Introduction: Resonance frequency shifts observed from the phase (Φ) of fMRI signals may report on susceptibility changes due to variation in blood volume and oxygen extraction fraction, and therefore may provide information complementary to magnitude signals. Nevertheless, the use of Φ fMRI signals during functional tasks and at rest has been very limited so far compared to the use of magnitude (M) signals because of the large contribution of physiologic and instrumental noise. In previous work at low fields, fMRI Φ maps generally display only few sparse voxels representing the largest veins, or are very noisy [1-2]. We investigated whether Φ could be detected more sensitively when using advanced technology (7T scanner, array detectors) and optimized processing methods to remove noise contributions.

Methods: 8 subjects (4m/4f, age 30±3) participated in the IRB-approved study. Multi-echo GE-EPI SENSE-rate3 BOLD-fMRI was performed at 7T (GE-Medical-Systems) using 32 receive-only coil elements and parameters: echo-time = 31.5 ms, repetition time = 2.3 s, flip angle = 65°, number of slices = 4, voxel-size = 2.5x2.5x2.5 mm³, number of scans: 158. Two conditions were investigated: 1) visual fixation on a central dot during presentation of a visual stimulus (B/W checkerboard, flickering at 7.5Hz, block-design: 34.5s OFF/34.5s ON cycle); 2) resting with the eyes closed. For each time-point and voxel, the Φ fMRI images were pre-processed as follows: subtraction of the first Φ time-point; removal of phase wrap from time-course signals, and removal of linear drift over time. The background spatial low-frequency Φ variations were fitted for each slice and time point with a 4th order polynomial function. These signal fluctuations were pre-processed to be correlated to the respiratory chest motion and were employed, on a voxel-by-voxel basis, as physiological noise regressor (Φnoise-regressor) for both M and Φ fMRI data. Physiological and instrumental noise correction [3] was applied on both M and pre-processed Φ fMRI images. This included the removal of noise sources: 1) temporal drifts (3rd order polynomials); 2) noise mostly related to the phase of respiration (Φnoise-regressor); 3) noise related to the phase of cardiac cycle (4 cardiac RETROICOR regressors); 4) signal fluctuations due to changes in the respiratory volume rate and 5) cardiac rate. For removal of noise source 2, Φnoise-regressor was compared to the use of 4 respiratory RETROICOR regressors. The % fMRI signal variance explained (VE, %) by the respiratory RETROICOR regressors (Fig. 2). The overlap of Φ and M maps (both positive and negative) was much larger when using the Φnoise-regressor and reached (35.9 ± 2.9) % and (37.3 ± 2.7) % during stimulation and rest respectively, compared to (4.9 ± 1.5) % and (5.0 ± 1.5) % for the RETROICOR regressors. Similar time-courses (Fig. 2C) were observed for Φ and M signals (average absolute correlation value ± s.e. across subjects was 0.52±0.02 and 0.42±0.01 during stimulation and rest, respectively, p< 10^-3) indicating the same BOLD origin of Φ and M signal changes. 

Results: For each source, VE during stimulation in the visual cortex is shown in Fig. 1. Similar results (not shown) for noise sources 1-5 were found at rest. The VE by low-frequency drifts and Φnoise-regressor (~94% and ~20% in Φ and M data, respectively) was higher than the VE by drifts and the respiratory RETROICOR regressors (p< 0.05). In addition, when pre-processed with the Φnoise-regressor, Φ activation maps showed much more widespread activity than when pre-processed with the respiratory RETROICOR regressors (Fig. 2). The overlap of Φ and M maps (both positive and negative) was much larger when using the Φnoise-regressor and reached (35.9 ± 2.9) % and (37.3 ± 2.7) % during stimulation and rest respectively, compared to (4.9 ± 1.5) % and (5.0 ± 1.5) % for the RETROICOR regressors. Similar time-courses (Fig. 2C) were observed for Φ and M signals (average absolute correlation value ± s.e. across subjects was 0.52±0.02 and 0.42±0.01 during stimulation and rest, respectively, p< 10^-3) indicating the same BOLD origin of Φ and M signal changes. 

Discussion and Conclusions: Widespread BOLD-related Φ signal changes/frequency shifts could be detected at 7T by the use of optimized pre-processing to remove unwanted Φ signal fluctuations. The measured Φ signal changes do not seem to be confined to venous sinuses, and are attributed to susceptibility changes in pial and intracortical veins. BOLD Φ signal changes may therefore provide complementary information to BOLD M images and allow quantitative assessment of blood oxygenation.