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Original Article

Effect of Modafinil on functional connectivity in healthy young people using resting-state fMRI data

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Abstract: Background: Examining the differences in the Functional Connectivity (FC) network while using Functional Magnetic Resonance Imaging (fMRI) between two groups can expand the understanding of neural processes and help diagnose and prevent neurological progression disorders. The present study evaluated the Modafinil effect on the FC of brain Regions of Interest (ROI) among healthy young individuals between the Modafinil and placebo groups. Method: The data used in this study were downloaded from the open fMRI site and analyzed after preprocessing. Data included brain scan images of 26 healthy young men with no history of neurological disorders. These people are divided into two groups of drugs and a placebo. The drug group was given 100 mg of Modafinil, and the placebo group was assigned the same dose. Data were analyzed using a longitudinal variance component model. Result: After taking the drug and placebo by the two groups, the study of the difference between FC in the drug and placebo group and the baseline effect showed a statistically significant difference in one pair of ROIs. Also, in examining the difference between FC in the drug and placebo groups of the longitudinal trend, there was a statistically significant difference between 5 pairs of ROIs. Conclusion: After taking Modafinil and placebo, it was observed that FC in most areas in the drug group increased compared to the placebo group, indicating Modafinil has cognitive enhancement properties and has a role in visual, auditory, memory learning, and self-awareness functions and enhances these functions.

Keywords: fMRI, functional connectivity, longitudinal model of variance component, modafinil, narcolepsy, cognitive dysfunction

Introduction

Today, Functional Connectivity (FC) is an appropriate approach to studying the human brain structure and studying neural networks' function [1-4]. FC in fMRI studies is determined using correlation coefficients. This method is based on the temporal correlation of the blood oxygen level-dependent (BOLD) signal in different areas of the brain or neighboring vaccines. The primary purpose of this method is to identify areas and vaccines in the brain that have similar time correlations [5]. One type of analysis to examine functional correlations in Functional Magnetic Resonance Imaging (fMRI) data is the use of resting-state [6]. Resting fMRI was primarily used by Biswal et al. [7]. Resting fMRI has been widely used during recent years by neuroscientists. This form of imaging is used to understand the human brain's function in healthy and sick people [8]. Using fMRI at rest state requires no training, and imaging is more comfortable among the elderly, children, and mentally ill patients [9].

fMRI also models resting intrinsic brain connectivity based on task-based brain activity formation [10]. Narcolepsy is a neurological disorder that disrupts sleep-wake cycles, and most people with depression or drug use develop the disease [11, 12]. Modafinil was first used in 1997 for the treatment of narcolepsy. Modafinil affects sub-regional cerebral cortices such as the Thalamus, Hypothalamus, and Amygdala. These sub-cortices cause people to wake up [13]. Modafinil is used off-label to treat cogni-

tive dysfunction and psychiatric disorders such as schizophrenia [14-16]. Modafinil's use in healthy young subjects has caused a statistically significant FC difference between FPC and DAN [15]. This drug has also increased FC in the brain areas of the putamen, left Para hippocampus, and left posterior Insula.

A study about Modafinil's effect on FC can help use this drug to treat cognitive disorders. Studies have shown that Modafinil increases healthy individuals' cognitive enhancement and fluid intelligence [16, 17]. Furthermore, this study investigated Modafinil's effect on FC between the Modafinil and placebo groups over time. The model introduced by Hart et al. was used to achieve the stated goal [18]. Numerous studies have shown differences in FC between two groups of subjects (e.g., the patient or placebo group and a comparable control group) [19, 20]. Recently, several studies have examined fMRI data longitudinally [21, 22]. In 2018, Hart et al. introduced a longitudinal model based on variance components. This model divides the error term into three parts: co-variability from the heterogeneity, temporal autocorrelation in fMRI data, and within-subject covariation from the longitudinal design [18]. Two general basic assumptions introduced by Hart et al. have been investigated in the present study: the group difference in the baseline FC and the group difference in the longitudinal trend in FC. The meaning of FC group difference in the baseline is to evaluate the difference in functional connectivity between the two drug and placebo groups at baseline. This assessment is a difference in the degree of correlation between the areas of interest in the two groups of drugs and placebo at the base time, i.e., the first scan taken from individuals. Also, the difference between FC and Longitudinal trend means that the difference in functional connectivity over time between the drug and placebo groups is evaluated. This assessment is also a difference in the degree of correlation between areas of interest in the two groups of drugs and placebo over time.

Material and method

Data

The present study data were downloaded from the accessible Open fMRI site. The access number of this data is on-site ds000133. The data used in this study are data from a prospective clinical trial conducted in 2012. The type of clinical trial was interventional. All participants in the study were male. Right-handedness and left-handedness were also assessed, and all right-handed individuals were selected to minimize differences between participants in the groups. All men participating in the study were young, and the minimum age of participants was 25 years, and the maximum age of participants was 35 years. All had the same level of education (13 years of study experience). These individuals were randomly divided into two parallel groups. Inclusion criteria were healthy people and no history of neurological diseases, including epilepsy. Participants in the study also lacked high blood pressure and heart disorders. These people also had no history of alcohol consumption.

Individuals with speech disorders were excluded from the study. Also, people who had a history of psychotropic drugs were excluded from the study. Another exclusion criterion was severe hypersensitivity to Modafinil, in which none of the subjects showed severe hypersensitivity. The data was used in this study, approved by the ethics committee of the University of Chieti (PROT 2008/09 COET on 14/10/2009), and conducted following the Helsinki Declaration. Written consent was also obtained from all participants in the study.

Three sets of brain scans were taken before taking the drug and placebo. After the initial scan, subjects in the drug group were given 100 mg of Modafinil, and issues in the placebo group were given the same proportion of placebo. After taking the drug and placebo, three brain scans were taken by the people in the two groups. They were asked to stare at the gray dot on the LCD in the scanner through a mirror above their heads and rest during the imaging. The Philips Achieva 3T performed functional imaging of the BOLD signal [15].

All data preprocessing steps were performed by FSL software version 6.0.1. SPM package version 12 was used in MATLAB 2019 software; the WFU-pick atlas module was extracted using previous Region of Interest (ROI) studies. The IBASPM ATLAS 71 was used to extract the regions, which divides the brain into 71 ROIs. Using previous studies, areas affected by

Table 1. Names of interest areas extracted from the IBASPM ATLAS 71 atlas

Favorite area name	Favorite area number
Cingulate Region Left (CRL)	1
Cingulate Region Right (CRR)	2
Inferior Frontal Gyrus Left (IFGL)	3
Inferior Frontal Gyrus Right (IFGR)	4
Insula Left (IL)	5
Insula Right (IR)	6
Putamen Left (PL)	7
Putamen Right (PR)	8
Superior Frontal Gyrus Left (SFGL)	9
Superior Frontal Gyrus Right (SFGR)	10

Modafinil were selected. Ten ROIs were used in this study, with the names and numbers of regions shown in **Table 1**. According to the number of interest areas used in this study, 45 comparisons were performed.

Statistical analysis

A longitudinal model of variance components was used to evaluate Modafinil's effect on different brain regions between the drug and placebo groups. This model's key element is the error term's variance structure, which models the automatic correlation of data from fMRI time series(Σ), covariance variance due to heterogeneity, and covariance variance due to differences in each individual over time(Ψ). A linear model with parameters β_0 and β_1 was used to investigate the group difference in the FC base effect and the group difference in the FC longitudinal trend. In fact, β_0 indicates the baseline effect of FC in the drug and placebo groups. In other words, β_0 specifies the difference in functional relationships between the two groups at the base time, while β_1 shows the longitudinal trend of FC in the drug and placebo groups. Therefore, β_1 determines the difference in FC between the two groups over time. The longitudinal model used in this study is as follows:

$$y = X\beta + \varepsilon$$

$$var(\varepsilon) = \Sigma + \Psi$$

Hart et al. Estimated Σ in the first step. Estimation Σ was performed using the method introduced by Roy in 1989 [23]. After that, they estimated β and Ψ by the GLS approach. Σ shows the internal within-visit variance and the automatic correlation in the fMRI time series. Ψ also presents the covariance variance caused by individuals' heterogeneity and the interpersonal changes due to the longitudinal pattern. The Ψ element is divided into two components, Ψ_0 and Ψ_1. The Ψ_0 models within-visit variability, and the Ψ_1 represents a within-subject over time in the model. Different structures for Ψ_0, Ψ_1 and Σ can be considered to obtain parameter estimation and increase the model efficiency. Changing the different structures for Ψ_0, Ψ_1 and Σ allows the model to be more flexible assumptions for variance. These assumptions apply to most GLS models. In the present study, the compound symmetry structure for the components Ψ_0 and Ψ_1 and for Σ is considered as an unstructured model [18]. P is the ROI defined in this model, and Q is the number of pairs of ROIs compared. Also, y is the average of signal BOLD in each ROI, and X is the design matrix. In this model, if we consider β as a vector with the length of 2Q, the first Q element shows β_0 and the last Q element composes β_1. Given that 10 ROIs were selected in the present study, the number of pairs of comparable areas is obtained from the following form of $\binom{10}{2}$. Hence, Q = 45 and 2Q = 90. After estimating β, the first 45 elements constitute β_0 and the last 45 elements build β_1. Complete information on how to estimate the parameters can be found in the article by Hart et al. [18].

Results

Pair ROI correlation diagrams to evaluate the main and interaction effects before taking Modafinil

As mentioned, the longitudinal model of the components of variance pursues two main objectives. These objectives aim to investigate the group differences in the FC base effect and the group differences in the FC longitudinal trend. The basal product and longitudinal trend of FC were calculated in the drug group of Modafinil and placebo. The primary purpose of the introduced longitudinal model is to show the difference in FC at baseline and the difference in FC over time between the two groups of drug and placebo. In the present study, β_{CN} and $\beta_{Modafinil}$ Coefficients were used to show the size of functional relationships in the extracted regions in this study. The suffix CN is for the pla-

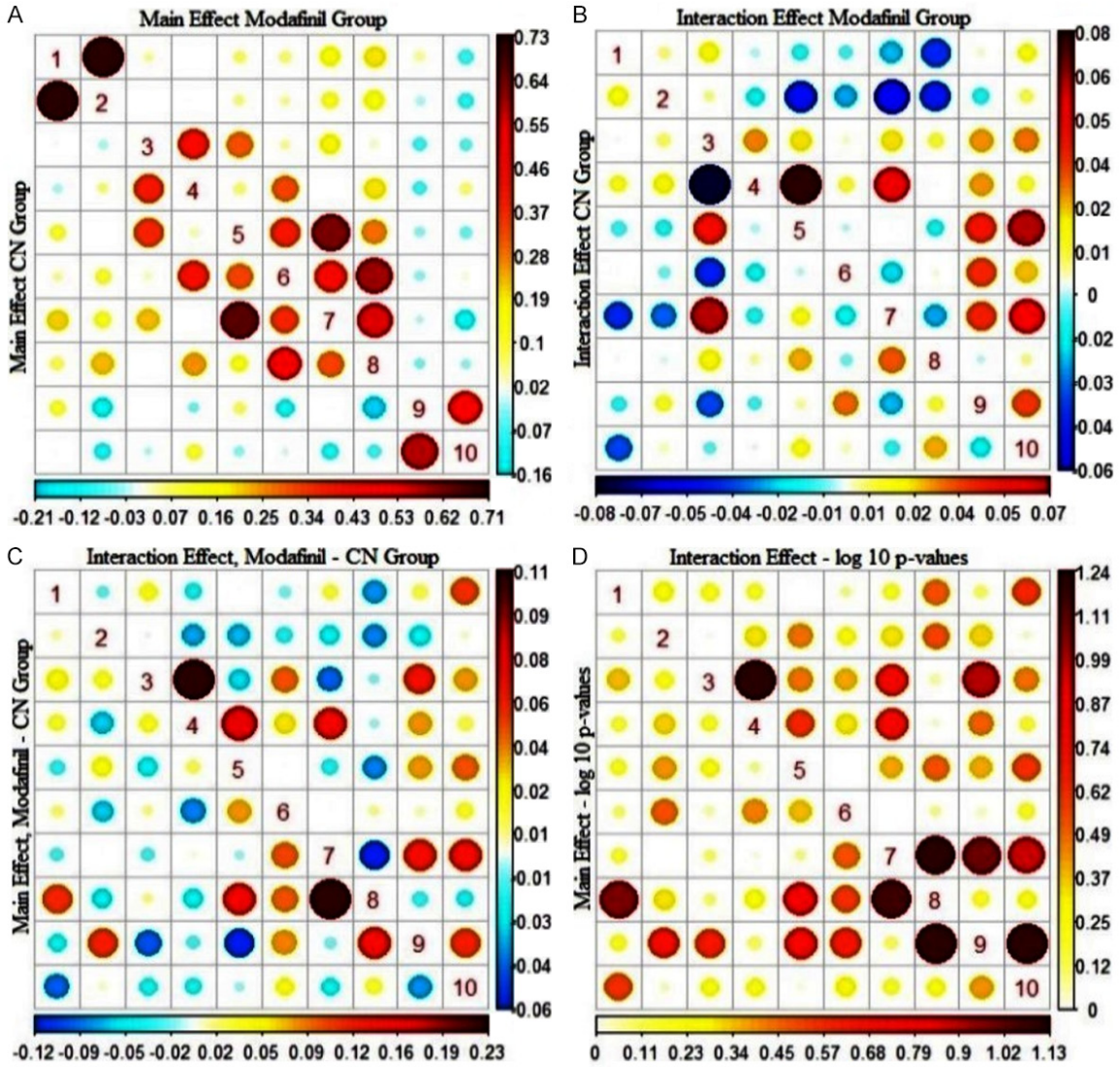

Figure 1. Pair ROI correlation diagrams to evaluate the main and interaction effects before taking Modafinil. A. Estimating FC baseline effects in the pair of ROIs before drug and placebo administration (the lower triangular chart shows the placebo group and the upper triangular chart shows Modafinil group). B. Estimation of longitudinal effects of FC in the pair of ROIs before drug and placebo (the lower triangular chart shows the placebo group, and the upper triangular chart shows the Modafinil group). C. Differences between the coefficients of the Modafinil group and the placebo group before taking the drug and the placebo in the FC network study (The upper triangular diagram shows the longitudinal rate of difference between the two groups in the FC network and the lower triangular diagram shows the base effect of the two groups in the FC network). D. -log10 *p*-values for comparing pairs of areas before drug and placebo at the longitudinal rate and baseline effect of FC (Triangular diagram above shows the -log10 *p*-value for the difference in the longitudinal momentum of the pair of regions in FC).

cebo group, and Modafinil is for the drug group. Fitting the longitudinal model of the components of variance to the images before using the drug and placebo showed no statistically significant difference in the baseline and longitudinal trend of FC between the two groups. **Figure 1A-D** shows diagrams of baseline efficacy, FC longitudinal trend, differences in estimated coefficients of the Modafinil and placebo groups, and -log10 *p*-value for the differences in the Modafinil and placebo groups' coefficients before the drug placebo use. -log10 *p*-values were used to make the *p*-value diagram more intuitive.

Differences in the estimation of coefficients and p-values after taking Modafinil

The results of fitting the longitudinal model of variance components to investigate the group

Table 2. Differences in the estimation of coefficients and *p*-values obtained by comparing pairs of ROIs after drug and placebo

Pairs of areas of interest	Differences in estimating the pairs of regions	*p*-values
1, 2	0.023	0.182
1, 3	0.118	0.004*
1, 4	0.098	0.036*
1, 5	0.017	0.577
1, 6	0.011	0.721
1, 7	0.029	0.269
1, 8	0.035	0.269
1, 9	-0.032	0.355
1, 10	-0.027	0.539
2, 3	0.104	0.014*
2, 4	0.077	0.125
2, 5	0.046	0.135
2, 6	0.028	0.356
2, 7	0.019	0.572
2, 8	0.023	0.415
2, 9	-0.030	0.442
2, 10	-0.038	0.361
3, 4	0.022	0.601
3, 5	0.003	0.945
3, 6	0.029	0.492
3, 7	0.004	0.908
3, 8	-0.023	0.547
3, 9	0.044	0.265
3, 10	0.072	0.014*
4, 5	-0.011	0.729
4, 6	-0.023	0.492
4, 7	0.011	0.696
4, 8	-0.053	0.146
4, 9	0.073	0.050
4, 10	0.033	0.338
5, 6	-0.023	0.493
5, 7	-0.019	0.325
5, 8	0.001	0.979
5, 9	0.018	0.681
5, 10	0.077	0.028*
6, 7	0.039	0.111
6, 8	-0.009	0.697
6, 9	0.005	0.898
6, 10	0.035	0.357
7, 8	0.021	0.489
7, 9	0.005	0.906
7, 10	0.053	0.144
8, 9	0.005	0.905
8, 10	0.026	0.503
9, 10	0.045	0.201

An '*' indicated the values were significantly different between the pairs of regions.

difference in FC's basal effect after using the drug and placebo showed a statistically significant difference in a pair brain region. In addition, the results showed a statistically significant difference in baseline FC effect between putamen right and inferior frontal gyrus right. When examining group differences in FC's longitudinal course following the use of the drug and placebo, it was found that after taking Modafinil and placebo, FC in many areas in the group consuming Modafinil compared to the placebo group increased. A statistically significant difference was observed in functional connectivity between the five pairs of CRL and IFGL, CRL and IFGR, a CRR and IFGL, IFGL, and SFGR, IL and SFGR. **Table 2** was obtained by comparing the pairs of ROIs and calculating the difference in estimating the two groups' coefficients in the FC longitudinal process. The results show that out of 45 pairs of ROIs in 34 pairs of regions, FC in the Modafinil group increased compared to the placebo group. The results also show that in the areas of interest (1 and 3), (1 and 4), (2 and 3), (3 and 10), and (5 and 10), there was a statistically significant difference between the group of Modafinil and placebo in the longitudinal trend.

Pair ROI correlation diagrams to evaluate the main and interaction effects after taking Modafinil

Figure 2A-D is designed to show the baseline effect of FC in the two groups of Modafinil and placebo, respectively, the longitudinal trend of FC in the two groups of Modafinil and placebo, the difference between the estimated coefficients in the baseline, and the longitudinal movement of FC in the two groups of Modafinil and placebo and to showcase the -log10 *p*-value of group differences due to FC baseline and FC longitudinal trend in the two groups of Modafinil and placebo after drug and placebo.

Figure 2A shows the baseline effects of FC in the two groups. The FC in the two groups of Modafinil and placebo is similar in most areas. For instance, functional connectivity due to FC baseline in areas 1 and 2 in the two groups of drugs and placebo is more than in other areas. Moreover, functional connections due to FC baseline in pairs (5 and 7), (6 and 8), (9 and 10), and (7 and 8) 8 in the drug and placebo groups are more than other points. **Figure 2B** shows the estimation of FC's longitudinal

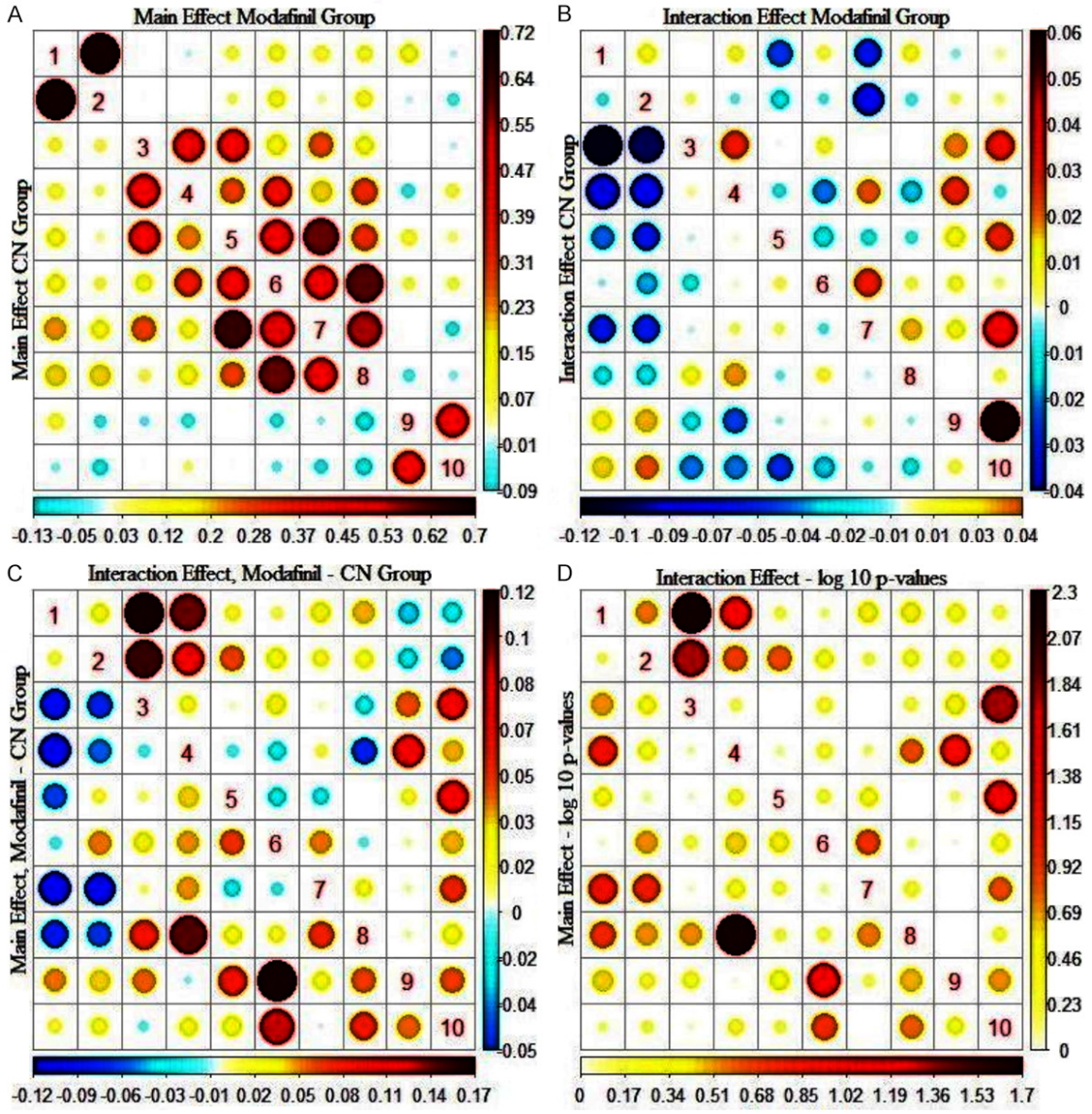

Figure 2. Pair ROI correlation diagrams to evaluate the main and interaction effects after taking Modafinil. A. The estimation of the basal effects of FC in the pair of ROIs after drug and placebo (the lower triangular diagram shows the placebo group, and the upper triangular graph shows the Modafinil group). B. Estimates of the longitudinal effects of FC in the pair of ROIs after drug and placebo (the lower triangular diagram shows the placebo group, and the upper triangular graph shows the Modafinil group). C. Differences between the coefficients of the Modafinil group and the placebo group after taking the drug and placebo (The upper triangular diagram shows the longitudinal rate of difference between the two groups in the FC network, and the lower triangular graph shows the baseline effect of the two groups in the FC network). D. The -log10 *p*-values for comparing the pair of regions in the longitudinal rate and the basal effect of FC after drug and placebo (Triangle diagram shows the -log10 *p*-values for the difference in the base and interaction affect the pair of FC regions).

effects on pairs of ROIs. For example, it was demonstrated that FC overtime was more remarkable in regions 9 and 10 and the drug group than elsewhere. It was also observed in the placebo group that FC over time between areas (3 and 1), (3 and 2), (4 and 1), (4 and 2) is less than other areas. In **Figure 2D**, it is evident that -log10 *p*-value in the primary effect of FC, in the pair of regions 8 and 4 is more prominent than other regions, indicating a statistically significant difference in FC and the immediate impact between the two groups of

Modafinil and placebo. Also, in examining the longitudinal trend of FC according to the figure, it is clear that the pairs of areas (1 and 3), (1 and 4), (2 and 3), (3 and 10), and (5 and 10) have more prominent points than other areas; this indicates a statistically significant difference in the longitudinal course of FC between the two groups of Modafinil and placebo. **Figure 2C** shows the difference between the estimated coefficients of the Modafinil and the placebo groups in the FC network study. It is clear from the FC that has within most ROIs and longitudinal trends since reddish spots, indicating an increase in functional connectivity, are more common. For example, the difference between the drug and placebo groups' coefficients shows that FC has increased over time between the two groups and in pairs of regions (1 and 3), (1 and 4), (2 and 3), (2 and 4), as well as regions (5 and 10). Moreover, for example, in the study of the primary effect of FC, it is observed that the pairs of regions (8 and 4), (9 and 6), (10 and 6) experienced an increase in functional connectivity.

Discussion

The present study's primary purpose was to apply a longitudinal model in the FC of resting fMRI neuroimaging data. The data used in this study were downloaded from the open fMRI site with access number ds000133 and analyzed after preprocessing. The basic requirements for implementing the longitudinal model introduced in the present study were individuals' resting state and dividing individuals into two groups. The results of fitting the longitudinal model to the data manifested the statistically significant difference in FC between the putamen right and inferior frontal gyrus right areas after drug and placebo to investigate the differences in the FC network's primary effect in the two groups. Furthermore, in the study of FC's longitudinal trend between the two groups of drugs and placebo after the intervention, it was shown that the FC network is cingulate between 5 pairs of CRL and IFGL, CRL and IFGR area CRR and IFGL, IFGL, and SFGR, IL, and SFGR. After taking Modafinil, it was concluded that FC in the five pairs of the mentioned regions in the Modafinil group is more than the placebo group.

The present study concluded that Modafinil increases functional communication in the CRL and IFGL, CRL and IFGR regions, and CRR and IFGL. These areas directly affect emotional formation and processing, memory, learning, speech and language processing, and executive function. The data used in the present study were data analyzed by Esposito et al. in 2013 [15]. In a study by Esposito et al., it was concluded that Modafinil increases functional communication in areas of the brain that affect fluid intelligence. The main difference between the present study and Esposito et al. is the longitudinal model's use. In the study of Esposito et al., Simple statistical methods such as independent t-test and one-way analysis of variance and repeated measures design were used. While in the present study, a new longitudinal model was fitted to the data, the simulation results of this model have shown that it can model the differences in functional relationships in two different groups of people with fMRI images. Another fundamental difference in the present study from that of Esposito et al. is that new areas were identified that were directly affected by the drug modafinil and increased the function of these areas. This study clearly shows that functional communication in the CRL and IFGL, CRL and IFGR regions, and CRR and IFGL, in the modafinil group increased compared to the placebo group, which grew functions such as memory and speech.

The present study's examination of brain regions showed that Modafinil increased functional associations in IFGL and SFGR regions and IL and SFGR. These areas are also directly affected by working memory and survival-related functions such as taste and visceral sensation. Cera et al. examined the effects of Modafinil on FC in sub-regional regions of the brain [16]. The main area used in this study was Insula. Cera et al. showed that functional behavioral differences were observed in the front and back of Insula in the Modafinil group. Also, different FC patterns were observed in the internal nodes of the anterior right part of the Insula in the modafinil group. This study (Cera et al.) revealed that FC increased in the putamen, left Para hippocampus, and left posterior Insula after Modafinil administration. In the study of Cera et al., more straightforward statistical methods were used again compared with the present study. Both studies have shown that Modafinil affects Insula and its

functions in this area. The essential function of the Insula is the survival function of the taste buds. The present study also found that working memory, learning, and emotion increased in the group that took Modafinil.

A 2007 study by Wang et al. examined the FC network of the two groups of people [24]. The model introduced in the study of Wang et al. was a simple linear model. The method used in the present study models the interpersonal and intrapersonal changes and autocorrelation resulting from the time series of fMRI data also presents valid inference on group differences in the baseline FC network and change in FC over time.

In 2018, Staffaroni et al. conducted a longitudinal study of DMN connections. Staffaroni et al. analyzed the DMN network instead of the FC network in the study. The longitudinal model introduced in the survey by Staffaroni et al. was a repeated measure design. The model's flaw used in Staffaroni et al. was using single network connectivity, while network pair connections were a better choice. Furthermore, the longitudinal model used in the present study examined the difference between FC in the two groups. Therefore, the studied brain networks and the model introduced in the two studies differed.

Conclusion

Using the longitudinal model of variance component increases the model's power to detect the FC difference between two groups with more reliable results. Therefore, this study's clinical outcomes are more reliable than similar studies since the used longitudinal model analyzes the functional connections between different brain areas with more power.

Finally, the results revealed a difference in FC, between 5 ROI, after taking Modafinil and placebo. This difference was also statistically significant, and FC increased in the Modafinil group compared to placebo. Each of these areas performs a specific function. For example, the brain areas of the Insula and inferior frontal gyrus make up humans' visual, auditory, and speech functions. The cingulate and putamen areas of the brain affect the learning performance of individuals or, in other words, are responsible for enhancing learning in humans. The superior frontal gyrus also involves people's self-awareness. Based on the above, it can be concluded that Modafinil has a role in visual, auditory, speech, memory learning, and self-awareness functions and has increased these functions. There was also a statistically significant difference between the different brain regions due to the basal effect of FC. These results manifest that FC enhances cognitive function in healthy young people.

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Disclosure of conflict of interest

None.

Abbreviations

FPC, Fronto Parietal Control network; DAN, Dorsal Attention Networku.

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