contrast have been investigated using a wide variety of techniques ranging from comparisons of phase images and susceptibility maps with histology and correlation with independent measures of tissue composition to studying the effects of altering tissue composition and structure by, for example, iron extraction, demyelination, addition of contrast agents, functional activation, and modelling and modification of microstructure.

INTRODUCTION TO PHASE CONTRAST

Phase images underpin the rapidly expanding field of tissue magnetic susceptibility mapping. Conventional MRI uses only the signal magnitude, but utilising the phase of the complex MRI signal in gradient-echo T2*-weighted imaging has revealed a new and rich contrast, particularly at high magnetic field strengths [1]. The phase images are complementary to the magnitude images and have allowed dramatic improvements in the visualisation of tissue structure and composition.

Despite the increased contrast-to-noise observed in phase images of the brain [1], phase contrast suffers from two disadvantages: it is often non-local, extending beyond the area of altered tissue magnetic susceptibility [2], and it is orientation-dependent, varying with the orientation and geometry of the tissue with respect to the main magnetic field (B_0) direction [3].

Phase images suffer from phase wrapping or aliasing and there are a large variety of unwrapping algorithms available, e.g. [4-6], each with their own advantages and drawbacks. The measured phase also depends upon imaging parameters such as the echo time (TE) and the voxel aspect ratio [7, 8]. It is important to be aware that the phase will also be affected by hardware differences in vendor systems such that there are two phase sign conventions [9]. In almost all cases, phase images are processed to remove large-scale background phase variations caused primarily by the relatively large susceptibility difference between tissue and air in cavities and outside the body. These background phase variations are usually much larger than the phase differences of interest between brain tissues and there are a plethora of techniques for removing them, e.g. [10, 11]. However, it is important to note that, as a result of removing these background phase variations, the contrast observed in phase images and susceptibility maps is relative rather than absolute.

Tissue magnetic susceptibility maps [12, 13] calculated from processed phase images overcome, to a great extent, the non-local and orientation-dependent nature of the contrast in phase images. Conversely, the contrast in phase images depends on the underlying tissue magnetic susceptibility.

TISSUE COMPOSITION:

IRON CONTENT

Therefore, a predominant source of contrast in phase and susceptibility images is tissue composition as this directly affects the tissue magnetic susceptibility. For example, tissues rich in ferritin (stored iron) are relatively paramagnetic and show strong contrast in phase images and susceptibility maps. Several investigators have found strong correlations between the measured tissue magnetic susceptibility in brain regions such as the red nucleus, substtantia nigra and putamen and their iron content, often estimated from post-mortem studies [10, 12, 14, 15]. Tissue MRI susceptibility values have also been found to correlate with iron content measured in the same tissue using independent methods such as X-ray fluorescence imaging and inductively coupled plasma mass spectrometry [16, 17].

Phase contrast between cortical layers has also been shown to have a strong contribution from tissue iron as extracting the iron from fixed visual cortex has been shown to virtually eliminate the intra-cortical phase contrast [18]. In that study, the phase images showed a very small, (opposing) residual contrast that may be due to increased myelination in some cortical layers such as the stria of Gennari (see below). The dependence of susceptibility and phase image contrast on iron content has been exploited for several clinical applications, for example to improve targeting of structures for deep-brain stimulation [19] and as a marker of increased iron content in the substantia nigra in patients with Parkinson's disease [20].

DEOXYHAEMOGLOBIN

Deoxyhaemoglobin is another major source of phase contrast. It is well-established that deoxyhaemoglobin is paramagnetic with respect to most tissues and this is the basis of functional MRI and susceptibility-weighted imaging (SWI) [21]. Despite being the dominant source of phase contrast in and near blood vessels, the contribution of endogenous deoxyhaemoglobin to the intrinsic phase contrast between grey and white matter in the brain has been shown to be negligible [22]. Deoxyhaemoglobin-induced (vessel-based) phase contrast has been extensively exploited

clinically in SWI as we will hear from Dr Karen Tong later in this session. A swiftly emerging application is the utilisation of phase and susceptibility contrast for functional imaging [23, 24].

MYELIN

In addition to paramagnetic contributors to phase contrast, prominent diamagnetic sources include myelin which is thought to have a slightly more diamagnetic susceptibility than other tissues due to its high lipid content [1, 25]. Demyelination, induced by a cuprizone diet [25] or in shiverer mice [26], has been shown to almost completely remove the contrast between grey and white matter. Changes in the phase contrast in and around Multiple Sclerosis lesions has been attributed to changes in both myelination and iron content [27-30].

ETC

It follows from the examples above that any diamagnetic or paramagnetic tissue contents can contribute to susceptibility and phase contrast if present at sufficient concentrations and/or having a large enough (positive or negative) susceptibility. Thus, we can observe calcifications and distinguish them from haemorrhages in phase and susceptibility images [31, 32] as calcium compounds are strongly diamagnetic. A recent study has also used susceptibility mapping to measure the effect of copper accumulation in the brain in Wilson disease [33].

MICROSTRUCTURE & ANISOTROPY

In addition to its composition, tissue's structure at several different scales affects phase contrast. Even if a tissue structure's overall macroscopic shape and geometry remain constant, if its microstructural orientation with respect to B_0 is altered, this changes the phase contrast [34]. This phenomenon has been explained by susceptibility anisotropy [35]. Susceptibility anisotropy has been measured in white matter (whose fibres are found to be more diamagnetic when they run perpendicular to B_0) and seems to arise from the highly ordered macro-molecular structure of the lipid bilayers in the myelin sheath [36]. This effect has been exploited in Susceptibility Tensor Imaging [35, 37, 38] to reveal white matter structure via a mechanism complementary to that utilised in Diffusion Tensor Imaging.

Tissue cellular architecture, orientational ordering and compartmentalisation play an important role in phase contrast [38-40], with protons diffusing within, exchanging between and selectively sampling compartments with different susceptibilities and magnetic fields. Fibre-orientation-dependent phase contrast has been explained by a simple two-pool model in which the myelin sheath is modelled as a hollow cylinder of anisotropic susceptibility with water in the sheath having a reduced T2 and proton density than its surroundings [38].

CHEMICAL-EXCHANGE-INDUCED PHASE SHIFTS

Tissue magnetic susceptibility and microstructural effects are not the end of the story when it comes to sources of phase contrast: recent research suggests that chemical exchange between water and macromolecular protons may contribute substantially to the observed gray to white matter phase contrast. Studies in protein solutions have found an exchange-induced frequency shift proportional to the protein concentration [41, 42]. Exchange-induced frequency shifts have also been measured between gray and white matter [43]. This source of phase contrast differs from magnetic susceptibility, susceptibility anisotropy and microstructural effects in that it is local and independent of orientation. Both proteins [42] and lipids [44] have been hypothesised as a major source of exchange-induced phase contrast.

CONCLUSION

Major sources of phase contrast in the brain include tissue composition (that alters its magnetic susceptibility) as well as tissue structure from molecular, through microscopic to macroscopic scales. Tissue compartmentalisation and chemical exchange also contribute to phase contrast and disentangling the different contributions is complicated. We can conclude that different contrast sources dominate in different brain regions and can be exploited to study various pathologies.

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