Resolving resting state correlations in noncompliant subjects using short TE fMRI data

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Introduction: Correlated resting state networks may offer insight into diseases affecting diverse brain networks (e.g., mild cognitive impairment [1]). However, many patient groups may show poor compliance during traditional resting state fMRI scans, exhibiting severe motion artifacts that hinder our ability to identify the relevant signal correlations [2]. In this study, we incorporate cued head motion into a typical resting state paradigm to simulate amplified motion artifacts that may be present in clinical populations. We use a dual-echo sequence to simultaneously acquire data at very short (~3 ms) and BOLD-weighted (~35 ms) echo times (TEs). Short TE data have recently been shown by ourselves and others [3,4] to reflect multiple noise sources, including bulk head motion and associated spin history effects. By treating the short TE data as voxelwise noise regressors, we hypothesize that the BOLD-weighted data can be "cleaned up" such that we can identify resting state networks in datasets highly confounded by motion.

Methods: Ten subjects were scanned using a 3 T GE HDx scanner (Milwaukee, WI, USA). Data were acquired using a dual-echo gradient echo spiral readout sequence (TE1/TE2/TR=3.3/35/2000 ms; 64 spiral; FOV=22 cm; 18 slices; resolution=3.4 x 3.4 x 5.0 mm^3). A 5 min 40 sec resting scan with eyes open (**rest**) was performed, followed by a second scan of equal duration with additional cued head motion (**rest+motion**). A yellow fixation cross was displayed in the center of the screen. During the **rest+motion** scan, at ~10 s intervals, the cross briefly turned red, prompting the subject to nod their head (in any direction).

Respiratory bellows, a pulse oximeter, and gas analyzers connected to a nasal cannula were used to obtain physiological data during all scans. End-tidal O_2, end-tidal CO_2, RVT [5], and cardiac rate [6] data were extracted and interpolated to each fMRI acqusition timepoint. Eight RETROICOR [7] regressors were created from the respiratory and pulse data. The first three volumes of both datasets were discarded. Motion correction (MCFLIRT, FSL) was performed on the BOLD-weighted TE2 datasets, and the resulting transformations were applied to both the TE1 and TE2 data to achieve consistent registration. Brain extraction (BET, FSL) and quadratic detrending (AFNI, NIH, Bethesda, MD, USA) were also applied.

Traditional preprocessing methods were performed: the results of motion correction (3 translation and 3 rotation parameters), RETROICOR regressors reflecting the cardiac and respiratory phase, and established physiological regressors ($P_{ET}CO_2$, $P_{ET}O_2$, RVT, and cardiac rate) were regressed from the TE2 data. An extended preprocessing was also performed, in which the voxelwise short TE timeseries were also regressed from the BOLD-weighted TE2 data. We focused on the highly studied default mode network [8] using seed correlation methods: a spherical seed region in the posterior cingulate/precuneus was defined in MNI space (12 mm diameter, centered at [-4,-49,40]) and registered to each dataset (FLIRT, FSL). The voxel timeseries within this mask were averaged, and the correlation coefficients between this seed timeseries and individual voxel timeseries throughout the brain were calculated. Correlation coefficients were thresholded at 0.35 ($p<5e-6$, uncorrected).

Results: In the **rest+motion** data, which simulate a non-compliant patient acquisition, the traditionally preprocessed BOLD fMRI data were dominated by the bulk head motion artifacts related to the cued head nodding. The short TE data correlation maps exhibited similar patterns; large numbers of voxels, extending smoothly across large spatial areas, regardless of underlying tissue contrast, exhibited signal changes that were strongly correlated/anticorrelated with the seed region. After the extended preprocessing and removal of the short TE signal fluctuations from the BOLD data, the seed correlation maps were reduced in size, localized to gray matter, and distributed in patterns similar to the default mode network map observed in **rest** data. Fig. 1 illustrates this phenomenon in 1 subject. For comparison, the corresponding maps from the **rest** condition are also displayed. To identify possible negative consequences of the extended preprocessing technique in compliant subjects, the correlation maps of the **rest** data using the traditional and extended preprocessing methods are directly compared (Fig. 2, three subjects).

Discussion: Our results confirm that a short TE echo is a useful tool in correcting fMRI data of noncompliant patients. By greatly reducing the dominant motion-related correlations, the "default mode" network patterns were salvaged, at least partially, in the **rest+motion** data. The **rest+motion** condition is not a true *resting state* (attending to a fixation cross, anticipating the cues, and head nodding), and, thus, an imperfect simulation of a non-compliant subject. This may contribute to the incompleteness of the recovered default mode correlation maps. There may be blood volume-related signal changes in the short TE data that are highly correlated with the BOLD resting state fluctuations due to neurovascular coupling, causing the short TE data regressors to remove some of the desired signal variance. There may also be BOLD contamination in our short TE data, particularly in the higher spatial frequencies that are acquired later in the spiral readout.

However, the overlap maps of Fig. 2 suggest that the correlation maps in **rest** data are not greatly affected by the additional short TE noise regressors, and the short TE data show correlation maps (Fig. 1) that are not distributed in the default mode network patterns. This suggests that the use of short TE data for correcting gross head motion artifacts, whilst beneficial in non-compliant subjects, doesn't dramatically reduce the significance of seed correlation maps in compliant subjects.

Conclusion: Short TE fMRI data, acquired simultaneously with BOLD-weighted fMRI data, can be used to correct gross head motion artifacts in noncompliant subjects and resolve resting state network seed correlation maps.

References: [1] Rombouts HBM (2005) 26; [2] van Dijk NeuroImage (2012) 1; [3] ISMRM 2012 abstract submission #1930; [4] Buur NMR Biomed (2009) 22; [5] Birn Neuroimage (2006) 31; [6] Shmueli NeuroImage (2007) 38; [7] Glover (2000) MRM 44; [8] Raichle PNAS (2001) 98.

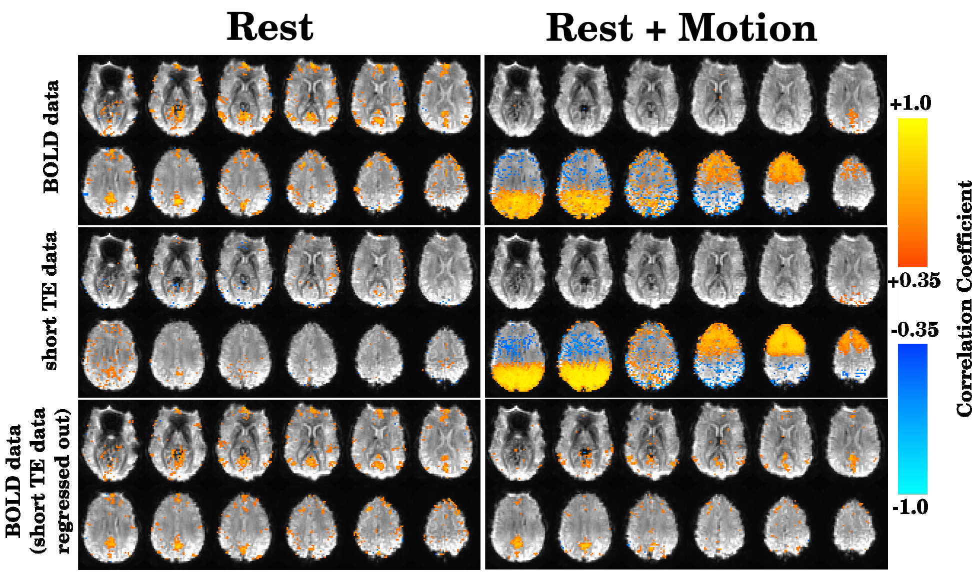

Fig 1. Examples of default mode network seed correlation maps for one subject. In the **rest** dataset, the use of the short TE data as voxelwise regressors in preprocessing did not visibly affect the results. In **rest+motion** data, the addition of short TE data regressors resolved correlation networks not visible after traditional preprocessing.

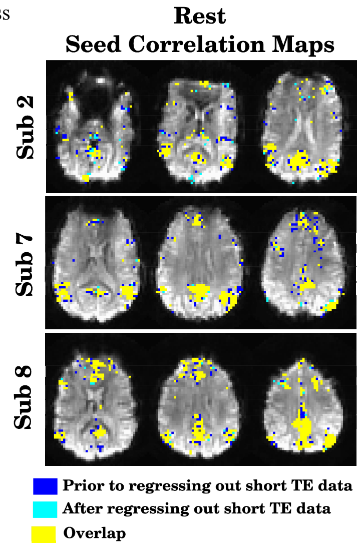

Figure 2. Correlation maps of the BOLD-weighted **rest** data ($p<5e-6$, uncorrected). Results of traditional preprocessing (blue) and extended preprocessing (cyan) following removal of short TE data regressors are compared, and the overlap (yellow) indicates good agreement.