Reducing Physiological Effects in Resting State fMRI by Dephasing Blood and CSF Signals

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Introduction: It is well known that the intravascular signals contribute a significant part in BOLD fMRI signal, constituting about half of the functional contrast at 3T. And physiological effects such as cardiac/CSF pulsation may also contribute to the BOLD signal. Although extensively studied in task/event related fMRI, the role of vascular and physiological effects in resting state (RS) functional connectivity is yet to be fully understood. RS-fMRI detects the spontaneous neuronal activities which had been considered as baseline fluctuation in routine BOLD fMRI studies. Since the RS-fMRI is in fact analyzing such fluctuation in the baseline signals, it will be important to understand the original of such fluctuation, and their effects to the resultant functional connectivity networks. By implementing flow dephasing with low VENC value, this study aims at estimating the contribution of the intravascular (IV) blood signal and physiological effects to local and long range resting state signal characteristics.

Methods: In order to remove the blood signals in draining veins and reduce CSF signal, we inserted a pair of bipolar gradients into a GE-EPI sequence, between the excitation RF pulse and the readout. With a very low velocity encoding (VENC) value, the bipolar gradients will dephase the signal from flowing spins faster than the VENC value. With total duration of 10ms and amplitude of 24mT/m, the VENC value is 0.98cm/s, which can effectively dephase the blood signal in most of the draining veins [1]. Then we collected RS fMRI data using both this dephasing EPI (Dephs-EPI) and normal EPI on 7 healthy volunteers, who gave their written consents prior to the scans. The scanning parameters were identical for both sequences: TR/TE = 2000/30 ms, flip angle = 80°, voxel size = 2.3×2.3×3.5 mm^3 and bandwidth = 2000Hz/px. 31 slices, oriented paralleled to AC-PC line, were used to cover the whole brain, and totally 210 measurement were collected. For preprocessing, all EPI data were normalized to the MNI template. After regressing out the motion, low passed filtering with a 0.01~0.08Hz filter and spatially smoothing with a 6mm kernel, the maps of temporal SNR (tSNR), signal difference (ΔS) caused by dephasing, amplitude of low frequency fluctuation (ALFF), fractional ALFF (fALFF) and coherence regional homogeneity (cReHo) [2] were calculated. Seeding ROIs (in MNI coordinate) were selected to determine the functional connectivity for default mode network (DMN, [4, -53, 26]) and Thalamus network (AAL 77&78). All data were collected on a Siemens Verio 3T system, and processed using REST and SPM8 algorithms.

Results: Compared to normal EPI, the Dephs-EPI signal on the average is reduced by ~3.5% in GM, ~2.6% in WM and ~7.2% in CSF. This signal reduction is rather homogeneous in GM and WM, but can be as high as 30% for CSF in the ventricles and around the insula lobule (Fig.1). These areas also have reduced tSNR in Dephs-EPI due to the reduced signal intensity. The paired t-test results of ALFF, fALFF and cReHo maps are shown in Fig.2. With flow dephasing, significantly higher ALFF and cReHo values are seen in CSF areas with highest reduction in Fig.2 (cool colors), while reduced ALFF, fALFF and cReHo values are mostly seen in GM. The one sample t-test connectivity maps of DMN and thalamus networks and the paired t-test results between EPI and Dephs-EPI are shown in Fig.3. The connectivity difference is sparse and small for DMN, but is rather clustered and significant in the Thalamus network.

Discussion: BOLD effect, as a means to detect changes in venous oxygenation and hemodynamics relative to baseline signal, has proved to be effective and straight forward in studying the task/event related brain activity. RS-fMRI, on the other hand, detects the temporally correlated fluctuation of the baseline signal caused by spontaneous neuronal activities, and it remains a largely unanswered question whether such spontaneous neuronal activities will have the same BOLD characteristics (e.g. hemodynamics changes) as those observed in task/event related fMRI studies. By removing the IV components in major veins, we aim at estimating the IV contribution to RS-fMRI connectivity results. Contrary to BOLD fMRI studies where IV signals can contribute up to half of the functional contrast at 3T, our results showed that IV signals may affect RS-fMRI results differently, depending on the specific connectivity network of interest. We are demonstrating this with two representative networks, i.e. DMN and Thalamus network. For the DMN, typical and significant connectivity patterns were obtained with both routine EPI and Dephs-EPI data, and only a few sparsely distributed regions were found to have reduced connectivity for blood dephased data in the temporal and superior frontal lobes (Fig.3 left upper image), which were not located in any of those typical DMN regions. However, the Thalamus network had significantly decreases in large clusters in middle/posterior cingulate, cuneus, motor cortex and superior temporal gyrus, but little difference around the thalamus itself (Fig. 3). As both networks were extracted from the same data sets, it's obvious that the IV effects to the connectivity are not globally uniform but regionally specific. It appears that removing IV signal of major veins 1) does not significantly alter short range connectivity strength, but 2) may affect long range connectivity depending on the specific network. This can be explained using the two-compartment model which divides the BOLD effects as IV and EV (extravascular) components. The fluctuation in IV signal is determined by fluctuation in local blood oxygen level and hemodynamics (e.g. CBF and CBV) in draining veins, as well as physiological effects such as cardiac pulsation, all of which may vary for different brain regions. EV signals at resting state, on the other hand, can be considered mainly related to local blood oxygen level in micro vasculature via diffusion related dynamic averaging mechanism [3], and thus are not sensitive to fluctuation in hemodynamics or physiological effects. Thus it can be expected EV signals is highly similar to IV signals in terms of temporal variation, and removing IV signal should not significantly affect the connectivity results. In light of this, since the seed region for DMN (e.g. [4, -53, 26]) contains mainly the GM in precuneus, which has similar blood oxygenation, hemodynamic baselines and physiological effects as other DMN regions, similar amount of IV signal and/or physiological effects will be removed by the dephasing gradients and the remaining signal components will still result in minimally changed connectivity results. However, thalamus derives its blood supply immediately from arteries [4] and thus has very different hemodynamics and physiological effects from cortex GM. Being close to arteries and ventricles, physiological components may contribute a greater portion to the RS signal extracted from the thalamus seed region, and thus may lead to incorrect connectivity results in regions that also contain similar physiological effects. Removing the IV signal can thus reduce such false positive results, as demonstrated in Fig.3. The short range connectivity is demonstrated to remain high since all signal components are expected to be the same within the thalamus, as long as the removal of IV signal and physiological effects is uniform. The dephasing gradient induced signal reduction will not be the cause of such differences as the tSNR and signal reduction is small in GM (Fig.1). Moreover, CSF signal is also significantly reduced via flow dephasing, leading to increased ALFF and cReHo in CSF rich regions (Fig.2), and this can be beneficial for more accurate connectivity calculation in such areas.

In conclusion, with the application of flow dephasing gradients, the IV and physiological effects in resting state signal can be reduced or removed, leading to a more precise estimate of connectivity.

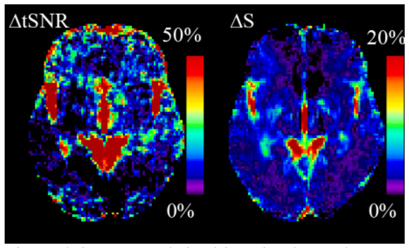

Fig.1 Relative tSNR and signal intensity changes between Dephs-EPI and EPI data. Hot colors: EPI > Dephs-EPI.

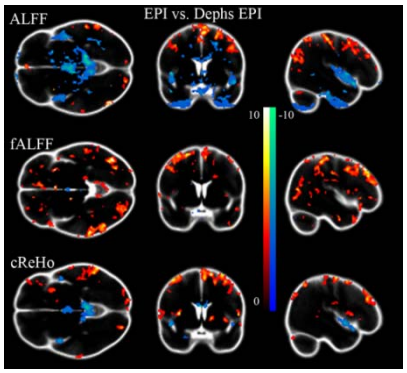

Fig.2 Paired t-test results between Dephs-EPI and EPI from all subjects, overlaid on a CSF template. Hot colors: EPI > Dephs-EPI.

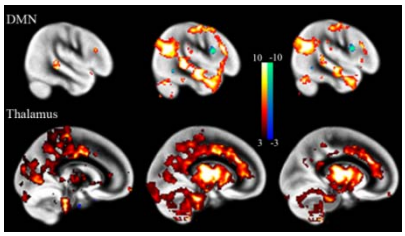

Fig.3 Paired t-test (left) and one sample t-test of the connectivity obtained with EPI (middle) and Dephs-EPI (right), overlaid on a GM template. Hot colors in left column: EPI > Dephs-EPI.

Reference:

[1] Haacke and Ye. Neuroimage. 2012; [2] Zang, *et al.* Neuroimage. 2004; [3] Yablonsky and Haacke. MRM. 1994 ; [4] Schmahmann, Stroke, 2003;