A method for functional network connectivity using distance correlation

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***Abstract*— In this paper, we present a novel approach for functional network connectivity in fMRI resting activity using distance correlation. The proposed method accounts for non-linear relationships between the resting state networks and can be used for both single subject and group level analyses. We showed that the new strategy improves the capacity of characterization of pathological populations, such as, patients with disorder of consciousness, when compared to related approaches.**

I. Introduction

Cumulative research in hemodynamic brain activity measured in resting conditions, using functional magnetic resonance imaging (fMRI), suggests that healthy brain is organized of large-scale resting state networks (RSNs) of cognitive relevance [1]. At least ten of these entities have been consistently identified at the group level: default mode network (DMN), executive control network left (ECL), executive control network right (ECR), saliency, sensorimotor, auditory, cerebellum and three visual networks medial, lateral and occipital [2]. Each resting network is composed by a set of spatial regions that share a common time course.

Several pathological conditions, such as disorders of consciousness, dementia and Alzheimer's, among others, have been studied using the RSN approach [3], [4]. These studies mainly focused on changes in the spatial pattern of one network, typically the DMN. A recent approach aimed at identifying multiple RSNs simultaneously at the individual level, by taking into account both spatial and temporal properties of the networks [2]. According to this approach, patients with disorders of consciousness showed the DMN, ECL, ECR and auditory networks as non-neuronal more often compared to healthy controls; further voxel-based analyses in these RSNs indeed showed decreases in functional connectivity as a function of the level of consciousness. Apart from the alterations in the spatial pattern of the investigated signal, temporal changes or dynamic activity of the RSNs is of equal importance to better comprehend brain function in pathology [5].

A complementary RSN analysis strategy, which considers temporal variations of the fMRI dynamics, is the functional network connectivity (FNC). In this approach, the level of interaction during spontaneous activity among different RSNs is assessed by computing pairwise measurements of connectivity between the RSN time courses. Typical measures of interaction include: Pearson's correlation coefficient that aims capturing linear relationships among the time-courses [6], Granger causality that characterizes directional connectivity [7] and temporal slicing window that allows to explore the temporal changes of the RSN connectivity [8]. These approaches are based on the underlying assumption that RSN brain dynamics follows linear regimes. However, recent evidence suggests that neuronal function of cortical ensembles during resting state may follow non-linear behaviors [9], therefore, usual interaction measurements may be limited to capture this phenomena.

In this paper, we propose a novel FNC method that accounts for non-linear relationships between different RSNs. Our method is based on a multiple RSN identification approach and quantifies the interaction by using the distance correlation (DC) [10]. The method allows both single-subject and group-level evaluation and accounts for non-linear relationships between the RSN time courses. We show that this approach will improve the capacity of characterization of the resting dynamics in pathological populations, such as, patients with disorder of consciousness (DOC), and keeps similar levels of reproducibility as related approaches.

II. Materials and Methods

A. Participants and data acquisitions

Data from 76 subjects were used for this study: 27 healthy controls (14 women, mean age 47 $\pm$ 16 years), 24 patients in minimal conscious state and 25 with vegetative state/unresponsive wakefulness syndrome (20 women, mean age 50 $\pm$ 18 years). All patients were clinically examined using the French version of the Coma Recovery Scale Revised (CRS-R) [11]. Written informed consent to participate in the study was obtained from all patients or legal surrogates of the patients. For each subject, fMRI resting data were acquired in a 3T scanner (Siemens medical Solution in Erlangen, Germany). Three hundred fMRI volumes multislice $T2^*$-weighted functional images were captured (32 slices; voxel size: $3 \times 3 \times 3\ mm^3$; matrix size 64; repetion time = 2000 ms; echo time = 30 ms; flip angle = 78; field of view = 192 mm^2). An structural T1 image was also acquired for anatomical reference.

B. Preprocessing

fMRI data was processed using SPM8[1]. Preprocessing includes: realignment, coregistration of functional onto structural data, segmentation of structural data, normalization into

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[1]http:www.fil.ion.ucl.ac.uk/spm

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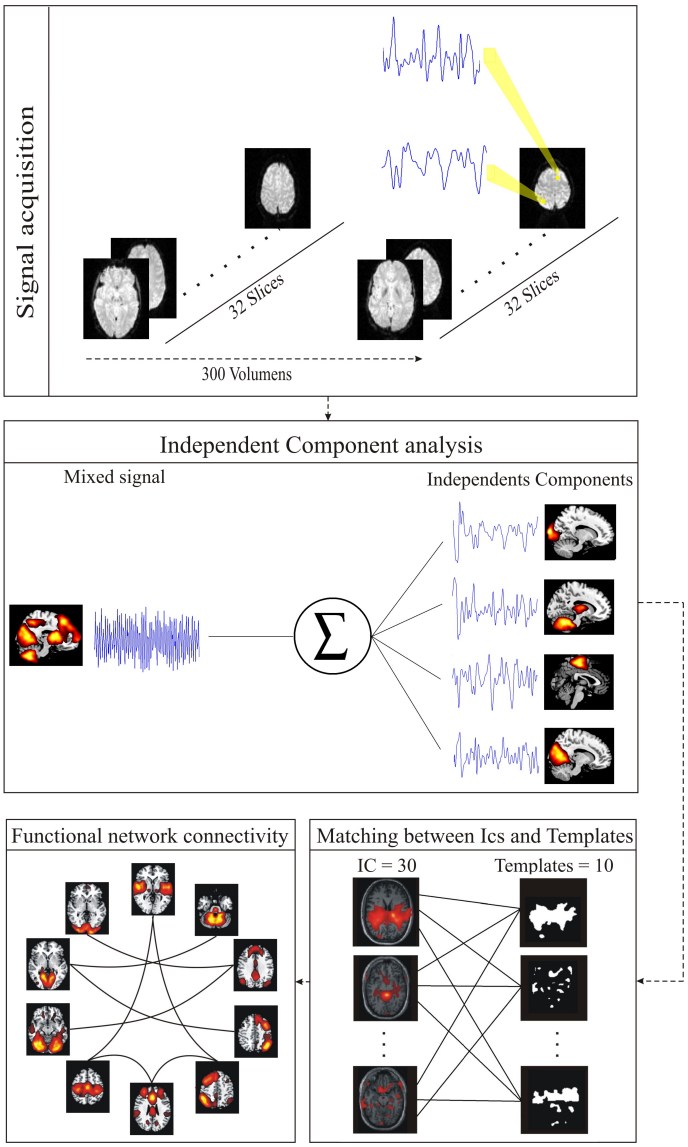

Fig. 1. Functional network connectivity (FNC) pipeline.

MNI space and spatial smoothing with a Gaussian kernel of $8\,mm$. Large head motions were corrected using ArtRepair[2].

C. FNC method

The proposed FNC approach is illustrated in Figure 1. In particular:

1) Spatial Independent Component Analysis: The first step for the RSN identification was the fMRI signal decomposition into sources of neuronal/physiological origin. For this task, we used ICA, which aims to decompose the signal into a set of statistically independent components (ICs) of brain activity. Because in the fMRI data the spatial dimension is much greater than temporal one, we used spatial ICA (sICA), which decompose the signal into maximally independent spatial maps [12]. In sICA each spatial map (source) have an associated time course, which corresponds to the common dynamic exhibit by this component. These RSN time courses were subsequently used for all the FNC computations. For the ICA decomposition we used 30 components and the infomax algorithm as implemented in GroupICA toolbox[3].

2) RSNs Identification: After the ICA decomposition, the different RSNs were identified at individual level. The common approach for this task is the group level identification. In this method, the fMRI data of whole population is concatenated along the temporal dimension. Later, sICA is applied to identify the sources of brain activity at the group level. Following, each RSN is manually identified [6]. Finally, individual time courses are extracted for each RSN by applying a dual regression (back-reconstruction) onto the original subject data [6]. This approach is based on a homogeneity assumption of the fMRI dynamic across the whole population. Nevertheless, in severely affected brains, this condition may be not valid [2].

In this work, we used an alternative approach that aims identifying each RSN directly from the single subject sICA decomposition. In particular, we ran a single subject sICA, and then, the set of ICs that maximize the similarity with a set of RSN templates (figure 1) were selected [2]. This approach has been proved to be robust in non-homogenous populations, as the herein studied, and can be used directly for individual assessment of subjects in clinical applications. After the RSN spatial map identification, a machine learning based labeling method was applied to discriminate between IC of "neuronal"or "artifactual"origin. In particular, a binary classification method based on support vector machines and an spatio-temporal feature vector for description each IC was used [2].

3) Time series interaction measurement: For the computation of the RSN time series interaction, we propose to use an alternative measure of interaction the DC [10], which accounts non-linear dependencies between random variables in arbitrary dimensions between them.

Distance Correlation. DC aims to measure dependencies between two random variables X and Y with finite moments in arbitrary dimension, not necessarily of equal dimensions [10]. For defining DC, we started with an observed random sample $(X,Y) = \{(X_k, Y_k)|k = 1, 2, \ldots, n\}$ of the joint distribution of random vectors X in $\mathbb{R}^p$ and Y in $\mathbb{R}^q$. Using these samples a transformed distance matrix A can be defined as follows:

$$a_{kl} = \|X_k - X_l\|\,,\ \bar{a}_{k\cdot} = \frac{1}{n}\sum_{l=1}^{n} a_{kl},\ \bar{a}_{\cdot l} = \frac{1}{n}\sum_{k=1}^{n} a_{kl},$$

$$\bar{a}_{\cdot\cdot} = \frac{1}{n^2}\sum_{k,l=1}^{n} a_{kl},\quad A_{kl} = a_{kl} - \bar{a}_{k\cdot} - \bar{a}_{\cdot l} + \bar{a}_{\cdot\cdot}$$

$k, l = 1, 2, \ldots, n$. Similarly, B is defined to characterize distances between samples for Y. Following, the empirical distance is defined by $V_n^2(X,Y) = \frac{1}{n^2}\sum_{k,l=1}^{n} A_{kl}B_{kl}$.

[2]http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm

[3]http://icatb.sourceforge.net/

Finally, the empirical DC corresponds to the square root of

$$R_n(X,Y) = \begin{cases} \frac{V_n^2(X,Y)}{\sqrt{V_n^2(X)V_n^2(Y)}} & V_n^2(X)V_n^2(Y) > 0 \\ 0 & V_n^2(X)V_n^2(Y) = 0 \end{cases}$$

where $V_n^2(X) = V_n^2(X,X)$. Note that A and B can be computed independently of p and q, and both contain information about between sample elements distances in X and Y. $V_n^2(X,Y)$ is a measure of the distance between the probability distribution of the joint distribution and the product of the marginal distributions, i.e., $V_n^2(X,Y)$ quantifies $\|f_{X,Y} - f_X f_Y\|$, with f_X and f_Y the characteristic function of X and Y, respectively, and $f_{X,Y}$ the joint characteristic function [10]. In contrast to PC, $V_n^2(X,Y)$ vanish if and only if X and Y are independent variables [10]. The DC corresponds to a normalized version of $V_n^2(X,Y)$, which takes values between 0 and 1, with zero corresponding to statistical independence between X and Y, and 1 total dependency.

Lagged Distance correlation. For the FNC computations we assumed that two RSN time series X and Y provide the n observations of the joint distribution characteristic of the RSN temporal dynamics. Prior to the DC computations, the RSN time courses were filtered thought a bandpass Butterworth filter with cut-off frequencies set at $0.05\ Hz$ and $0.1\ Hz$. This frequency range was previously used in other studies [2]. Similar to Jafry et al [6], we used a maximum lagged approach. For this, we defined the lagged DC (LDC) as

$$R_n^{\Delta}(X,Y) = R_n(X,Y^{\Delta})$$

where Y^{Δ} is the time course circularly shifted Δ temporal units. We varied Δ between $+6s$ and $-6s$ in TR units ($2\ s$) [6]. The maximal DC value for the 7 shifts was defined as the interaction measure between the two RSN time courses. This maximal lagged DC was assessed between all pairwise valid combinations (both RSNs labeled as "neuronal") where the number of combinations of 10 RSNs, taken 2 at a time results in $10!/(2!(10-2)!) = 45$ possible combinations.

D. Group Analysis

For the group analysis the maximal LDC and the maximal lagged PC were calculated for all the subjects. Following, valid interaction quantities (i.e., between RSNs labeled as "neuronal") were averaged for each group (healthy controls, MCS and VS/UWS). A Student's t-test was used to assess significant values of interaction at the group level ($p < 0.05$). Differences between VS/UWS and MCS, which corresponds to one of the most clinically relevant discrimination problems in DOC domain, were assessed by using a two sample t-test ($p<0.01$), these computations were Bonferroni corrected for multiple comparisons ($n = 45$ possible pairs). Cohen's d effect sizes for DC and PC were computed to measure the capacity of discrimination. Reproducibility for both dependency measures was evaluated by computing an F-test ($p < 0.05$) to compare the variance of the maximal lagged PC and LDC. To have comparable values maximal LDC was normalized to the range 0 and 1.

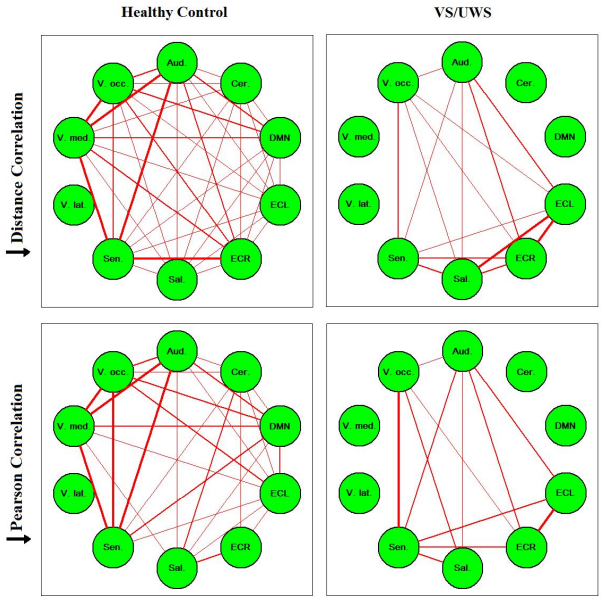

Fig. 2. Individual subject FNC analysis in two subjects. The line tickness corresponds to the connectivity strength.

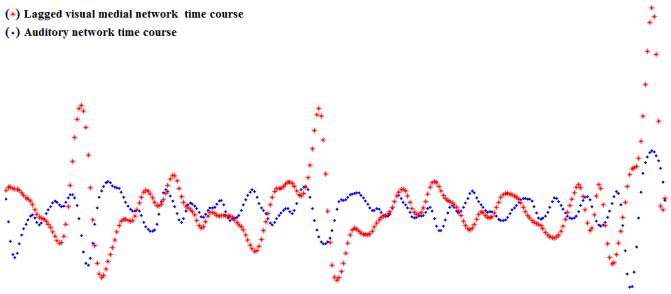

Fig. 3. Auditory and the visual medial time course in a healthy control.

III. Results

Figure 2 shows the individual connectivity results for two measures of interaction (maximal LDC - top and maximal lagged PC - bottom) for two subjects: healthy control (left) and VS/UWS patient (right). As observed, DC was able to capture dependencies that were not originally captured by PC.

Figure 3 shows the corresponding lagged time courses the RSNs auditory and visual medial network time series extracted from a healthy control. In this case, non-linear dependencies were poorly captured by the PC (0.005) in comparison to DC (0.42).

Figure 4 shows the connectivity at the group level for the two measurements (DC and PC) in three groups: healthy controls (top), MCS (middle) and VS (bottom). A reconfiguration of the connectivity was observed in altered states of consciousness (VS/UWS and MCS) when compared to control subjects. In general, DC was able to capture more relationships among RSNs for the three groups. Significant

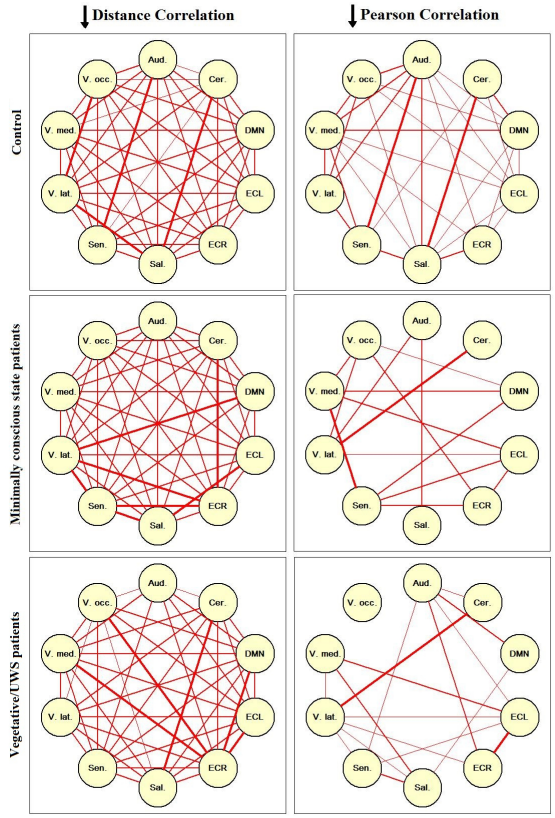

Fig. 4. Functional connectivity group results. The line tickness corresponds to the connectivity strength.

differences between VS/UWS and MCS patients were found for ECL - ECR and visual medial - salience connections ($p < 0.05$, Bonferroni corrected), for both measurements DC and PC. In both connections the effect sizes were large. However, DC resulted in a higher Cohen's d values: $d = 5.33$ (DC) compared to $d = 4.45$ (PC) for ECL - ECR, and $d = 3.45$ (DC) compared to $d = 3.42$ (PC) for the visual medial - salience. Results indicate that there is no significant differences in the variances of both measurements (DC and PC) indicating similar levels stability.

IV. Conclusion

In this work, we proposed a new functional network connectivity (FNC) approach for fMRI resting state brain activity. The strategy is based on an multiple RSN identification approach, and the lagged distance correlation, a novel measure that aims to capture non-linear relationships between time series. We demonstrated that the novel approach improves the capacity of characterizations of functional connectivity in subjects with severe brain damage.

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