Functional Connectivity Analysis: Performance Comparison of Gradient and Spin Echo EPI Simultaneously Acquired

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Target Audience: Researchers interested in functional connectivity of brain regions affected by signal loss. This work could be of particular interest for the field of functional connectivity in neuropsychiatric research.

Introduction: An increasing number of functional magnetic resonance imaging (fMRI) studies focus on functional connectivity (FC) patterns in neuropsychiatric conditions. The basis of fMRI-based FC analysis is mostly the comparison of BOLD signal time series of voxels or brain regions that aggregate to functional networks. However, one major limitation of fMRI is signal dropout in standard T2*-weighted gradient echo planar imaging (GRE-EPI), especially pronounced in brain regions showing strong susceptibility variations, e .g. regions close to the aired sinuses[1-3]. For example, signals originating from the medial prefrontal cortex (mPFC, e.g. subgenual anterior cingulate, orbitofrontal cortex) that play an important role in emotion processing and stress regulation[4] are frequently impaired or completely lost. Considering that reduced signal quality (e.g. smaller signal-to-noise ratio) in the primary seed region will limit the identification of functionally correlated cortical and subcortical areas, we tested an alternative, mainly T2-weighted signal acquisition method: spin-echo EPI (SE-EPI). Recent studies have suggested that the use of SE based fMRI locally enhances signal quality and improves regional functional specificity in these critical brain regions[1-4].

Purpose: The aim of this work is to evaluate if SE-EPI is more suitable to retrieve reliable functional connectivity patterns in the mentioned critical brain areas. The two principal hypotheses were that (1) in contrast to GRE-EPI, less signal dropout is observed in SE-EPI in ventro-mPFC and (2) that these signals carry basal features of neuronal (resting-state) functional connectivity. For this purpose, a hybrid EPI (HEPI) pulse sequence was developed to allow sampling of both the GRE-EPI and the SE-EPI simultaneously in a single shot with close to optimal acquisition parameters for both contrasts.

Methods: Sixteen healthy subjects (13 women), age 25.6 ± 2.8 years (mean ± SD) were enrolled with approval of a local Ethics Committee. For each subject, 10 minutes long resting-state data was acquired using HEPI with a 3T scanner and a 12 channels coil (GE Healthcare, Waukesha, WI, USA). For each slice excitation, this sequence first collects a GRE-EPI readout (TE1=27 ms), followed by a refocusing pulse and a SE-EPI collection (TE2=75 ms). A common problem with simultaneous GRE and SE sequence is the slice profile mismatch between these two echoes[5]. To avoid that problem, slice profile matched RF pulses based on Shinnar-Le Roux were used[6]. Note that both GRE-EPI and SE-EPI are readouts of the same slice excitation pulse, thus providing simultaneous data for the 'classical' GRE-EPI and the subsequent SE-EPI. Common acquisition parameters were: 64x64 acquisition matrix, slice thickness 3 mm with 1 mm interslice gap, interleaved slice order, TR 2.5s, acceleration factor 2, bandwidth ± 250 kHz.

Analysis: Image analysis was performed using SPM8 and FSL. The pre-processing included three different pipelines using different approaches to nuisance removal through linear regression. All pipelines included slice-timing correction, realignment, and normalisation to MNI space. Pipeline 1 used motion and motion derivatives as regressors only, pipeline 2 used motion (like pipeline 1) and CompCor[7] regressors (extracted with 4 principal components from white matter and cerebrospinal fluid, as well as 4 PCA regressors derived from the compartment with highest temporal standard deviation (upper 2%)), pipeline 3 used motion regression (like pipeline 1), followed by bandpass-filtered using a zero phase Butterworth IIR filter (order 5 and bandpass [0.005-0.1] Hz), after which CompCor regressors were computed and regressed out. Using the AAL-atlas[8], for each pre-processing pipelines we extracted the time-courses from 90 predefined cortical and sub-cortical regions from the residual images. In addition, time-courses from 18 regions in the cerebellum were extracted. We then calculated the cross-correlation matrix between all possible pairs of regions (resulting in a 108x108 matrix, which was subsequently Fisher z transformed). To test for residual influence of global signals, we further calculated a partial correlation against the time course of the whole brain mask (data not shown). Finally, for each of the three pipelines, a posterior cingulate cortex (PCC) seed-based analysis was performed. The seed was derived from an analysis of the default mode network (DMN) in an independent data set[9].

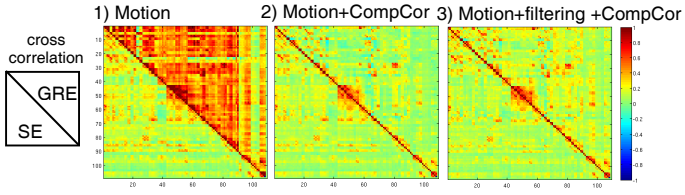

Fig. 1: Correlation analysis using the time courses of the extracted AAL and cerebellar regions for the three pipelines (mean of the individual Fisher z transformed matrix). Color coding is set to a maximum of ±1.

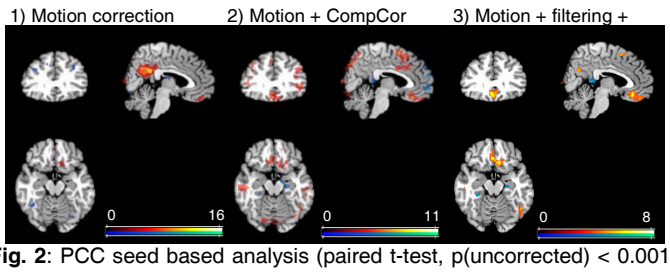

Fig. 2: PCC seed based analysis (paired t-test, p(uncorrected) < 0.001, cluster extent ≥ 20 voxels). Hot colors: SE-EPI>GRE-EPI; cold colors: GRE-EPI>SE-EPI.

Results and discussion: Fig. 1 summarizes the whole-brain cross correlation analysis. For pipeline 1, GRE-EPI showed much higher correlation values throughout the brain, which are drastically reduced after CompCor correction (2 and 3), therefore likely reflecting unspecific global signal contributions of non-neural origin. This is in line with significantly stronger correlation of the mean time courses of GM with WM or CSF in GRE-EPI and with reduced correlation values after partial correlation controlled for the whole brain signal (data not shown). While for pipeline 2, SE-EPI outperformed GRE-SPI in paired t-tests especially for functional coupling including prefrontal brain regions, GRE-EPI showed stronger functional connections between bilateral homologous regions. Restriction to the low frequency part of the signal fluctuations (pipeline 3) reduced differences between the two contrasts. Fig. 2 shows the difference between DMN extent using the PCC seed analysis. Pipeline 1 resulted in stronger autocorrelation of the PCC seed and stronger functional connectivity to the vmPFC in SE-EPI. Increased coupling to this region was also observed for pipeline 2, along with stronger coupling in the SE-EPI in regions belonging to the PCC anticorrelated network. This can be explained by stronger anticorrelations in GRE-EPI in regions belonging to the dorsal and ventral attention system, and suggests a stronger shift[10] to negative correlations after CompCor correction in the GRE-EPI data. For pipeline 3, SE-EPI again showed stronger functional coupling between PCC and vmPFC, while stronger anticorrelations to the attention system(s) are still visible for GRE-EPI, but less pronounced. These results were also confirmed by additional analysis based on the amplitudes of the low frequency fluctuations (data not shown).

Conclusion: In summary, our data suggest that as compared with the standard GRE-EPI, SE-EPI does not only allow to recover meaningful BOLD signal fluctuations in regions typically obscured by susceptibility artefacts, but also reveals functional connectivity values of similar strength in brain regions showing locally homogeneous B0 fields. SE-EPI further appears to be less sensitive to unspecific global signal fluctuations, thus providing cleaner data of potentially neural activity than GRE-EPI. These findings make SE-EPI an interesting approach in functional MRI, especially when signal fluctuations in critical brain areas are of interest, rendering SE-EPI a promising tool for research into mood and affective disorders. Future analyses of the data presented here will include comparison of GRE-EPI and SE-EPI using independent component analysis.

References: 1. Deichmann et al., Neuroimage 2003. 2. Schwarzbauer et al., Neuroimage 2010. 3. Weiskopf et al., MAGMA, 2007. 4. Price and Drevets, Neuropsychopharmacology, 2010. 5. Schmiedeskamp et al., MRM, 2012. 6. Fernandez et al., ESMRMB, 2012. 7. Behzadi et al., Neuroimage, 2007. 8. Tzourio-Mazoyer et al., Neuroimage, 2002. 9. Sämann et al. Cereb Cortex, 2011. 10. Hayasaka S. Front Hum Neurosci. 2013.