Efficient correction for artificial signal fluctuations in resting-state fMRI-data

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Introduction

Functional magnetic resonance imaging (fMRI) studies of the human brain have suggested that correlations of spontaneous low frequency fluctuations in the BOLD signal acquired without explicit task performance relate to known anatomical systems and reflect functional connectivity of the brain (for a review see [1]). Neuropsychiatric disorders are often accompanied by changes in inter-regional connection strength, and connectivity analysis may therefore allow for early detection of pathologies. Spontaneous low frequency fluctuations are, however, mixed with various other signals originating from residual motion artifacts, respiration and cardiac action. Voxel-based correlation in resting-state data is very sensitive to such non-neural signal changes and, therefore, functional data sets require adequate preprocessing to optimize connectivity mapping results. Extending approaches introduced recently [2] we use multiple regression analysis on data from 40 healthy subjects to remove connectivity artifacts due to changes in global, ventricle and white matter signal, as well as residual motion.

Materials and Methods

Forty healthy adults (age range: 21-40a) underwent a 360 seconds resting-state scan on a 3 Tesla Medspec S300 system (Bruker Biospin, Germany) using single-shot gradient-recalled EPI with the following parameters: 14 axial slices aligned to ac-pc, MA = 64 x 96, TE = 40 ms, TR = 1000 ms, slice thickness = 6 mm, slice gap = 1 mm, FOV = 230 x 190 mm.

Standard preprocessing was performed in SPM (www.fil.ion.ucl.ac.uk/spm), including correction for slice-timing differences and motion, normalization to MNI space and spatial smoothing with an isotropic Gaussian kernel of 9mm FWHM. Data sets were then low-pass filtered using IDL (RSI, USA) applying a 12-term FIR filter ($0.007 < f < 0.08$ Hz).

Each voxel underwent multiple linear regression analysis against: (1) 6 rigid-body realignment parameters, (2) global signal (averaged over the whole brain), (3) ventricular signals (from 5 ROIs in the lateral ventricles), and (4) white matter signals (from 4 ROIs above the lateral ventricles). Temporal derivatives of non-motion regressors were also included to account for small temporal shifts. Thus, a total of 26 regressors were used in the regression analysis. Regions for white matter and ventricular signals were defined over four regions in the white matter (left, right hemisphere, each in both anterior and posterior parts of the brain), 5 regions in the lateral ventricles (left and right dorsal parts, left and right posterior horn, ventral part of the anterior horns).
Despite the normalization within SPM, the anatomy differs from subjects to subject. To ensure regressor signals not containing signals from grey matter, predefined regions were automatically adapted.

Correlation: Correlation maps were generated by computing the cross-correlation coefficient *r* between the BOLD time course from a seed voxel in the right primary motor cortex rM1 and the time course from all other voxels of the brain. Correlation maps were converted to *z* values by Fisher's *r*-to-*z* transformation using $z = 0.5\ln(1+r) - 0.5\ln(1-r)$ [4] to enable statistical comparison across regions.

Quality control: Artifact compensation outcome was quantified based on correlation between the right primary motor cortex and: (a) left primary motor cortex, (b) supplementary motor area (SMA), (c) medial prefrontal areas, (d) visual areas, (e) ventricular system, and (f) white matter, respectively. Since the maximum voxel of the correlation varies spatially, the correlation with the left M1 is computed by averaging over a 3x3x3 voxel volume around the mirrored seed voxel. Visual areas are not part of the motor resting-state network and were thus included as reference regions. Ventricles and white matter ROIs are defined with the same method used for defining the regressors.

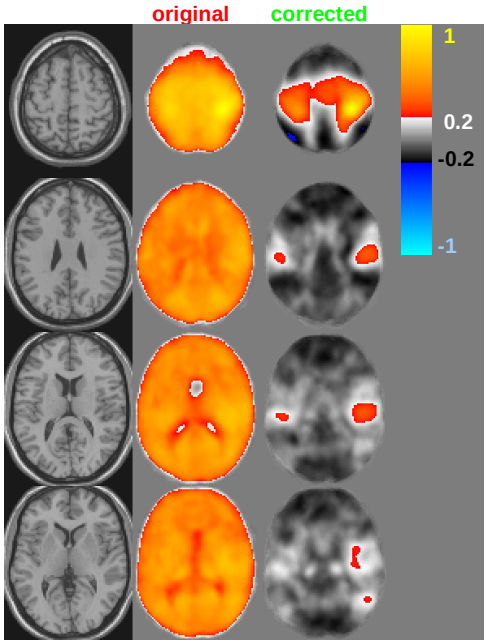

Fig. 1: Correlation maps of RMC with the complete brain averaged over 40 subjects
Original data show correlations all over the brain. After applying the correction scheme only correlations with functionally related areas remain.

Results

Figure 1 shows the mean correlation maps across all 40 subjects before and after correction. Data before multiple-regression exhibit high correlation coefficients to right M1 seed voxel throughout the brain. Also, correlations to the ventricular system and to white matter are alarmingly high. Before correction, statistically significant correlation coefficients to all regions tested were found (fig. 2, left). Applying the proposed correction scheme resulted in reduced correlation coefficients between right M1 and all ROIs (fig. 2, right). However, correlations between right M1 and SMA were still highly significant ($p < 10^{-18}$ and $p < 10^{-5}$, respectively) while all other correlations were no longer significant.

Discussion

Removal of white matter and ventricle signal, global signal, and realignment parameter time courses increased the specificity of resting-state analysis by reducing correlations to regions not part of the motor resting-state system. Erroneous connectivities between M1 and visual areas were successfully removed, while left-right M1 connectivity and M1-SMA connectivity was still highly significant after correction. It seems therefore highly advisable to apply artifact correction schemes like the proposed methodology to all resting-state connectivity studies. This is of particular importance for studies targeting the effects of pharmacological stimuli on functional connectivity.

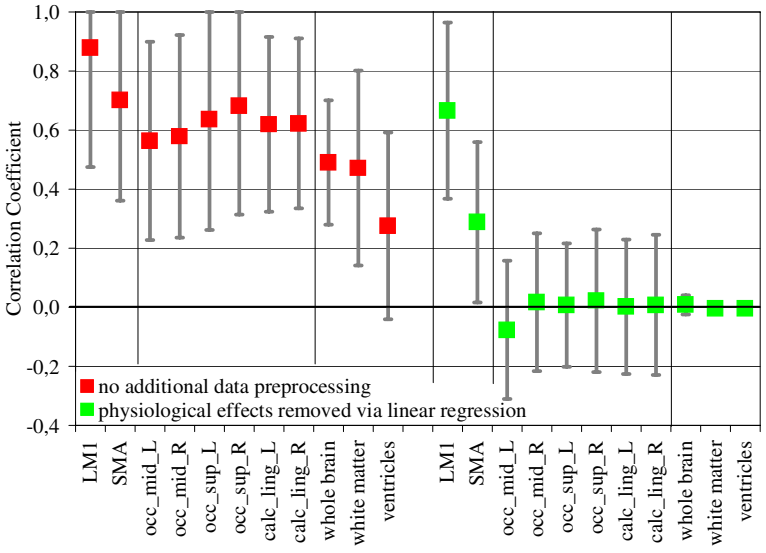

Fig. 2: Correlation with control-regions
Correlations with functionally related regions (LMC, SMA) endure the removal procedure with reduced scale, but with increased specificity. Correlations with non-functional related regions are completely suppressed and standard deviations decrease after regression.

References

[1] Fox MD & Raichle ME. *Nature Reviews Neuroscience* 8, 700–711, 2007
[2] Fox MD et al. *Proc Natl Acad Sci USA* 102: 9673–9678, 2005
[3] Biswal B et al. *Magn Reson Med* 34: 537–541, 1995
[4] Fisher RA, *Statistical Methods for Research Workers*, 1925