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ORIGINAL ARTICLE

Investigating the brain connectivity network in sleep disorders patients: A resting-state fMRI study

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Abstract

BACKGROUND: Functional magnetic resonance imaging (fMRI) has frequently been used to detect many neurological disorders within recent years. Investigating functional connectivity (FC) is one of the fMRI study methods. The present study aims at recognizing the differences and similarities of the FC network in patients with sleep disorder (narcolepsy) compared in comparison with healthy people.

MATERIALS AND METHODS: Resting-state scans from 26 people, including 13 patients with narcolepsy disorder and 13 healthy people (control), were downloaded from open fMRI databases and compared in different brain regions after pre-processing, using Variance Components Model in order to investigate the changes in the FC network.

RESULTS: The results demonstrate that four pairs of studied areas in the patient group have a statistical significance compared with the control group. Patients in some areas, such as angular gyrus and cerebellar lingual, cingulate gyrus and cerebellar lingual, cerebellar tonsil and thalamus, witness decrease in the severity of FC, while in-between regions of the cingulate gyrus and cerebellar tonsil face an increase of the FC.

CONCLUSION: Difference in the FC network in some regions among patients with sleep disorders (narcolepsy) compared to the healthy people is an essential indication of the causes of this disease and methods of curing it.

Introduction

In 1990, a class of imaging methods called functional magnetic resonance imaging (fMRI) was developed to detect changes in brain regions and time-varying variables in brain metabolism (Fox *et al.* 2005, Ogawa *et al.* 1990). This method of study examines brain changes both during the state of task and rest (Greicius, 2008). A resting-state check refers to when the person is scanned without the presence of any motion and any particular stimulus (Kwong *et al.* 1992, Nazari *et al.* 2019). Though the range of fMRI studies is very

broad, the three major objectives derived from these studies include the study of active brain areas and the recognition of their activity, the study of brain connectivity and classification, and prediction of brain activities (Buckner *et al.* 2008). Investigating of brain connectivity is divided into the two mainstream of effective connectivity and functional connectivity (FC) (Friston, 2011). In the study of effective connectivity, the causal relationship between different areas of the brain, and the severity and weakness of these connectivities are discussed (Li *et al.* 2010). If these relationships are correlated unilaterally to two-way communication, they will be studied under the FC category (Cavanna and Trimble, 2006). In the FC study, the time dependence of oscillation of Blood Oxygenation Level-Dependent (BOLD) signals in different regions of the brain is investigated, and it is concerned with the indirect relationship between the two distinct spatial regions in the brain (Greicius, 2008). According to some studies, the cerebral brain connectivity network has a dynamic state, which means it is not stable over time (Borumandnia *et al.* 2017, Maudoux *et al.* 2012). Many studies have been done over the effects of changes in brain connectivity on neurodegenerative diseases. Among the studies that examine the FC network during a neurological disorder, the correlation coefficients analysis between areas in patients with Alzheimer's disease using global distribution analysis in 2007(Wang *et al.* 2007). Likewise, the FC network at resting-state autism spectrum disorder was investigated through using a network-based statistical method (NBC) in 2018 (Pascual-Belda *et al.* 2018). The study of psychotic depression was performed by Oudega *et al.* with the help of resting data and regression analysis (Oudega *et al.* 2019). In 2017, the variance components model was introduced by Fiecas *et al.* to investigate the FC between the resting network of patients with dyslexia and healthy individuals. This model incorporates the time correlation of fMRI data and heterogeneity between individuals as two components of the error in the statistical model, which facilitates calculation and increases the statistical power in the used method (Fiecas *et al.* 2017). Sleep disturbance is one of the most common types of psychiatric disorders, among which the followings are of the most common types: insomnia, fatigue, and sleepiness with narcolepsy (Roth, 1995). Other sleep disorders are sleep apnea, periodic limb movement disorder, and parasomnias, which can be so serious as to disturb the normal individual function of mental, emotional and social activities (Hirshkowitz, 2004, Mindell and Owens, 2015). The present study aimed at using the proposed method of Fiecas *et al.* to investigate the FC network analysis of patients with narcolepsy sleep disorder in comparison with healthy people. Also, we examines the correlations between each of the regions-of-interest in patients compared with healthy people. The severity of the correlations in patients and healthy people is also examined, using variance components model and FC networks test.

Materials and Methods

Study Data

The data used in this study was taken from open fMRI databases (https://openfmri.org) collected by Nicoletta Cera *et al.* with the accession number of ds000133. This data is related to the resting imaging of 13 patients with sleep disorders and 13 healthy people, all of whom were male and right-handed. Data preprocessing was performed in spm12(www.fil.ion.ucl.ac.uk/spm/; Wellcome Department of Imaging Neuroscience, London, UK). One hundred forty-five functional scans related to each subject were first corrected for the average functional image. Then, the structural images of the samples were co-registered. With the size of the voxel $3\times3\times3mm^3$, the images were normalized afterward. Using a 6mm Gaussian Kernel, a smoothing step was performed. Using the TDLabes Atlas, a total of 14 regions of interest (ROI) were selected, which were related to sleep disorder according to previous studies (Cera *et al.* 2014, Seeley *et al.* 2007, Urrila *et al.* 2017). The paired correlation between the time series of all ROIs was calculated later. It contained a total of $q=\binom{14}{2}$ pairs. Table-1 presents the list of ROIs.

Statistical Analysis

The sample of N containing 26 individuals with a network containing p=14 ROIs or a p-variate time series in each individual was considered. Sample correlations between marginal time series in each ROI were calculated for determining the intensity of the FC network. With $q=\binom{p}{2}$ ROI pair for each individual, the FC network was estimated according to the sample

Tab. 1. ROIs and Their Numbers in Study

Number	Region of interest
1	Angular gyrus
2	Anterior cingulate
3	Cingulate gyrus
4	Fastigium
5	Fusiform gyrus
6	Cerebellar lingual
7	Cerebellar tonsil
8	Parahippocampal gyrus
9	Thalamus
10	Posterior cingulate
11	Insula
12	Lingual gyrus
13	Postcentral gyrus
14	Lentiform nucleus

correlation between q pair ROIs of N subject and then was compared among groups. The $Y=(r_{11},\ldots, r_{q1},r_{12},\ldots,r_{q2},r_{1N},\ldots,r_{qN})$ vector is the correlation coefficients of accumulated sample for each individual and the ε with the mean vector 0 and the covariance matrix Σ introduces the within-subject co-variability as the first type error statement of the model so that $\varepsilon_j=(\varepsilon_{1j},\ldots,\varepsilon_{qj})\sim N(o,\Sigma_j)$. The design matrix X is N_{q^*q}, and r_{ij} is i-th sample correlation coefficient in the j-th individual. The second error phrase ψ, assuming to be normal with the mean vector 0 and the covariance matrix Ψ controls heterogeneity of individuals so that $\psi_j=(\psi_{1j},\ldots,\psi_{qj})\sim N(o,\Psi_o)$. Consequently, the model is defined as follows:

$$Y=X\beta+\varepsilon+\psi$$

The parameters of interest here are vector β and matrices Σ and Ψ. It is assumed that the two expressions ε and ψ are independent of each other. Therefore, the covariance matrix is equal to:

$$Var\,(Y)=\Psi+\Sigma$$

Also, vector β shows the correlations matrix among ROIs within each individual. Therefore, Σ, β, and Ψ should be estimated. With these conditions, other details, and how to estimate the parameters are provided in the referencing article. In this paper, the FC networks test between the patient with narcolepsy disorder and the control group was performed using the variance components model (Fiecas *et al.* 2017).

Tab. 2. Results of the FC Test. Pairs of ROI among Patient Group Which Have Significant Difference in the FC Network.

ROIs	Difference in FC between groups	*P*-valve
Angular gyrus and cerebellar lingual	-0.070	0.047
Cingulate gyrus and cerebellar lingual	- 0.073	0.033
Cingulate gyrus and cerebellar tonsil	0.097	0.049
Cerebellar tonsil and thalamus	-0.038	0.045

Results

Results show that with q=91 pairs of ROI, the test at α level (which in this paper is regarded as α=0.05), four pairs of areas in the patient group have significant differences ($P\leq0.05$), with the decrease in intensity of the FC between three pairs of areas (area 1 and 6, region 3 and 6, regions 7 and 9), whereas in region 3 and 7 an increase in the FC was observed (Table-2). Furthermore, the matrix of correlations for all individuals, separately indicated for two groups, is shown in Figure-1. As can be seen, all correlations are positive and large. Furthermore, the results of the similarity or dissimilarity of the FC network in the patient and healthy group, which are performed using the variance component model, are shown in Figure-2. The vertical axis shows the estimated difference, while the horizontal axis is the p-value of tests to compare the

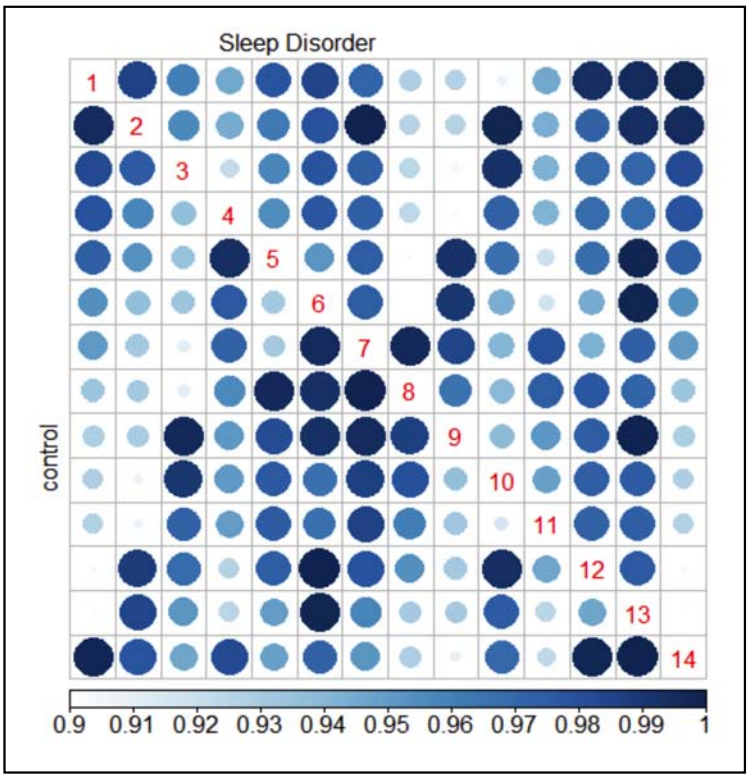

Fig. 1. The correlation matrix between ROIs for two groups: the upper triangle is within the correlation of patients, and the lower one is within the correlation of the control group.

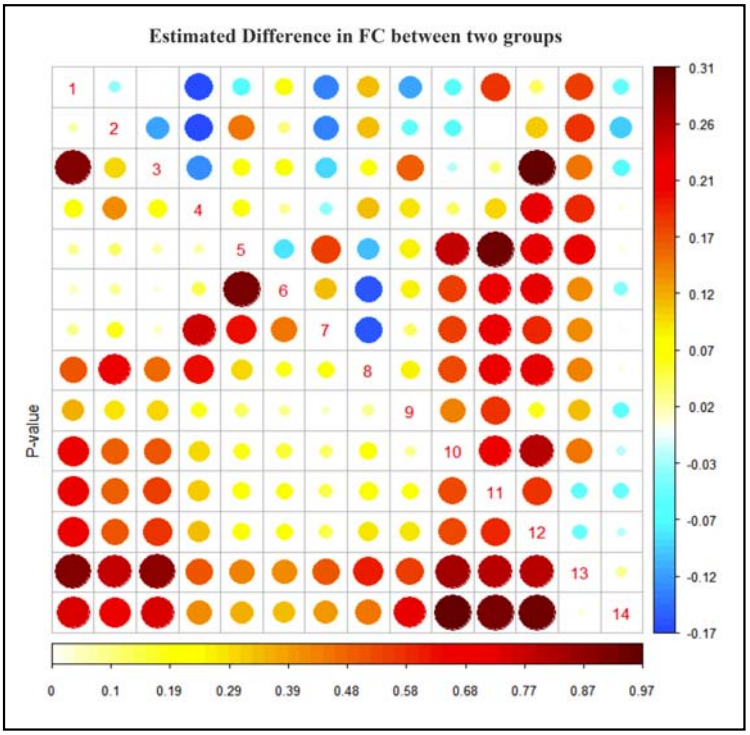

Fig. 2. The upper triangle is the estimated difference in FC for each pair of ROIs, and the lower triangle is the p-values of tests for no difference in FC between the two groups.

FC between the two groups. This figure confirms the findings in Table-2. Also, areas of the angular gyrus and cerebellar lingual, cingulate gyrus and cerebellar lingual, cerebellar tonsil and thalamus, cingulate gyrus and cerebellar tonsil with a p-value less than 0.05 are significant. Besides, there are other areas, such as cingulate gyrus and fusiform gyrus, fastigium and fusiform gyrus, cerebellar lingual and thalamus with p-value close to 0.05, which seems to signal a difference in the severity of the FC between the patient and the healthy groups.

Discussion

The present study investigated the difference and similarity of the FC network between the groups of patients with narcolepsy sleep disorder compared to healthy people. This study was conducted using the proposed model of Fiecas *et al.* The variance components model prototypes time-autocorrelation in data and heterogeneity among individuals as two components of error, which are neglected in other studies; hence, this model has higher statistical power than previous approaches in the FC studies. The present study manifested that the difference between the FC network in the patient and healthy groups in the four pairs of areas was significant. A decrease was observed in the patient group, between angular gyrus and cerebellar lingual, cingulate gyrus and cerebellar lingual, cerebellar tonsil and thalamus in the FC severity and a slight increase in spotted in FC in the cingulate gyrus and cerebellar tonsil regions. Other studies that investigate functional developmental changes in patients with the sleep disorder include the study of chronic insomnia disorder with fMRI resting data by graph theory analysis where dorsal attention network and sensory-motor network in these patients showed altered nodal centralities (Li *et al.* 2018). Other investigations in this area include the study of brain activity in chronic insomnia disorder during a work memory task, which was performed using a two-sample t-test and showed more activity in the right lateral inferior frontal cortex with the right superior temporal pole shown in the patient group (Son *et al.* 2018). Likewise, the study of the FC in short sleepers with or without dysfunction, using a parcellation covering the cortical, subcortical and cerebellar gray matter at 5mm resolution, has manifested that short sleepers without dysfunction have increased in the FC between sensory cortices and bilateral amygdala and hippocampus (Curtis *et al.* 2016). In the study of Fiecas *et al.* the similarity or disparity of the FC between dyslexia and healthy subjects was studied, with the results being consistent with the present study. The variance components model, as autocorrelation of time series and heterogeneity of individuals, inserted into the model, has more statistical power in the analysis, but since it uses all the time course, it requires more computations. It should be added that the flexibility of the model increases the computational challenge, and in practice, the use of more ROIs requires modifications in the model.

Conclusion

Brain imaging in the resting state is a useful approach to assessing the structural and functional correlations of sleep disorders, as well as recognizing the brain

outcomes of various therapeutic approaches. Hence, modern imaging techniques provide a valuable tool for gaining insights into the potential pathophysiological mechanisms of sleep disorders in adult individuals.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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