Direct Phase Imaging in Neonate

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Introduction: Direct phase images have been shown to yield superior gray (GM) and white matter (WM) contrast at high field compared to conventional magnitude images [1]; however, the contrast mechanisms are still being discussed. Previous studies are limited to high field and adult volunteers or patients [2]. In this study, phase imaging in neonates is demonstrated for the first time. Since the neonatal brain contains little or no myelin and little iron, it is possible to separate the different contributions from tissue susceptibility [1] and water macromolecule exchange (WME) [3], which are the two major sources of contribution to the *in vivo* phase contrast.

Methods: Experiments were carried out on a 3 T MR scanner (Siemens TIM Trio, Erlangen, Germany) using a 12-channel head coil. Ten neonates (average post-conceptional age: 42 weeks) were included in the study. Neonates were sleeping inside the scanner and were constantly attended to by a research assistant. No sedation was applied. Informed written consent was provided by the parents following the guidelines of the local IRB. Phase images were acquired with an RF-spoiled 2D gradient echo sequence (320x288 matrix, 0.5x0.5 mm^2 in-plane resolution; TR/TE = 980/35 ms; flip angle = 50°; 20 slices, slice thickness 2 mm). In addition, 3D-MPRAGE images (256x256x160, 1 mm^3 isotropic resolution, TR/TE = 2500/3.98 ms, TI = 1100 ms) were acquired. MATLAB and SPM5 were used for data processing, using in-house software developed for phase data reconstruction. The GM/WM phase differences were determined in several brain regions, using carefully selected regions of interests (ROIs) in GM and WM that were void of observable vessels. In addition, regions of early myelination in the internal capsule were compared to surrounding WM regions without myelination to estimate the phase contrast due to early brain myelination.

Results: A typical 3T phase image from a 4-week old neonate is shown in Fig. 1. The neonate data show a higher phase in GM compared to WM (Fig. 1a), consistent with results from adults. In contrast, magnitude images show reversed GM/WM contrast with respect to the adult brain. Unfortunately, due to strong head motion of the neonates, only one third of all the phase image data (four neonates) were of high quality and could be used to analyze the GM/WM phase contrast.

Despite the rather small phase contrast effect at 3 T, reliable quantification of the GM/WM phase contrast was possible (see Table 1), yielding an average GM/WM phase difference of 0.0038 ppm. Additionally, the partially myelinated WM region in the internal capsule was also selected (Fig1. b). The estimated phase difference between the internal capsule and surrounding WM regions without myelination is -0.0034 ppm. These observations are robust across all four neonates. In comparison, adult phase images at 3 T showed higher GM/WM phase contrast (0.01 ppm occipital, not shown).

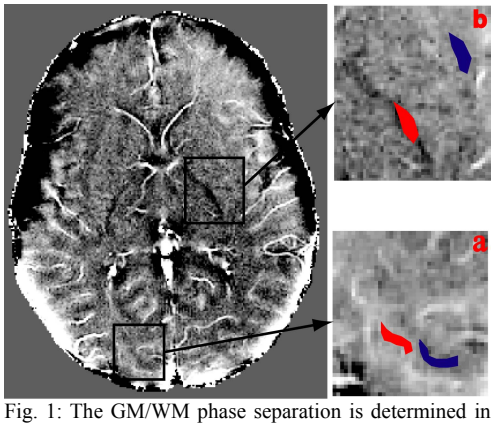

Fig. 1: The GM/WM phase separation is determined in selected ROIs (a). GM (red) and WM (blue) regions without visible veins were selected. The average GM/WM separation is 0.0038 ppm. b) In selected WM-regions with (red) and without (blue) myelination in the internal capsule the phase shift related to myelination was determinated (-0.0034 ppm).

Table 1: The GM/WM phase separation in selected ROIs (average 0.0038 ppm).

ROI	Subject 1	Subject 2	Subject 3	Average
occipital lobe	0.0039	0.0037	0.0036	0.0038
frontal cortex	0.0036	0.0035	0.0034	0.0035
parietal lobe	0.0041	0.0040	0.0037	0.0040
thalamus	0.0037	0.0036	0.0040	0.0038
internal capsule*	-0.0035	-0.0030	-0.0038	-0.0034

*Phase separation from WM myelination in the internal capsule was -0.0034 ppm.

Discussion: The human neonatal brain contains little iron and no myelin. Thus, the major sources of susceptibility phase contrast are blood hemoglobin, macromolecules, and iron in WM. Previous studies of iron depositions in the neonate rat brain suggested a highly localized iron distribution, mostly in WM. High iron content leads to a more positive phase, which is not observed in this study. Additionally, a recent phase imaging study in rats at 14.1 T [4] suggested that the blood hemoglobin contribution to the GM/WM phase contrast is small. Therefore, tissue iron and hemoglobin are unlikely to account for the GM/WM contrast in neonates.

The presence of macromolecules will lead to a negative (diamagnetic) susceptibility phase contribution. Neonates have higher macromolecule content in GM compared to WM [5]. Therefore, if a diamagnetic macromolecule contribution was the dominant effect, one would expect a negative phase contrast in GM compared to WM in neonates, such as for T_1 or T_2. However, phase reversal is not observed in neonates in this study.

The difference in macromolecule content between GM/WM is estimated to be 20 mg/g in neonates. The corresponding WME shift is 0.004 ppm [3], which is consistent with our experimental results, suggesting that WME is the dominant effect for neonatal *in vivo* GM/WM phase contrast. The 2 – 3 times higher phase contrast in adults can thus be associated with myelin and iron. Likewise, the dominant effect of WME in neonate suggests that the WME contrast mechanism contributes about 30% to the adult *in vivo* phase contrast. This result therefore will help to refine the susceptibility model [6] for *in vivo* phase contrast analysis.

Conclusion: Phase contrast imaging in neonates provides insights to the various factors contributing to phase contrast, such as WME and myelination. Phase differences between GM and WM are significantly reduced in neonates prior to myelination and seem to originate primarily from WME contrast. Therefore, direct phase imaging can study brain development and related pathologies in neonates.

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