Individual-subject mapping of functional networks from sparse spontaneous BOLD events

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Target audience: Scientists who are interested in investigating the dynamics of functional networks in spontaneous brain activity with BOLD fMRI.

Purpose: In recent years, there is increasing interest in the application of resting state fMRI to investigate dynamics of functional networks in health and disease. While most analysis approaches assume temporal stationarity of functional networks, it is becoming more evident that spontaneous activity in functional networks also comprise more dynamic and transient brain states [1-5], which could last few minutes or be as short as few seconds as in the time scale of BOLD events [6]. Current efforts aim at characterizing such transient brain states, e.g. in terms of spatial similarity or switching rates across groups of individuals [4], in order to improve our understanding of the dynamic processes that constitute them. However, grouping across individuals inherently excludes the identification of brain states relating to an individual's specific cognitive processes as well as those that reflect more intrinsic neuronal fluctuations. Here, we show that functional networks can be robustly mapped in individual subjects at rest based on sparse and brief spontaneous BOLD events using the sparse paradigm free mapping (PFM) technique [7].

Methods: Acquisition: 15 subjects were scanned in a 7T Philips Achieva MR scanner (Best, Netherlands) using a volume transmit and a 32-channel receive head coil (Nova Medical, MA, USA). fMRI data was acquired using a 3D-PRESTO (600 scans, TR/TE=800/30 ms, flip angle=8º, voxel size=2.4mm isotropic, 34 oblique slices including regions of the superior frontal and occipital cortices) while subjects were asked to remain at rest and visually fixate on a cross. Anatomical T1-w (3D MPRAGE, TR/TE=7/3ms, flip=8º, 0.5mm isotropic, 238 slices) and T2*-w (segmented 3D EPI, EPI factor=13, TR/TE=90/27ms, flip=20º, 0.5mm isotropic, 300 slices) images were also acquired per subject. Heart rate (pulse oximeter) and respiration (pneumatic belt) were recorded in all sessions. **Analysis:** Analyses were performed using AFNI (NIMH/NIH) and in-house Matlab and IDL scripts. Functional datasets were initially corrected for head motion, low frequency drifts and respiratory and cardiac related fluctuations with the RETROICOR [8], CR [9] and RVT [10] procedures, and spatially smoothed with a 3mm FWHM Gaussian kernel. Datasets were then analyzed with Paradigm Free Mapping (PFM) using the new 3dPFM AFNI program. PFM carries out a voxel-wise deconvolution of the haemodynamic response for each time point in the fMRI time series using a regularized L1-norm estimator, enabling the detection of BOLD events in each voxel without prior information of their timing. Here, we used the Dantzig Selector along with the Bayesian Information Criterion [7]. Two activation maps were then computed for each subject to explore the PFM results: a 'PFM F-map' showing the F-statistic of the detected events (converted to Z-values), and a '%PFM-events' map showing the percentage of time points where the deconvolved time series is non zero. In addition, spontaneous events were grouped together into functional network maps by computing seed-voxel correlation maps from the PFM deconvolved datasets (seeds: posterior cingulate cortex, intraparietal sulcus, precentral gyrus, cuneus, anterior cingulate cortex). Additionally, k-means clustering of the deconvolved datasets (uncentered correlation distance, k=1,...,20, 50 random initializations) was also used as a more automatic technique to group voxels with similar patterns of spontaneous BOLD events.

Results: Figure 1 shows the results for an exemplary subject. Similar results were obtained for all subjects. Spontaneous BOLD events detected with PFM were precisely circumscribed to the majority of grey matter (GM) voxels (Fig. 1A: PFM-F maps ($q<0.05$, FDR correction); 1B: %PFM-events maps). Notably, the %PFM-events maps show that the deconvolved time series comprised a small number of spontaneous events per voxel (range across subjects: mean 0.83-5.39%, maximum 16%-17.16%), which also varied across brain regions; yet the resulting seed-voxel correlation maps ($p<10^{-6}$ uncorrected) exhibited high resemblance to typical functional connectivity maps of the default mode network (Fig. 1D), dorsolateral attention (Fig. 1E), visual (Fig. 1F), motor (Fig. 1G) and executive networks (Fig. 1H). Similarly, Fig. 1C illustrates that single-subject brain parcellation in distinct functional networks can be achieved by means of k-means clustering (shown for k=5), using the deconvolved time series in which information about spontaneuous brain activity is sparse and mostly zero.

Discussion: Our results demonstrate that few transient BOLD events convey sufficient information to reveal synchronous spontaneous activity in functional brain networks, extending our previous results with less spatial coverage and sample size [6]. Spontaneous brain activity was found widespread across GM, resembling previous observations in long single-subject task-based fMRI data [12]. Our results clearly benefited from the high BOLD sensitivity available at 7T and fast imaging with 3D PRESTO, thereby allowing consistent mapping of functional networks from few spontaneous BOLD events in individual subjects. Furthermore, the amplitude and timing of the detected single events can be analyzed to quantitatively examine time-varying changes in spontaneous brain connectivity within and between functional networks at short time scales. Importantly, assuming a physiological haemodynamic model for the deconvolution overcomes that large artefactual changes in the amplitude of the signal could be identified as BOLD events. Since the method is data-adaptive and based on statistical selection criteria (e.g. BIC), the number and/or the amplitude of the detected events can vary according to the temporal characteristics of the signal, thus obviating the need for setting ad-hoc thresholds in the amplitude of the signal or the number of significant events that must be identified, either in specific ROIs or across the entire brain. All in all, our results demonstrate that the proposed methodology would enable a finer evaluation of between-subject differences in functional connectivity patterns measured with BOLD fMRI and allow the characterization of brain states reflecting cognitive processes, intrinsic neuronal fluctuations, and potentially the identification of signatures of disorder.

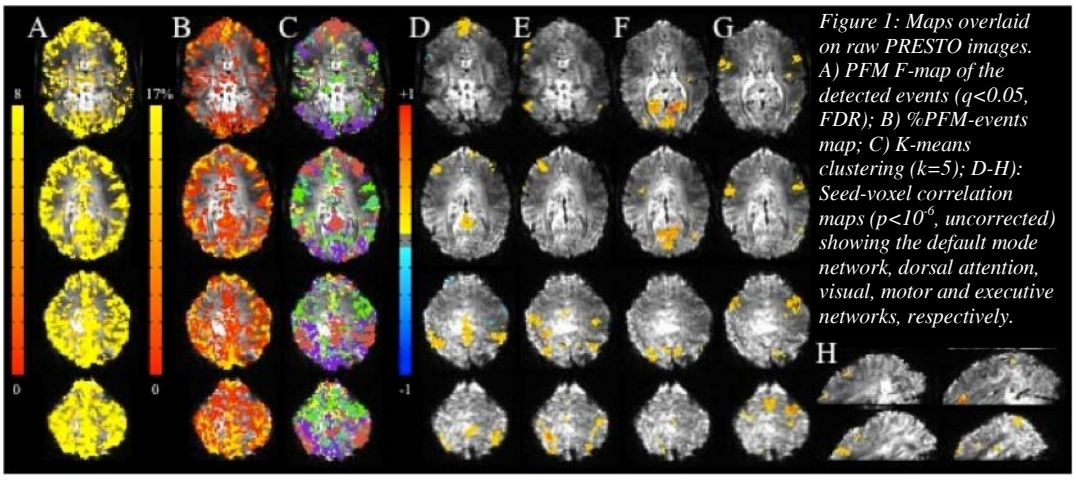

Figure 1: Maps overlaid on raw PRESTO images. A) PFM F-map of the detected events ($q<0.05$, FDR); B) %PFM-events map; C) K-means clustering ($k=5$); D-H): Seed-voxel correlation maps ($p<10^{-6}$, uncorrected) showing the default mode network, dorsal attention, visual, motor and executive networks, respectively.

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