Information transfer between rich-club structures in the human brain

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Abstract. The performance of the human brain depends on how effectively its distinct regions communicate, especially the regions which are more strongly connected to each other than to other regions, or so called "rich-clubs". The aim of the current work is to find a connectivity pattern between the three brain rich-club regions without any a priori assumptions on the underlying network architecture. Rich-clubs for the analysis were previously identified with structural MRI. Functional magnetic resonance imaging (fMRI) data from 25 healthy subjects (1000 time points from each one) was acquired and Transfer Entropy (TE) between fMRI time-series from rich-clubs was calculated. The significant results at the group level were obtained by testing against the surrogate data generated on a novel approach. We found stable causal interactions between rostral Anterior Cingulate Cortex L and Dorsal Anterior Cingulate Cortex L, dorsal Anterior Cingulate Cortex L and Paracentral Lobule R but not vice versa. Our work provides an approach to causal analysis of experimental data and demonstrates the applicability to real fMRI study.

Keywords: *effective connectivity; information transfer; rich club; transfer entropy.*

1 Introduction

Some studies have shown the existence of highly interconnected regions (hubs), that play a key role in global information integration between different parts of the brain [1]. These regions are of critical importance due to their role as integrator which was demonstrated in studies on patients with damaged links between rich-clubs [2]. This study aims at finding a causal pattern between three previously defined (Kartashov et al., in press) rich-clubs based on Transfer Entropy (TE) as well as provides a possible significance test of obtained TE values.

Many researchers explore the connectivity between rich-clubs in terms of statistical dependencies between spontaneous activities in them (i.e. functional connectivity). These dependencies do not show anything about causal effect one neural

system exerts over another. To be able to reproduce biological principles of the brain in artificial systems we need to know this functional architecture in terms of effective connectivity. There are two main groups of methods proposed to measure effective connectivity for fMRI study. One group consists of model-based approaches like DCM (Dynamic Causal Modelling) [3]. Previously its application to resting-state fMRI was demonstrated [4–6]. Another group consists of methods with no prior assumptions or hypotheses on the brain structures interaction. One of these methods taken from information theory is called Transfer Entropy (TE). TE was first introduction by Schreiber [7] and has been recognized as a powerful tool to detect the transfer of information between joint processes. The most appealing features of TE are that it has a solid foundation in information theory and it naturally detects directional and dynamical information transfer. TE has been previously applied to assess interactions between brain networks (but not rich-clubs) [8,9]. One of the novelties of the current work is a proposed procedure of generating surrogates and formulating a null hypothesis for significance testing.

2 Materials and Methods

2.1 Transfer Entropy

In 1956 Norbert Wiener proposed the definition of causality: an improvement of the prediction of the future of a time series X by the incorporation of information from the past of a second time series Y is an indication of a causal interaction from Y to X. In 2000 Schreiber proposed [7] a new information theoretic measure – Transfer Entropy (TE), which is a non-parametric statistic measure of the amount of directed (time-asymmetric) information transfer between two or more random processes, for details see [9].

2.2 Subjects

MRI data were obtained from 25 healthy subjects, mean age 24 (range from 20 to 35 years). Consent from each participant was provided. The participants were instructed to close their eyes and lie still and relaxed. Each participant was asked about wakefulness during the study; those who fell asleep in scanner were excluded from the study. Permission to undertake this experiment has been granted by the Ethics Committee of the NRC "Kurchatov Institute". 1000 time points (with a repetition time of 2 s) were acquired resulting in approx. 35 min. of scanning.

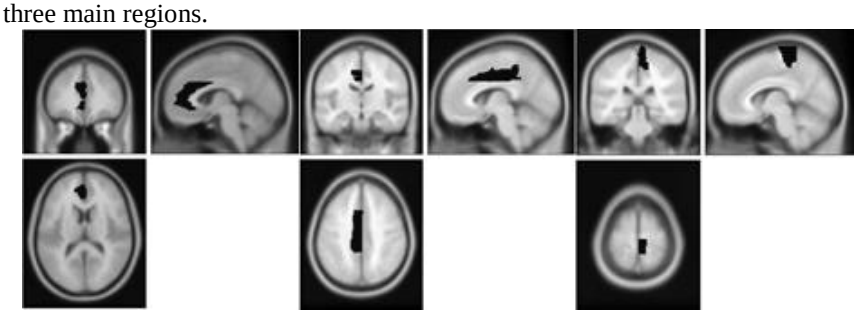
2.3 Scanning parameters

MRI data were acquired using a SIEMENS Magnetom Verio 3 Tesla. The T1- weighted sagittal three-dimensional magnetization-prepared rapid gradient echo sequence was acquired with the following imaging parameters: 176 slices, TR = 1900 ms, TE = 2.19 ms, slice thickness = 1 mm, flip angle = 9°, inversion time = 900 ms, and FOV = 250 × 218 mm^2. fMRI data were acquired with the following parameters: 30 slices, TR = 2000 ms, TE = 25 ms, slice thickness = 3 mm, flip angle = 90°, and FOV = 192 × 192 mm^2. Also the data which contain the options for reducing the spatial distortion of EPI images was received.

2.4 Preprocessing and TE calculation

fMRI and anatomical data were preprocessed using SPM8 (available free at http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) based on Matlab. Preprocessing included the following steps: adduction the center of anatomical and functional data to the anterior commissure, correction for magnetic inhomogeneity using field mapping protocol. Slice-timing correction for fMRI data was performed (the correction of hemodynamic response in space and then in time to avoid pronounced motion artifacts) [10]. Anatomical data were segmented into 3 possible tissues (grey matter, white matter, cerebro-spinal fluid); both anatomical and functional data were normalized.

Rich-club regions were previously identified by DTI from the same 25 participants (Kartashov et al., in press). The three main regions are: Rostral Cingulate Cortex L (ACC) [-4 35.5 14], Dorsal Cingulate Cortex L (ACC) [-5.5 -15 41.5], Paracetral Lobule R [7.5 -31.5 68]. In square brackets there are corresponding MNI coordinates of regions centers of masses, see Fig.1 for spatial localization. We used the SPM toolbox—WFU pickatlas (available free at http://uvasocialneuroscience.com/doku.php?id=uva_socia:wfu_pickatlas) to create a mask for the three main regions.



a)Rostral ACC b)Dorsal ACC c)Paracentral_Lobule

Fig. 1. Spatial localization of chosen regions of interest, superimposed on the T1-weigthted MNI template.

After preprocessing, fMRI time series from three regions of interest (ROIs) were extracted and additionally preprocessed to remove physiological artifacts (heartbeat and breathing) in 3 different ways: 1) linear detrending 2) squared detrending 3) calculating and subtracting the envelope curve for the signal. In addition, we analyzed the raw fMRI signal to understand whether physiological noise could lead to TE values miscalculation. After all preprocessing was done, averaged signal intensities from each ROI were taken for further analysis.

TE values for each pair of rich-clubs were then calculated using non-uniform embedding and nearest-neighbor estimator, see [9] for details. For nearest neighbor estimation pre-compiled .mex files were used from OpenTSTOOL (http://www.dpi.physik.uni-goettingen.de/tstool/link.html).

2.5 Group-level significance testing

By definition, TE values can be exactly zero only when no time-series vector candidates are found in non-uniform embedding procedure for TE calculation. In all other cases TE values are strictly positive, which leads to a problem of null-hypothesis formulation at the group level: all mean TE values in a group are positive (and zero only when for all participants there are no significant candidates). This means that surrogate data is needed to form differences between real and surrogate TE values. This surrogate data cannot be obtained by random permutations of fMRI time-series values due to complex structure of fMRI data with correlations and autocorrelations. To account for these dependencies, surrogate data was constructed in the following way: for each subjects its real data (1000 time points for each ROI) were split into 10 blocks of 100 time points and these blocks were shuffled 100 times to produce 100 synthetic data sets. This procedure generates data which: 1) has no causal relations 2) has the same first and second order statistical moments as the source data. For these datasets TE values were recalculated forming a null-distribution of TE values (for each subject and for each ROI to ROI interaction). Thus the null-hypothesis of no causality is: the median of TE values differences between real and surrogate data is equal to zero, which leads to Wilcoxon signed-rank test to reject this hypothesis. As we have multiple comparisons (3 rich clubs and 6 possible connections), Bonferroni correction should be done.

3 Results

After group analysis, the following results were obtained, see Fig.2.

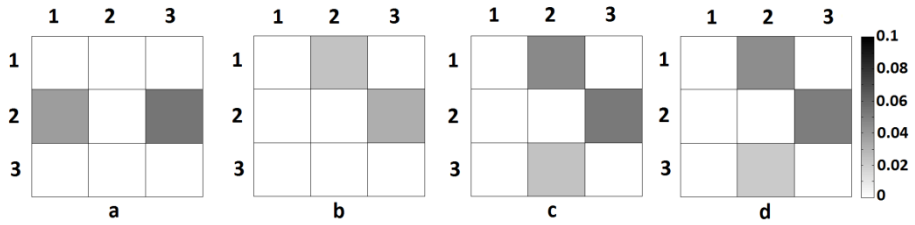


Fig. 2. Matrices of causal connections between rich-club regions. Left to right: calculated from **a)** raw data, **b)** envelope curve removing, **c)** linear detrending, **d)** squared detrending. In rows there are source regions, in columns – target regions. 1 – rostral ACC, 2 – dorsal ACC, 3 - Paracentral Lobule Group-level significant results are shown ($p<0.01$, Bonferroni corrected). TE values scale in bites is shown on the right.

In general, all preprocessing types showed similar result at the group level, unlike the raw fMRI data. This could mean that there is a lot of false correlations (and autocorrelations) in raw data due to physiological and equipment noise, which were thoroughly studied before [11,12]. The presence of such correlations leads to overestimation of TE values, which is in agreement with our simulation results.

There are significant information flows between Rostral ACC and Dorsal ACC; Dorsal ACC and Paracentral Lobule R, but not vice versa. When applying linear and square detrending, there is also a significant directed connection from Paracen-

tral Lobule R to Dorsal ACC. It is worth mentioning that these connections are significant (at single-subject level) in most subjects, which can be another proof of the reliability of proposed testing procedure.

4 Disscussion

In the current work we aimed at assessing causal interactions between the three rich-club regions: Rostral ACC, Dorsal ACC, Paracentral Lobule R without any underlying assumptions, as well as to propose a possible approach of significance testing at the group level. These rich-club regions were taken from the other work (Kartashov et al., in press), but all structural and functional data was available for the current analysis. Three different types of preprocessing were applied to account for physiological and scanner noise. The final result for all preprocessing types is almost the same: at the group level the difference is in one connection, which is significant for linear and square detrending procedures, and non-significant for envelope curve removing.

There are different approaches of generating surrogate data for significance testing ranging from simple values randomization to epochs shuffling in EEG experiment [13]. The structure of EEG data (each trial is a couple of seconds epoch with hundreds of time-points) allows for epoch shuffling, while in fMRI we have only one time point per trial due to poor temporal resolution. Thus, in order to capture statistical dependencies in experimental data we need to shuffle blocks not too small to keep correlational structure in data and not too big to get rid of existing causal relations between time-series. Here we propose shuffling blocks of 100 samples to be enough to satisfy both of these requirements.

Our study show the direct effect one neuronal system exerts over another when subject is at rest, not performing any task (basic level of consciousness). The regions responsible for control functions of the brain, multi-tasking, emotional evaluation, detecting errors and decision making (rostral and dorsal ACC) have an influence on areas controlling motor and sensory innervations (Paracentral Lobule R). The observed data also show the influence from rostral ACC (emotional component) on dorsal ACC (cognitive component), which in turn influences the sensorimotor regions (Paracentral Lobule R).

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