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Reduction of resting state network segregation is linked to disorders of consciousness

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ABSTRACT

Recent evidence suggests that healthy brain is organized on large-scale in regions spatially distant and partially temporally synchronized. These regions commonly are called Resting State Networks (RSNs). Many RSNs has been identified in multiples spatial scales in healthy subjects and their interactions has been used to define the functional network connectivity (FNC). The main idea in FNC is that the dynamic shown in the interactions among RSNs in control subjects, can change in pathological and pharmacological conditions. However, this hypothesis assumes that functional structure of healthy brain, remains in other brain states or conditions. In this work, we proposed a novel methodology in order to find the new brain functional structure for disorders of consciousness conditions, based on multi-objective optimization approach. Particularly, we find the best partition of RSNs set, that maximize two modularity measures (Kapur and Otsu measures). Our results suggest that the brain segregation level, may be linked to consciousness level.

Keywords: Community, disorders of consciousness, NSGA II, resting state networks, segregation.

1. INTRODUCTION

Recent studies on functional magnetic resonance imaging (fMRI) suggest that healthy brain in resting state is organized into large-scale of resting state networks (RSNs).[1] The existence of at least ten of these RSNs (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) have been consistently reported in healthy subjects.[2] Each RSN encompasses a set of spatial regions with a common functional behavior or time-course, and corresponds to a functional description of a high level brain system of cognitive/sensorial relevance.[3] The RSN time courses, in turn, can be used to construct a large scale functional connectome that describes interactions among high level brain functional systems, in the so called Functional Network Connectivity (FNC).[4] In this approach, the degree of interaction among the RSNs time-courses is quantified, resulting in a very-large-scale functional network whose nodes are RSNs. In contrast, to other functional networks, which are conformed by smaller brain areas, the FNC model of connectome aims to characterize high level interactions among complete brain functional systems.[5,6]

Several brain pathological conditions including disorders of consciousness, dementia, Alzheimer disease, among others, have been studied by using the RSN approach.[2,5–10] Most studies mainly focus on changes in the intrinsic connectivity of one RSN, typically, the DMN. Nevertheless, there is evidence that suggests that rather than one, multiple RSNs maybe affected during pathological conditions. For instance, patients with disorders of consciousness may show alterations of the intrinsic connectivity on at least four RSNs:[2] DMN, ECL, ECR and auditory. Recent studies have also linked changes in the interactions among these functional systems to pathological brain conditions.[5,11] For instance, dysfunctional time-sustained hyper-connectivities between ECL - ECR and visual medial - salience have been recently related to conditions of severe impairment in patients with DOCs.[5] This panorama suggests that pathological brain states may be associated to changes in individual high level functional systems, but also to alterations in the communication among them.

The brain is a highly complex functional structure, with a densely connected network that balances regional segregation with integration throughout multiple spatio-temporal scales.[12,13] The brain segregation, observed for instance in resting state spontaneous fluctuations, suggest that cortical areas can be specialized in perceptual, cognitive or sensory processing tasks. In other hand, the brain integration, observed for example in the *rich club* topology that supports efficient brain communication,[14] suggest that even if the brain is organized into segregated systems, these systems are still interacting among them.[15] The segregation and integration do not operate as independent phenomenas, rather both properties seems to be required to provide a coordinated activation.[16] It have been suggested that perturbations in the unbalance between segregation and integration, may be associated with pathological brain conditions.[17] For instance, recent computational models suggest that too much integration among brain systems, which are normally segregated, may facilitate the abnormal propagation of information across the brain.[18,19] Similarly, evidence in subjects with DOCs suggests that aberrant integrations (or segregation) among RSNs may be linked to these conditions.[5,6]

Recently, it have been suggested that segregation mechanisms are strongly supported by a particular graph structure called community.[20] A community refers to a sets of brain regions that are strongly related among each other, while connections to others communities remains low. In the structural brain connectome, convergent evidence suggests that community structures are in the very base of the structural segregation mechanisms.[17] Actually, there are not methods to find the communities among brain RSNs by using only the raw data, i.e., without using graph theory and any prior information. In this sense, we propose a novel strategy to find community structures that does not require any prior knowledge about the expected number of communities, and also overcomes the limitations of the traditional functional graph representation. The proposed method is based in an multi-objetive optimization strategy that aims to maximize a novel modularity criterion based on clustering measurements. More specifically, we aim to find the graph partition that better balance a Kapur and the Otsu criterion,[21] two widely knowledge segmentation criteria commonly used by the image processing community. Our aim is to find clusters maximally informative and minimally variant intra-cluster and simultaneously, maximally variant extra-clusters. By using this combination we account for both integration and segregation properties. The proposed method was used to study the segregation phenomena in RSNs of patients with DOCs. Our results suggest a breakdown in the segregation of high level functional networks for patients with DOCs when compared to healthy controls.

1.1 Previous work

In the recent years, different methods have been proposed to extract communities out of functional and structural brain data. These methods can be categorized in: 1) graph based, which corresponds to methods assume an intermediate graph representation of the brain connectivity. The main idea of these approaches to find subgraphs directly from the graph by using, for instance, graph based clustering methods or by characterizing the statistical properties commonly observed for the communities in a network, examples of this category include the min-cut, GirvanNewman methods and clique based methods.[22] 2) modularity maximization, which are methods that aim to find the graph partition with a maximal modularity. Modularity refers to a measure of the quality of a particular partition of a network into communities, and can be defined as the fraction of the edges that fall within the given groups minus the expected such fraction if edges were distributed at random.[23] Because exhaustive search of graph partitions is in general intractable computationally, approximated optimization algorithms are commonly used to find the optimal partition;[20] 3) clustering, the idea of these methods is to find directly the communities as clusters, an example of these methods include hierarchical clustering and independent component analysis.[24] Graph based methods are based on an intermediate graph representation of the functional interaction to compute the communities. These graph representations are critically supported on binary relationships between brain regions that may oversimplify the complex functional relationships, which may appear as the result of interactions of more than two regions.[20] Clustering methods do not assume any bina ip. However, they require prior knowledge about the expected number of clusters. Modularity maximization methods do not require an expected number of communities, but are also strongly supported on a graph representations of brain connectivity.

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2. MATERIALS AND METHODS

Figure 1 illustrates the proposed approach. First, the data are preprocessed (Section 2.2). Following, the signal is decomposed into functional sources by using spatial Independent Component Analysis (Section 2.2.1). Later, a RSN identification procedure is applied to identify the sources corresponding to a set of RSNs (Section 2.2.2). Finally, a multi-objetive optimization method is used to find the partition that provides the better balance between an Otsu and Kappur criterion (Section 2.3).

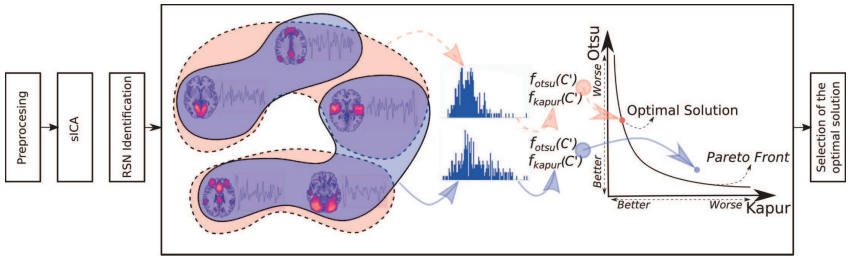

Figure 1. Quantification of segregation approach pipeline. Firstly, the data are preprocessed. Subsequently, the fMRI signal is decomposed into functional components by using sICA. Later, a RSN identification procedure is applied to identify the sources corresponding to a set of RSNs. Additionally, a multi-objetive optimization method is used to find the partition that provides the better balance between an Otsu and Kappur criterion. Finally, a selection of the optimal solution procedure was used, in order to find the best solution at Pareto front level, run level, subject level and population level.

2.1 Data acquisition

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).[25] 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. For the resting state acquisition, patients were instructed to close their eyes, relax without falling asleep and refrain from any structured thinking (e.g., counting, singing etc.).

2.2 Preprocessing

fMRI data was processed using SPM8*. Preprocessing includes: realignment, coregistration of functional onto structural data, segmentation of structural data, normalization into MNI space and spatial smoothing with a Gaussian kernel of 8 mm. Large head motions were corrected using ArtRepair†.

2.2.1 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. In standard ICA, one considers the mixture as linear and the sources as statistically mutually independent and non Gaussian.[26] In the fMRI data the spatial dimension is much greater than temporal one, then, we used spatial ICA (sICA), which decompose the signal into maximally independent spatial maps.[27] In sICA each spatial map (source) have an associated time course, which corresponds to the common dynamic exhibit by this component. Therefore, the original signals (fMRI data) is represented by a $t \times v$ data matrix X, where t is the number of time points in the time course for fMRI data and v is the number of voxels in the volumes. The temporal behavior for each component is summarized in the matrix A (with dimensions $t \times k$, t times point in the record for each source, and k components) and the structure spatial for each component in the mixture is denoted for the matrix S (with dimensions $k \times v$, k the numbers of components by v voxel in the component). A mathematical formulation of the sICA model, can be denoted by using the previous notation as:

$$\underset{t \times v}{X} = \underset{t \times k}{A} \times \underset{k \times v}{S}$$

The RSNs time courses obtained with sICA were subsequently used for all the FNC computations. For the sICA decomposition 30 components ($k = 30$) were used, this selection was performed based on previous work that have shown that this number of components is enough to characterize the different RSNs both for healthy controls and patients with DOC. The infomax algorithm as implemented in GroupICA toolbox was used to perform the decomposition[2] ‡.

2.2.2 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.[4] Finally, individual time courses are extracted for each RSN by applying a dual regression (back-reconstruction) onto the original subject data.[4] 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 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]

2.3 Segregation method

For the segregation method we propose to find the partition of the RSNs set that maximizes a modularity (segregation) measurement. For this, two measures that quantify the level of segregation of a specific partition of the RSNs were proposed. The first one aims to quantify the level of information of each community by using a similar idea to the Kapur criterion. The second one considers the combination between both inter-community and intra-community variances by using the Otsu criterion. This idea is similar to the multi-level thresholding approach recently proposed for image segmentation.[21] Following this approach a multi-objective optimization problem was solved to find the optimal Pareto frontier based in the two modularity measurements.

2.3.1 Kapur Criterion

First, let $C = (c_1, c_2, \ldots, c_n)$ a vector that assigns each RSN to a particular community. 10 networks were used with the following order: auditory - 1, cerebellum - 2, DMN - 3, ECL - 4, ECR - 5, saliency - 6, sensorimotor - 7, visual networks medial - 8, lateral - 9 and occipital - 10. The number of communities is noted by k and ranges between $1 \leq k \leq n$, therefore $c_i \in \{1, 2, \ldots, k\}$. The proposed measurement aims to maximize the sum of entropies for each community, similarly to the Kapur's method,[28] as follows:

$$f_{Kapur}(C) = H_1 + H_2 + ... + H_k \quad (1)$$

*http:www.fil.ion.ucl.ac.uk/spm
†http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm
‡http://icatb.sourceforge.net/

where H_j corresponds to the Shannon entropy of the set composed by the concatenation of all the time-courses of components c_i that are assigned to the k-th community, i.e, the set composed by all the samples of the time courses of the components in T_j, with $T_j = \{i, \text{such that } c_i \text{ is equal to } j\}$. More specifically:

$$H_j = -\sum_i p_i^j \ln p_i^j \tag{2}$$

where p_i^j is the probability occurrence of intensity i in the time courses of all the components inside T_j. Note that (1) aims to quantify the amount of information among each community. High values for this function can be expected when each community contains highly informative RNSs.

2.3.2 Otsu Criterion

The Otsu's method[29] is based on the discriminant analysis. Their main idea is to maximize the inter-cluster variance, and simultaneously, to minimize the intra-cluster variance, as follows:

$$\begin{aligned} f_{Otsu}(C) = (u_1 - u_2)^2 + (u_1 - u_3)^2 + \ldots + (u_1 - u_k)^2 + \\ (u_2 - u_3)^2 + (u_2 - u_4)^2 + \ldots + \\ (u_2 - u_k)^2 + \ldots + (u_{k-1} - u_k)^2 + \end{aligned} \tag{3}$$

where $u_j = \sum_i i p_i^j$.

2.3.3 Multiobjetive optimization

Both criteria (1) and (3) are explicitly measurements of modularity-segregation for the FCN network. The Kapur's criterion search the partition that is maximally informative, and Otsu's criterion look for the minimally variant segmentation inside each community and simultaneously, the maximally variant segmentation between communities. However, even if both criteria aims to measure the same network property they differ in their nature. In order to consider both criteria simultaneously, we propose to find the partition that maximizes simultaneously both criteria. This search problem can be solved by using a multi-objetive optimization formulation, as follows:

$$C^* = argmax_C(f_{Kapur}(C), f_{Otsu}(C)) \tag{4}$$

In this formulation commonly there is no a solution that maximizes both objective functions simultaneously. Therefore, the solution is selected from the Pareto front, i.e., the locus of solutions that cannot be improved in any of the objectives without degrading at least one of the other objectives.[30]

2.4 Optimization Algorithm

The exhaustive search of the solution among the complete set of possible RSNs segmentation is computationally intractable. Therefore, we used an heuristics algorithm to approximate the solution. Specifically, we used the fast elitist multi-objetive genetic algorithm (NSGA-II).[30,31] This algorithm aims to find the non-dominated or pareto-optimal solutions, which are those solutions in the set which do not dominate each other, i.e., neither of them is better than the other in all the objective function evaluations. The solutions on each pareto-front are pareto-optimal with respect to each other.

2.4.1 Chromosome representation

In the NSGA-II approach the possible solutions are codified as chromosomes consisting of n genes, each one organized in a vector structure. In this case, we used C as the chromosome codifying a possible solution.

2.4.2 Optimization parameters

For the NSGA-II optimization we used a multi-objective genetic algorithm with simulated binary crossover (SBX) and polynomial mutation operators implementation [§]. For this experimentation the initial set population was set to 70 and generation number to 70. These parameters were experimentally determined based on convergence and reproducibility criteria. For the others parameters, the default values in the implementation were used.

2.4.3 Optimal solution selection

First, the NSGA-II was used at the subject level to find a non-dominated, as a result 70 feasible solutions were found. Then, a matrix $S_p \in R^{70\times n}$ was constructed by using each feasible solution as row. To find a single solution the mode over the values of each column of S_p were computed. This process resulted in a vector s_r which represents the solution for a single run. Because NSGA-II is a non-deterministic algorithm each run can result in a different solution. In order to find an stable solution per-subject, we repeated the optimization 20 times for each subject. Then a similar procedure was used to find an stable solution per-subject, i.e., a matrix $S_r \in R^{20\times n}$ was constructed by using the reduced run solutions of the subject $s_r^1, s_r^2, \ldots, s_r^{20}$ as rows. Following, the modes over the columns of S_r were used again to reduce S_r to a single solution s_s. Finally, to find the solution at the population level a matrix $S_s \in R^{q\times n}$ was constructed by using the solutions for the q subjects in a determined population. Then the mode was used again over the columns of S_s to find the solution at the population level. An illustration of this procedure is shown in figure 2.

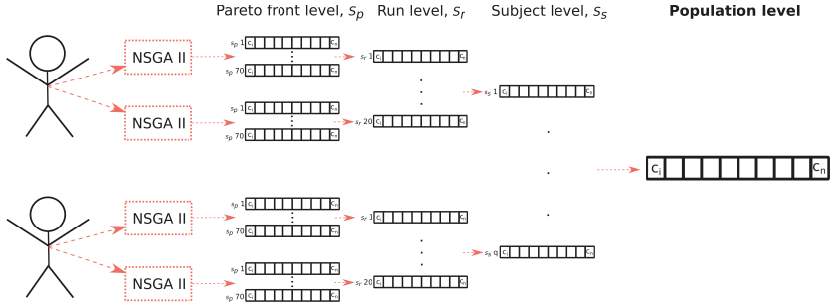

Figure 2. Optimal solutions selection flow. Four level of optimal solution selection was applied. In the first level, the mode solution into Pareto front is obtained by one subject in a particular experimental replica, later, the mode solution is anew obtained for all runs by a particular subject. Finally, the mode solution among all subjects in a particular population is calculated, this structure is a characteristic solutions at population level.

3. RESULTS AND DISCUSSIONS

Figure 3 shows the communities obtained at the population level for the healthy control and the DOC (VS/UWS and MCS) populations by using the procedure described in 2.4.3. As observed, in controls two visual systems (medial and lateral) are grouped into a single community and visual occipital emerge as an independent community. In contrast, in the DOC population these three visual systems conform a single community, suggesting a reduction in the segregation level. A similar result is observed for ECR and ECL that constitute independent communities for healthy controls and conform a single community for DOC. Evidence associated with the reduction in the segregation level between ECR and ECL in DOC condition, had already been reported.[5,6] Interestingly, this networks are thought to control mechanism of attention to external stimuli and processing of sensory information, two mechanisms that possibly are associated with the emergency of the consciousness.[32]

[§] https://atlas.genetics.kcl.ac.uk/ rschulz/

Specifically, the executive systems (ECL and ECR) are thought to be involved in handling novel situations, maintain the attentive control on current task goals as well as responding to salient new information or alerting stimuli in the environment.[33]

A reduction of segregation level is associated with decreased specialization in brain function.[34] In this context, segregation level is measured through number of communities emerging. Recent evidence, suggests that some brain state or brain pathological conditions may be characterized by alteration in brain segregation level.[35–37] These evidence has been quantified by using graph theory, however, reduce the brain dynamic to only pairs of interactions, can be an oversimplification inadequate. In our approach, not is necessary this simplification of problem, because, our methodology is based only on the raw data.

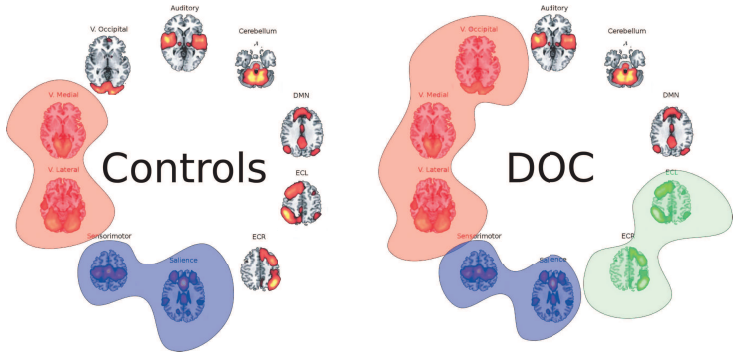

Figure 3. Communities at the populations level. Left communities obtained for healthy controls, and right communities obtained for DOC population (VS/UWS and MCS)

In our results, the number of communities in the DOC population decrease compared to healthy controls indicating a reduction in the segregation level related to loss of consciousness. Our results bear out the recent evidence suggesting that the brain integration and brain segregation must coexist in the best balance for an suitable brain functions.[35] All RSNs reported in the literature, have been consistently and reproducibility identified in healthy subjects,[2] but, any approach has validated the existence of these RSNs in DOC conditions. Our results suggest, that some RSNs can not exist as segregated entities in DOC condition. Therefore, models as FNC could not be appropriate to characterize pathological conditions as DOC.

4. CONCLUSIONS

In this work, we proposed a novel method to find the communities in resting state. Our approach is based in a multi-objective optimization problem that considers two mutually exclusive criteria of modularity-segregation. Our results suggests that the proposed method can find highly the structural conformation of the networks into communities without using any prior information. Our results suggests that the segregation levels in DOC conditions is reduced when compared to control subjects. These results suggest that the segregation level maybe linked the consciousness levels.

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