Extended Analysis of Functional Connectivity Using Low Frequency BOLD Fluctuations (LFBF)

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Introduction: In functionally related regions of the brain, synchronised fluctuations of cerebral blood flow have been observed with BOLD MRI as well as with other techniques. Experimental studies suggest that these fluctuations are likely to reflect oscillations of neuronal activity [1, 1a]. Current evaluation strategies in LFBF analysis focus on primary functional networks (e.g. motor, visual, or auditory) and calculate cross-correlation figures based on the condition of synchrony (fcMRI, functional connectivity MRI) [1b, 3, 5]. We attempted to extend the fcMRI analysis into the time domain by means of estimating the time-dependent cross-correlation function. Preliminary studies in 5 normal controls (including a repetitive study) reveal the impact of synchrony as well as the additional information when considering the time dependence of the cross-correlation function.

Materials and Methods: For the resting state fcMR study, BOLD-weighted timeseries data (1024 measurements) were acquired on a 1.5T system (Siemens Sonata, Erlangen/Germany) using an EPI-FID sequence; TE = 50 ms, TR = 250 ms, flip angle = 30°, slice thickness = 5 mm (gap 1 mm), matrix size = 64x64, field-of-view = 240x240 mm^2, 3 slices were acquired prescribing slices containing Heschl´s gyrus (auditory system) and the visual cortex (V1, V5). Corresponding T1-weighted slices and high resolution anatomical 3D T1-weighted images were acquired for anatomical reference.

FcMRI scans were acquired in 6 normal controls; in one subject, repeated scans were done six times within 60 min. Careful positioning using orthogonal localizers and midsagittal alignment at the inferior borders of the corpus callosum assured reproducible slice positioning which was monitored on T1w before and after each scan.
For data evaluation, T2*w images were Hamming filtered [2]; furthermore, images from resting state were digitally low-pass filtered (frequency 0.096 Hz) to remove temporal fluctuations arising from cardiac and respiratory-related physiological noise [3].

For cross-correlation (cc) estimation in resting state timeseries, reference ROIs (5x5 pixels) were positioned in the right visual cortex (V1) (slice #1) and in left Heschl´s gyrus (slice #3). Connectivity maps were calculated showing the time-dependent cross-correlation function between each single pixel and the reference ROI [4].

Results: Connectivity maps with respect to sychrony showed robust and reproducible results in regard to the anatomic localisation and number of activated pixels when probing the „auditory“ or „visual network“. Extended analysis of the time-dependent cc-function revealed a high degree of similarity with regard to the time-dependence of the cc-function in areas showing highly synchronous correlations. Furthermore, additional anatomical regions showed high correlation with respect to the reference signal timecourse if a certain time delay was taken into account. The correlation values in those areas are within the range that is considered as relevant/significant in the synchronous evaluation.

Discussion and Conclusion: In an attempt to evaluate the time dependence of LFBF correlations it was demonstrated that the cross-correlation function might reveal meaningful information with respect to the timing between certain anatomic and functional brain areas. As the temporal evolution of the correlation function mirrors characteristics of contributing frequency components and their phase relation among each other, one might speculate that the degree of similarity patterns as well as the location of maxima and minima of the cc-function characterize the relationship of the neuronal network in more detail.

As LFBF may be influenced by the underlying basal neuronal activity, one would assume that different brain states might influence the reproducibility of fcMRI, especially in „resting state“. Acquiring LFBF in continuously activated state (e.g. finger tapping, verbal fluency) might focus on selected physiologic networks. Furthermore, the mathematical framework of FFT, lowpass filtering and cross-correlation functions assumes a highly periodic behaviour which may not be fulfilled.

References: [1] Leopold, D., Society for Neuroscience 32nd Annual Meeting, abstract #325.7, 2002. [1a] Leopold, D. et al, Cereb Cortex 13 (4), 422, 2003. [1b] Biswal B, et al, Magn Reson Med 34, 537, 1995. [2] Lowe, M.J. et al., Magn Res Med 37, 723, 1997. [3] Lowe, M.J. et al. NeuroImage 7, 119, 1998. [4] Lowe, M.J., Proc Intl Soc Magn Reson Med 8, 799, 2000. [5] Hirsch J. et al, Proc Intl Soc Magn Reson Med 12, 1072, 2004.

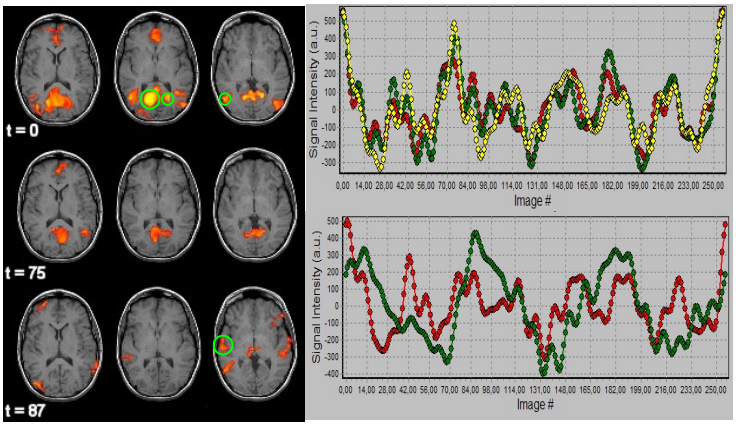

Fig. 1: Color-coded cross-correlation (cc > 0.4) maps; reference region was placed in right occipital cortex (V1) of 2nd slice. FcMRI maps (t = 0, synchrony) show high correlation within ipsi- and contralateral visual cortex (V1) as well as to visual areas (V5).
Fig. 2 top: CC-functions from highly correlated areas (t = 0) show high similarity with respect to the extrema's location and pattern (red = reference ROI in right occ visual cortex, green & yellow = target ROIs on contralateral side and right visual field V5.
Fig. 2 bottom: CC-functions with respect to the same reference ROI (right occ visual cortex, 2nd slice); target ROIs were placed into right visual area V5 (3rd slice, correlated at t=0, red curve), and right Heschl gyrus (3rd slice, high correlation at t=87 sec, green curve).