Cortical depth dependence of physiological fluctuations and whole-brain resting-state functional connectivity at 7T

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Target audience: Clinicians/researchers using high resolution fMRI, or studying physiological noise in fMRI signals.

Purpose: The detection of functional connectivity networks from resting-state fMRI requires the careful removal of noise sources such as systemic physiological fluctuations.[1] These fluctuations are driven by several mechanisms, such as dynamic B_0 changes in the head driven by respiration and tissue pulsation and CSF flow driven by the cardiac output, and therefore physiological noise contamination has been shown to vary across brain regions. Previously we demonstrated that physiological noise contributions vary systematically with cortical depth, presumably because cardiac pulsatility is greatest at the pial surface, but independent measurements of respiratory and cardiac signals were not available to determine the exact cause of this depth-dependence. Because of the regularity of the vascular hierarchy across cortical depths, investigating physiological noise sources across depths can potentially provide better insights into how various physiological signals contaminate the BOLD response and how these noise contributions vary with distance to large blood vessels.

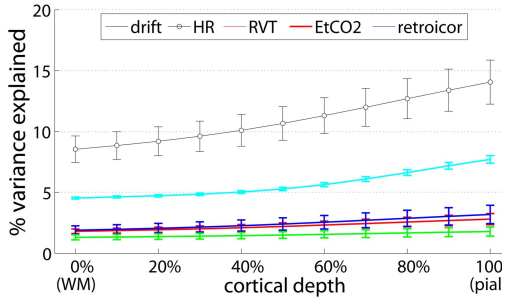

Fig. 1: Percent variance explained by physiological signals across cortical depth. Each signal explains a larger portion of the signal near the pial surface.

Methods: Two volunteers (having given informed consent) were scanned on a Siemens 7 T whole-body scanner (Siemens Healthcare, Erlangen, Germany) using a custom-built 32-channel receive array and birdcage transmit coil. Resting-state fMRI data were acquired with 1.1 mm iso. single-shot gradient-echo blipped-CAIPI[2] Simultaneous Multi-Slice EPI: TR/TE/fa/matrix/BW=1.7 s/26 ms/65°/174×174/1512 Hz/pix, no partial Fourier, MultiBand=3 (VERSE 1.7), FOV/3 CAIPI shift, online LeakBlock slice-GRAPPA reconstruction,[3] 87 oblique-axial slices, *R*=4 inplane acceleration (GRAPPA) with 10° FLEET-ACS[4], 160 time-points per run and 5 runs per session. Automatic cortical surface reconstruction, and brain segmentation was performed using *FreeSurfer* based on a 750 μm iso. Multi-Echo MPRAGE acquired in each session, which automatically generated all volume- and surface-based ROIs described below. Registration to EPI data and cortical "laminar" analysis across 11 depths were performed as previously described.[5]

During each imaging session we simultaneously recorded subject breathing with a respiratory belt, cardiac signals with a piezoelectric sensor placed on the index finger, and expired CO_2 with a small, MR-compatible sidestream capnograph placed in the nostril. Following the procedure of a previous study,[6] first-order RETROICOR[7], respiration volume per unit time (RVT)[8], and heart-rate (HR) signals were generated using the *FSL* tool PNM.[9] End-tidal CO_2 ($ETCO_2$) was estimated as the envelope of the CO_2.[10] Per-subject time-lags between the RVT and HR were estimated by identifying two cross-correlation with the resting-state BOLD signal extracted from gray matter and visual cortex ROIs.[6] The relative $ETCO_2$ delay was removed by cross-correlating to the RVT signal. All physiological regressor signals were resampled to the timing of the acquisition accounting for slice timing. The full physiological noise model included the three dual-lagged regressors along with respiratory and cardiac RETROICOR, 3rd-order polynomial drift terms, and 6 motion parameters for a total of 19 regressors.

Seed-based functional connectivity analysis was performed using conventional preprocessing—including removal of nuisance regressors comprised of the average time-courses from the white matter and ventricular CSF as well as 6 motion parameters and linear detrending.[1] The Default Mode Network (DMN) was examined using a seed derived from the surface-ROI of the Posterior Cingulate.

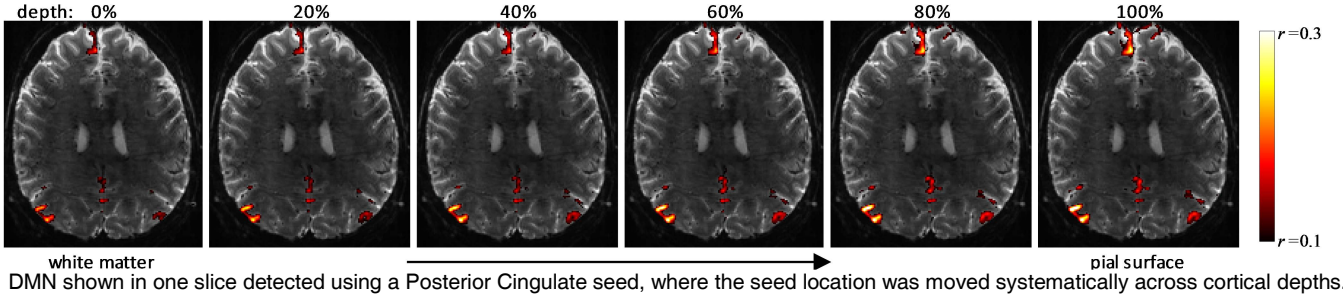

Fig. 2: DMN shown in one slice detected using a Posterior Cingulate seed, where the seed location was moved systematically across cortical depths. Modest changes in the DMN are seen, implying that the noise removal successfully removed noise components and the strong physiological signal contamination near the pial surface is not degrading the detection of the network.

Results: The optimal time lags for the RVT and HR signals varied somewhat across subjects (−9 s and +9 s; −15 s and +3 s) but were in agreement with previous studies.[6] The average voxel-level percentage variance explained by each set of regressors (derived from the adjusted R^2) is shown in Fig. 1 both for the gray matter ROI and as a function of cortical depth. All noise sources exhibit some depth dependence, with the drift term and the RETROICOR dominating. All levels are in good agreement with previous reports.[6] Results from the whole-brain depth-specific functional connectivity are shown in Fig. 2, where the PCC seed location is varied across depths. While the correlation levels are lowest when the seed is derived from the lowest depths, the distinct DMN pattern is clear from all seeds, which is in agreement with previous studies showing that the presence this global network does not merely reflect correlations of systemic physiological noise.

Discussion: Vascular density and vessel size vary systematically with cortical depth and therefore depth dependence of some physiological noise sources is expected. Furthermore, dynamic partial volume effects of fMRI voxels near the pial surface are likely to reflect cardiac signals due to tissue pulsation and CSF flow. These depth-dependent effects may cause a systematic detection bias by masking faint BOLD responses from particular depths, which, unless removed, could present a confound in laminar fMRI studies. The depth-specific seed-based functional connectivity results suggest that the physiological noise removal based on these physiological recordings was largely successful; however nuisance regressors derived local to the BOLD responses may ultimately be more effective.

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