Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2010 ; 2010: 4274–4277. doi:10.1109/IEMBS.2010.5626180.

Ultrafast method for mapping local functional connectivity hubs in the human brain

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Abstract

Brain networks with energy-efficient hubs might support the high cognitive performance of humans and a better understanding of their organization is of relevance not only for studying normal brain development and plasticity but also neuropsychiatric disorders. Here we propose an ultra-fast method to map the distribution of the functional connectivity density (FCD) in the human brain. The method was tested in 972 subjects from a large repository of magnetic resonance imaging (MRI) time series collected in resting conditions. Consistently across research sites, a region located in the ventral precuneus was the area with the highest FCD, which suggest that this is a prominent functional hub in the brain. In addition regions located in the paracentral lobule, cuneus, inferior parietal, and posterior cingulate cortices had localized high FCD, suggesting that these regions also include prominent functional connectivity hubs.

I. INTRODUCTION

Energy-efficient brain networks may have few nodes with dense local clustering (hubs) and numerous nodes with an average low number of connections [1–7] and some neuropsychiatric diseases have been linked to abnormalities in the configuration of these hubs [8, 9]. However, the investigation of hubs in the brain has been hindered by the cumbersome computational requirements of comprehensive analytical methods.

The functional connectivity of the brain in resting conditions can be studied using magnetic resonance imaging (MRI) time series [10]. The most popular technique uses correlation analysis of blood oxygenation level dependent (BOLD) signals for the identification of brain regions functionally connected to the seed regions [11]. Cluster analyses are also used to evaluate the degree of functional connectivity among multiple seed regions [12]. However, these methods rely strongly on a priori selection of specific seed regions and are also computationally demanding. For these limitations previous studies assessing the topological organization of the human brain restricted their analysis to $\sim 10^2$ seed regions [5, 13]. More recently data-driven approaches that are based on graph theory were proposed to assess the functional connectivity of the human brain [14]. However, these approaches are extremely demanding of computational power. For instance, taking into account that the human brain contains about 5×10^4 voxels (3-mm isotropic), and that a standard Windows XP platform (3.0GHz Dual core Intel processor) requires 20- μ sec to compute the Pearson correlation coefficient of two individual voxels time courses of 200 time points, the full computation of the correlation matrix requires more than 13 hours/subject. This time constraint is a serious limitation when evaluating data from numerous subjects (as in this study).

Here we propose an alternative voxel-wise data-driven method, Functional Connectivity Density Mapping (FCDM), to overcome the methodological limitations for the identification of hubs in the human brain. This fast technique allows calculation of individual functional connectivity maps with higher spatial resolution (3-mm isotropic or higher) to take full advantage of the native resolution of the functional MRI datasets. We took advantage of the highly clustered organization of the brain [14], to speed up the computation of the number of functional connections (i.e. edges in graph theory) by restricting the temporal correlation analysis to the local functional connectivity cluster. We hypothesized that the parietal cortex would contain prominent functional connectivity hubs that will be highly reproducible across subjects and research sites. We also hypothesized that the probability distribution of the FCD would have a power scaling with the number of functional connections per node, which is the main characteristic of the “scale-free” networks [6], rather than a Poisson distribution, the landmark of random [15] and “small-world” networks [2].

II. METHODS

Standard functional MRI and FCDM share similar data processing steps. For multi-subject studies, FCDM required two consecutive preprocessing steps: imaging realignment was required in order to minimize spurious motion-related effects [16], and spatial normalization was required to account for differences in brain size, shape, and orientation across subjects. We used statistical parametric mapping package SPM2 (Wellcome Department of Cognitive Neurology, London UK) for these purposes. Because of magnetic susceptibility differences at air/tissue interfaces in the head, the MRI signal is sensitive to head motion [17] and can be correlated with motion even after image realignment. Since the spontaneous signal fluctuations in the MRI signal are very small ($< 0.5\%$) it is essential to minimize motion related fluctuations in the MRI signal, a step that we will refer as motion filtering. Specifically, motion filtering involved multilinear regression of the time-varying MRI signals, $y_n = f(t_n)$, using the 6 realignment parameters ($\mathbf{x}_n$: 3 translations and 3 rotations): $y_n = \mathbf{a}\mathbf{x}_n + y_n^0$, where the fitting parameters a_i ($1 < i < 6$) are the amplitudes of the signal drift as a function of each motion component, and y_n^0 is the motion-filtered imaging time series. The removal of motion correlated fluctuations from the imaging time series, $y_n^0 = y_n - \mathbf{a}\mathbf{x}_n$, occurred for all volume elements (voxels) of the image and partially removed physiologic noise of cardiac and respiratory origin. A similar approach (*physiologic noise filtering*) could be used to further remove physiologic noise, which is one of the most important confounds of functional connectivity datasets [18], if respiratory and/or pulse rate data (ϕ_n) are collected simultaneously with the resting-state imaging time series ($y_n^{00} = y_n^0 - \mathbf{b}\phi_n$). We were not able to perform physiologic noise filtering because physiologic data was not available in this study. As in standard analyses of functional connectivity datasets, 0.01–0.10Hz band-pass temporal filtering was used to remove magnetic field drifts of the scanner [19] and physiologic noise of high frequency components [20].

Two parameters were used to calculate the FCD: the correlation threshold, T_C , was used to determine significant correlations between voxels and the MRI signal to noise ratio threshold, T_{SNR} , was used to evaluate which voxels of the image will be subject to correlation analyses. The number of functional connections between a given voxel and other voxels was computed through correlation using these threshold parameters. The number of significant functional connections per voxel in the local cluster, k , was computed using a three-dimensional searching algorithm developed in IDL (ITT Visual Information Solutions, Boulder, CO) that detects the boundaries of the voxel's cluster using T_C and T_{SNR} . Thus, a FCDM map reflecting k was computed and saved in Analyze format in hard drive for each subject. As in standard functional MRI studies, spatial smoothing (8-mm) was necessary to minimize the differences in the functional anatomy of the brain across subjects.

To evaluate the method we used data of 972 healthy subjects from the available datasets of the image repository “1000 Functional Connectomes” that met the imaging acquisition criteria of this study (3s < TR; full brain coverage; time points > 100; spatial resolution better than 4-mm; http://www.nitrc.org/projects/fcon_1000/).

Principal component analysis (PCA) [21] was used to analyze the variability of FCDM across subjects. FCD maps with zero empirical mean were calculated by subtracting the average FCD value across subjects from the FCD data. Then, we computed the principal components of FCDM datasets using the covariance of the data in IDL.

III. RESULTS

The FCD distribution varied across research sites (Fig 1), which is likely due to differences in acquisition parameters, instruments, demographic variables, and potential differences in resting conditions (e.g. eyes opened/closed, awake/sleep, etc). For most research sites the average distribution of the FCD reached the highest values in a region located in the ventral precuneus followed by regions located in inferior parietal, occipital, and cingulate cortices. However, the cerebellar vermis also reached high FCD values for some of the imaging datasets (Dallas, New York A, Ontario, Orangeburg, and Oxford). The variability of the FCD across research sites increased the standard deviation of the overall FCD, which did not have a normal distribution across research sites. The use of a single scaling factor for each research site, $1/k_0$, reflecting the mean FCD across subjects and voxels in the brain, k_0 , allowed us to normalize the distribution of the FCD and merge the datasets from different research sites.

The average inter-subject variability of the FCD maps across research sites was only $23.5 \pm 1.3\%$, and its first principal component accounted for $34.1 \pm 1.3\%$ of the variability and 11 ± 8 principal components were needed to account for 75% of the variance of the FCD across subjects and research sites. We assessed the statistical significance of the normalized FCD patterns across all 972 subjects, regardless of differences in demographic variables between studies and was statistically significant in all gray matter regions, even when correcting for multiple comparisons at the voxel level with a conservative family-wise error (FWE) threshold $P_{FWE} < 0.05$ (one-sample t-test). Across subjects, the FCD in the ventral precuneus and parietal hubs was 8.5 ± 0.2 (mean $\pm$ SE) and 5.9 ± 0.2 times higher than the average FCD in the brain, respectively (Fig 2).

The probability distribution of the FCD can be calculated as $P(k) = n(k)/n_0$, where $n(k)$ is the number of voxels with k functional connections and n_0 is the total number of voxels in the brain. For voxels with more than 5 functional connections, $P(k)$ decreases with k following a power scaling: $P(k) = k^\gamma$. The scaling factor, γ , did not vary significantly across threshold conditions and the power scaling between $P(k)$ and k was robust across subjects (Fig 3). The scaling factor γ varied from -4.0 to 6.5 across research sites.

IV. DISCUSSION

Here we propose a data-driven method to map the local FCD from resting-state MRI time series using correlation analyses. FCDM achieves fast computation by restricting the calculation to the local functional connectivity clusters. Typically, only 2 minutes are required to map the FCD in the whole brain from single subject data, which is more than 1000 times faster than what can be achieved using traditional approaches. The preprocessing methodology further includes necessary preprocessing steps to minimize motion and physiologic artifacts. Principal component analysis and t-test were used to quantify the robustness of FCDM using resting-state functional MRI datasets from the image repository

“1000 Functional Connectomes”. Specifically, there were not statistically significant FCDM differences on test-retest studies using paired t-tests. The principal component analysis showed that the variability of FCDM between-subjects was lower than 35% for all imaging datasets (972 healthy subjects).

The main finding of the study is that in resting conditions the spatial distribution of the FCD is highly localized in ventral (precuneus) and inferior parietal, posterior cingulate, and paracentral lobule, as well as occipital (cuneus and calcarine cortex) regions. Thus, as suggested by previous studies [8], these regions are likely the functional hubs of the brain. The ventral precuneus and the cingulate cortex are core regions of the default mode network [22]. These regions are more active at rest than during cognitive performance and show negative BOLD responses during cognitive functional MRI tasks [23]. The precuneus is a brain region whose activity is associated with the overall state of consciousness [24], and for which positron emission tomography (PET) studies consistently show to have the highest metabolism in brain (along with cingulate and visual cortical areas) [25, 26], suggesting that it is an important hub for intrinsic activity in the human brain. As we hypothesized, the probability distribution of the FCD had a power scaling with k , and this scaling was robust across different threshold conditions, subjects and research sites, suggesting that distribution of hubs in the brain has a “scale-free” organization.

V. CONCLUSION

Here we propose an ultra-fast data-driven method to map the FCD in the human brain. The distribution of the FCD is maximal in the ventral precuneus and has other local maxima in dorsal parietal and occipital cortices as well as in subcortical brain regions (thalamus and cerebellum). The FCD distribution is highly reliable across subjects and research sites, regardless of demographic differences and variable MRI acquisition and hardware. Thus, FCDM is a promising technique for the assessment of the functional properties of the brain networks even when subjects rest in the scanner in absence of any specific stimulation task.

Acknowledgments

This work was supported in part by the U.S. National Institute on Alcohol Abuse and Alcoholism under Grant 2R01AA09481).

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Fig 1.
Spatial distribution of the average FCD superimposed on middle sagittal MRI plane for all research sites (green labels) in this study. FCDM Parameters: $T_{\text{SNR}} = 50$ and $T_C = 0.6$.
Sample: 972 healthy subjects (total).

Fig 2. Distribution of the normalized FCD, k/k_0 , showing the main functional connectivity hubs in the brain (top row), and the statistical significance of the normalized FCD (bottom row) across 972 subjects, superimposed on sagittal MRI views of the human brain. Statistical significance threshold: $P_{FWE} < 0.05$, corrected for multiple comparisons.

Fig 3. Probability distribution of the FCD in the human brain for a typical subject of the Newark dataset and three difference T_C criteria (left) and for a group of 19 healthy subjects of the same dataset ($T_C = 0.6$; right) as a function of the number of functional connections per voxel, k , exemplifying the power scaling, $P(k) = k^\gamma$, of the FCD.