Original Article

Investigating the Effect of Modafinil on Marked Brain Regions' Functional Connectivity While Resting in Young, Healthy Individuals, Using Variance Component Longitudinal Model

Keyvan Olazadeh[1], Nasrin Borumndnia[2], Hamid Alavi Majd [*,1]

[1]Department of Biostatistics, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Urology and Nephrology Research Centre, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Introduction: In recent years, investigating the differences in Functional Connectivity (FC) network in different brain regions in Functional Magnetic Resonance Imagining (fMRI) has appealed to neurological researchers. Examining the functional connectivity differences between two groups can assist in improving neurological disorders cure. The present study explores the differences in functional connectivity between two groups, one using Modafinil and the other placebo, as to consider the impact of this medicine, concerning functional connectivity of regions of interests among young, healthy people.

Materials and Methods: Data was downloaded from website "Open fMRI." Downloaded data included 26 young, healthy men with no history of mental disease. They are divided into two groups of 13. The first group received 100 mgr Modafinil, and the second group 100mgr placebo. Three scans were taken from each group during the time. The data were analyzed through a longitudinal model, using a variance component.

Results: Exploring the functional connectivity difference between the two groups, using intervention and placebo in the baseline effect did not show a significant statistical difference, but investigating the functional connectivity difference between the two groups in longitudinal trends showed a significant statistical difference in Inter-Hemispheric and Right- Brainstem.

Conclusion: After statistical analysis over applying a longitudinal model using a variance component, it was observed that functional connectivity in most paired investigated regions in the group, using Modafinil comparing to the group using a placebo has decreased. According to the present study's findings, Modafinil did not increase functional connectivity in most investigated regions.

Keywords: fMRI, Functional Connectivity, Longitudinal Model of Variance Component, Modafinil

1. Introduction

Functional Magnetic Resonance Imaging(fMRI) in resting-state has attracted the attention of neurological researchers in recent years[1]. This imaging thoroughly investigates the cognitive brain disorders related to brain network topology changes[2]. This imaging method is used to diagnose mental disorders like schizophrenia and epilepsy[3, 4]. In resting-state, which Biswal and his colleagues first used, fMRI does not need MRI equipment and is useful in investigating and studying brain networks [5-8]. One of the brain networks, which is the focus of studies, is Functional Connectivity (FC). FMRI in

resting-state can assist in understanding and recognizing FC. FC can be used to assess the connections between brain areas and nervous systems' function [9-12]. Cognitive control is a brain function that affects emotional and mental systems[13, 14]. When this brain operation malfunctions, it causes neurological disorders in the brain, such as attention deficit, hyperactivity disorder, addiction, and depression [15-17]. To cure them have side-effects like dynamic systems damage[18]. The evidence has shown that psycho-stimulants can affect young, healthy individuals' cognitive controls and enhance the mentioned brain's function[19, 20]. Modafinil, used to treat narcolepsy, is one of the medicines that increase young, healthy people's cognitive control and has fewer side effects than other drugs [21]. This medicine raises dopamine, glutamate, additionally enhancing FC among brain regions[22, 23]. Earlier studies proved that Modafinil also increases FC in healthy people who suffer from sleeping disorders or insomnia and patients with various mental problems[24]. This study investigates the effect of Modafinil on some Regions of Interest (ROI) FC in the brain across time.

The longitudinal model introduced by Hart and his colleagues' study was applied[25]. Using longitudinal data in fMRI studies has gained neurological researchers' attention[26, 27]. Various studies have explored the FC difference between two groups of people in fMRI[28, 29]. In 2018, Hart et al. introduced a longitudinal model that differed from the previously introduced longitudinal models in the error component structure. The introduced model by Hart and his colleagues divided the faulty component into coverability arising from the heterogeneity across subjects, within-subject covariation coming from the longitudinal and temporal autocorrelation in the fMRI set of data. This model proposed two plausible hypotheses: group difference in FC baseline effect and group difference in FC longitudinal trend[25].

2. Materials and Methods
2.1 Data

The data applied in the present study was downloaded from an available website, "Open fMRI." The accessibility number of the mentioned site is ds000133. The downloaded data includes 26 young, healthy men aged 25-35 without any mental disease history. Healthy young people were selected for the purpose of evaluating the effect of Modafinil on increasing or decreasing FC in individuals. Written testimonials were taken from the participants, and then they were randomly divided into two groups of thirteen. Three sets of brain scans before and after using Modafinil and placebo were taken. Next, the first group received 100mgr Modafinil and the second group 100mgr placebo, similar to Modafinil. After using Modafinil and placebo in both groups, three sets of brain scans were retaken. During the procedure, scanning participants were required to stare at a mirror above their heads and look at the mirror's grey point while in a resting state. FC was performed by Philips Achieve 3T information relevant to the imaging. The applied apparatus is presented below:

(TE 35 Ms, matrix size 64664, FOV 256 mm, in-plane voxel size 464 mm, flip angle 75u, slice thickness 4 mm, and no gaps. sagittal, matrix 2566256, FOV 256 mm, cut thickness 1 mm, no holes, in-plane voxel size one mm61 mm, flip angle 12u, TR= 9.7 Ms and TE= 4 Ms.)

The pre-processing was done using FSL software. The FSL version applied in the present study was 6.0.1. After data pre-processing, the data was inserted in MATLAB software 2019, SPM package, version 12, module WFU-pick atlas was used to extract the ROI. In the WFU-pick atlas, Atlas TD Hemispheres was used. The mentioned atlas divided the whole brain volume into seven ROI. Regarding the seven brain regions selected, 21 comparisons between paired regions were

applicable. The name and numbers of extracted areas are presented in table 1.

Table 1. ROIs and their number set

Number	Region OF Interest
1	Inter-Hemispheric
2	Left Brainstem
3	Left Cerebellum
4	Left Cerebrum
5	Right Brainstem
6	Right Cerebellum
7	Right Cerebrum

2.2 Statistical analysis

Inference based on a longitudinal model using a variance component

To explore the effect of Modafinil on FC in various brain regions between the intervention group and the placebo group, a longitudinal model using a variance component was applied. This model's main element is the variance structure divided into coverability arising from the heterogeneity across the subject, within-subject, within-subject covariation coming from the longitudinal design, and coverability arising from autocorrelation in the fMRI set of data. Using this model, group difference in FC baseline effect and FC longitudinal process was analyzed. The model used was a linear model with β_0 and β_1 parameter. In fact, β_0 indicates baseline effect in the intervention and placebo group. In other words, β_0 shows FC difference in base time between intervention and placebo groups. β_1 shows FC longitudinal process in intervention and placebo groups. In another word, β_1 indicates an FC difference between the two groups during the time. The longitudinal model used in this study is as the follows:

$$y = X\beta + \varepsilon$$
$$var(\varepsilon) = \Sigma + \Psi$$

In this model, Hart et al. initially estimated Σ by Roy's approach in 1989[30]. After that, they estimated β and Ψ by the GLS approach. Also, y is average of signal blood oxygen level dependent (BOLD) in each ROI and X is design matrix. If we imagine β as a vector with the length of 2Q, the first Q element composes β_0 and the last Q element composes β_1. Taking into consideration that in the present study, seven ROI were selected, the number of comparable paired areas is gained through $\binom{7}{2}$, therefore, Q=21 and 2Q=42. After β estimation, the 21st first element is β_0 and 21st last element is β_1. Σ is calculated within-visit variance and autocorrelation in the fMRI time series. Σ is blocked diagonal where each Q×Q block, Σij, accounts for the within-visit variance present in visit j for subject i for the Q pairs of ROIs. Ψ calculates within-subject covariation resulting from heterogeneity among people plus inter-personal changes arising from longitudinal design. In this model, P represents ROI, and Q represents the number of paired ROIs compared with each other. A complete description of the model and the method of estimating the parameters is stated in the article by Hart et al. [25].

3. Results

As mentioned above, the longitudinal model using a variance component considers two significant goals that are investigating group differences in the FC baseline effect and FC longitudinal process. The FC baseline effect and FC longitudinal process were explored in Modafinil and placebo groups to achieve these goals. In this study, to demonstrate the amount of FC in extracted regions, β_{CN} and $\beta_{Modafinil}$ the coefficient was employed. The prefix CN represents the placebo group, and Modafinil means the medicine group.

The longitudinal model's processing results, using a variance component before and after using intervention and placebo to explore group differences in FC baseline effect and longitudinal process between two groups

did not show a statistically significant difference in any paired-brain regions. Figure 1 and 2 demonstrate the diagrams for baseline effect, FC longitudinal process, differences in estimated coefficient in Modafinil and placebo group and -10 log p-value for difference coefficient of Modafinil and placebo before employing the medicine and placebo. -log 10 p-values were used to make the p-value diagram more intuitive. Figure1.a shows the FC basic estimate in Modafinil and the placebo group before the intervention. According to the correspondence spots and comparing the paired-ROI in both groups, it was observed that both groups are similar in terms of FC in the baseline effect. This is demonstrated in figure 1.b. Therefore, the similarity between the two groups in longitudinal FC between paired ROI is the same. According to the figure 2.b diagram and -10 log p-value, a statistically significant difference in the 95% certainty level between paired-regions in Modafinil and placebo before the intervention was not observed. Although circular spots related to comparing 1 and 7 paired regions to other locations are more chromatic than others, this difference is not significant statistically. Thus, on the whole, a statistically significant difference between Modafinil and placebo groups in elation with paired-regions FC before the intervention was not seen.
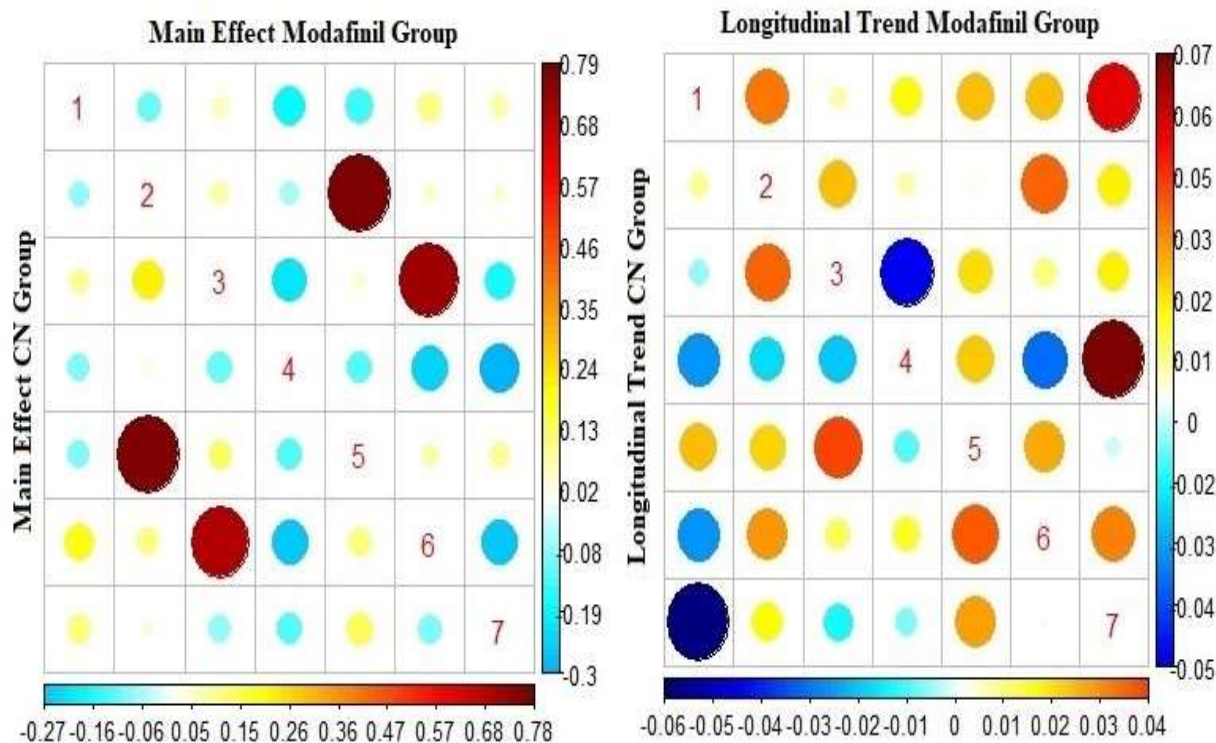

Figure.1.a

Figure.1.b

Figure 1.a shows FC estimation of baseline effect in paired ROI before using the Modafinil and placebo (the bottom triangular diagram of the placebo group and the top triangular of the Modafinil group). **Figure 1.b** shows FC estimation of longitudinal effect in paired ROI before applying the Modafinil and placebo (the bottom triangular diagram belongs to the placebo group. The top triangular map belongs to the Modafinil group).
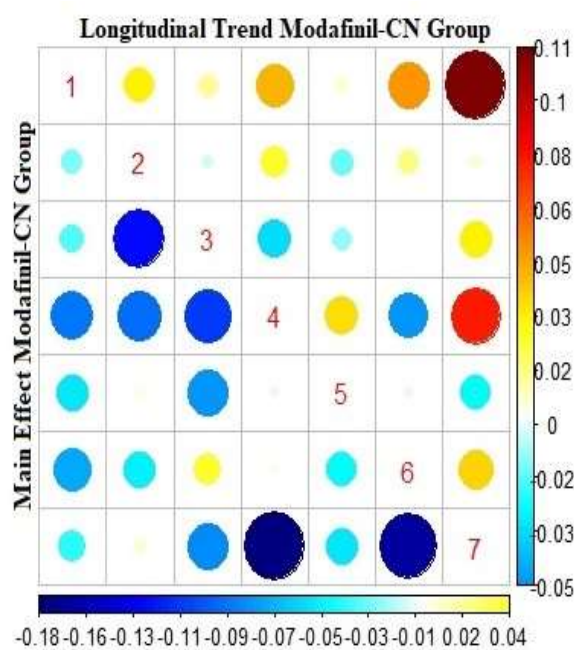
Archives of Advances in Biosciences is an open access article under the terms of the Creative Commons Attribution -NonCommercial 4.0 International License,
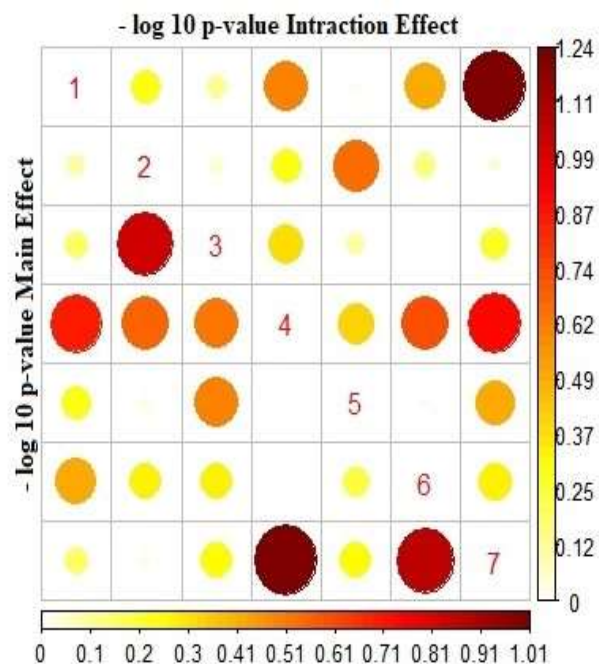
58

Figure 2.a

Figure 2.b

Figure 2.a shows the differences in coefficient of Modafinil and placebo groups before applying the Modafinil and placebo related to FC network investigation (the top triangular diagram demonstrates the longitudinal difference of both groups in FC network, and the bottom triangular one shows the baseline effect of both groups in FC network). **Figure 2.b** shows –log 10 p-values for comparing mentioned paired-regions before using the Modafinil and placebo in FC longitudinal and baseline effect (the bottom triangular diagram demonstrates –log 10 p-values for FC baseline effect difference of the paired regions. the top triangular diagram shows –log 10 p-values for longitudinal processing of the areas paired)

The results of processing the longitudinal model using a variance component after applying the Modafinil and placebo to explore the group difference in FC baseline effect did not show a statistically significant difference in any of the paired brain regions, which is an indicator of the inefficiency of Modafinil FC baseline effect on brain regions. During the investigation of group differences in FC longitudinal processing, it was observed that after applying Modafinil and placebo, FC in many areas in the group using Modafinil comparing to the group using placebo decreased. Comparing the paired-brain regions and calculating the differences in estimated coefficients between two groups in FC longitudinal processing, besides calculating the gained p-value of paired ROI comparison, table 2 results yield.

Table 2. Estimate coefficients and p-value to compare grouped differences in FC longitudinal rate after intervention

Number of pair ROI	β_{CN}	$\beta_{Modafinil}$	$\beta_{Modafinil} - \beta_{CN}$	p-value
1&2	0.063	-0.004	-0.068	0.159
1&3	0.094	0.002	-0.091	0.137
1&4	-0.004	-0.001	0.002	0.953
1&5	0.068	-0.018	-0.086	0.010*
1&6	0.091	0.009	-0.081	0.137
1&7	-0.010	0.047	0.058	0.132
2&3	0.028	0.010	-0.017	0.635
2&4	-0.050	-0.016	0.034	0.472
2&5	0.001	-0.004	-0.005	0.753
2&6	0.022	-0.014	-0.036	0.346
2&7	0.034	-0.001	-0.035	0.412
3&4	-0.021	-0.040	-0.018	0.680

3&5	0.027	0.013	-0.013	0.772
3&6	0.022	0.008	-0.013	0.537
3&7	0.043	-0.001	-0.045	0.252
4&5	-0.046	-0.009	0.036	0.410
4&6	-0.016	-0.060	-0.044	0.307
4&7	-0.007	0.049	0.056	0.267
5&6	0.007	-0.029	-0.036	0.431
5&7	0.039	0.003	-0.035	0.319
6&7	0.040	0.030	-0.009	0.818

The findings showed that FC in 16 out of 21 paired ROIs in the Modafinil group compared with the placebo group has decreased. The results also proved that a statistically significant difference in longitudinal FC processing was observed between the Modafinil and placebo groups in ROI numbers 1 and 5. So it can be said that after employing Modafinil, Inter-Hemispheric and Right-Brainstem had a significant difference in FC.

Figure 3 and 4 demonstrate FC baseline effect in both Modafinil and placebo group, differences in estimated coefficient in FC baseline effect and FC longitudinal processing in both Modafinil and placebo groups, plus -10log p-value in investigating FC baseline effect and FC longitudinal processing of the grouped differences in both Modafinil and placebo group.
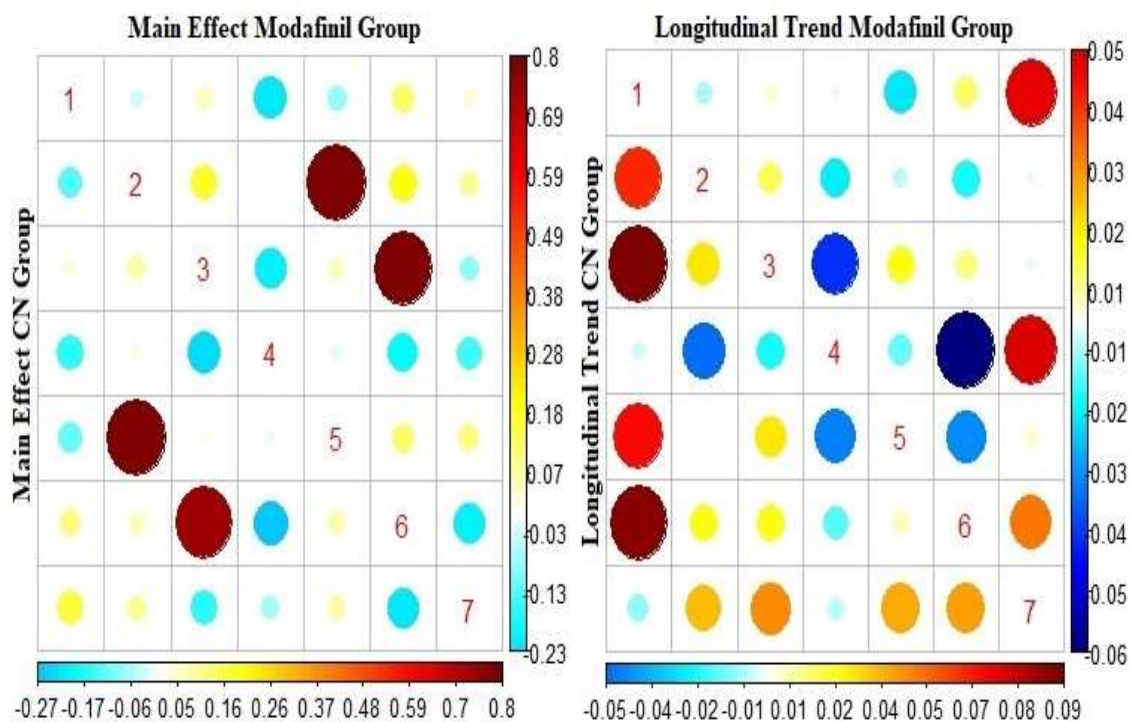

Figure 3.a   Figure 3.b

Figure 3.a shows FC baseline estimate effects in paired ROI after employing Modafinil and placebo (the bottom triangular diagram shows the placebo group, and the top triangular one shows the Modafinil group). **Figure 3.b** demonstrates FC longitudinal estimate effects in paired ROI after taking the Modafinil and placebo (the bottom triangular diagram shows the placebo group, and the top triangular graph shows the Modafinil group).
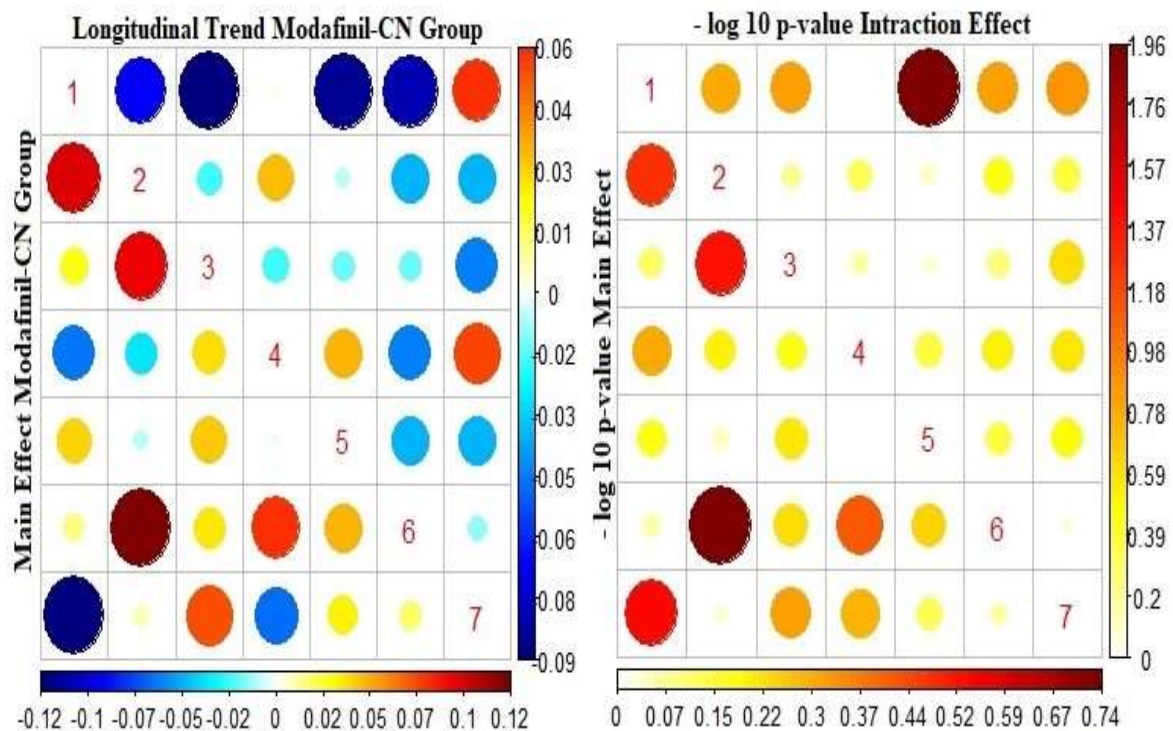
Figure 4.a

Figure 4.b

Figure 4.a demonstrates the Modafinil and placebo coefficient difference in investigating the FC network after using Modafinil and placebo (the bottom triangular diagram shows baseline effects of both groups in the FC network top triangular one shows the longitudinal difference of both groups in the FC network). **Figure 4.b** shows –log 10 p-values for comparing the mentioned paired ROI related to FC baseline effect and longitudinal processing after employing Modafinil and placebo (the top triangular diagram shows –log 10 p-values for longitudinal processing of the paired ROI, and the bottom triangular diagram shows –log 10 p-values for FC baseline effects of the paired ROI).

In figure 3.a, the FC baseline estimate effect for paired ROI in each group was drawn. FC in both Modafinil and the placebo group in most regions are alike. For instance, in Modafinil and placebo groups, the FC baseline effect in areas 3 and 6 is more than in other areas. In figure 3.b, FC longitudinal estimate effects for paired ROI in each group was drawn. For example, it was shown that FC in regions 1 and 7 during the time is more in the Modafinil group than in the other areas. It was also observed that FC in the placebo group during the time, in regions (1,3) and (1,6) is more than in the other areas.

In figure 4.b, it is clear that –log 10 p-values in FC baseline effects, in paired ROI 2 and 6 have more chromatic spots compared to other regions, while this difference is not statistically significant. Also, according to the figure exploring longitudinal processing of FC, it is evident that both areas 1 and 5

have more chromatic spots than other regions, which is an indicator of significant statistical difference in FC longitudinal processing between Modafinil and placebo groups.

4. Discussion

This study aimed to use a different longitudinal model on fMRI data during across time. The used model's difference in the present study compared to other longitudinal models was the faulty model's different structure. To fit the mentioned subject, the data must have been collected longitudinally. The fMRI data must have been analyzed in the resting state and then divided into two groups. The data selected in this study have all the features mentioned. The findings of the fitting to the data from before intervention did not show a statistically significant difference in connection with FC between both regions,

either for baseline effects or longitudinal processing. Exploring baseline effects of FC after the intervention, between the Modafinil and placebo group, compared to both areas, significant statistical relation was not observed, but investigating longitudinal processing of FC after the intervention, between Modafinil and placebo groups, corresponding to both regions, the significant statistical difference between Inter-Hemispheric and Right-Brainstem was seen.

Gerthesis and his colleagues did a study in 2013. The purpose of Gerthesis and his colleagues' assignment was to present a longitudinal model for DTI data. In Gerthesis and his colleagues' study, a longitudinal model was used to model health outcomes. The nature of DTI and fMRI data is different. The model presented by Gerthesis and his colleagues was different from the model shown in this study, and applying it for fMRI data was not possible. Therefore, a longitudinal model in fMRI was felt[31]. In the present study, the mentioned need was met, and a longitudinal model to fit fMRI data in the resting state, which was presented by Hart and his colleagues, was applied[25]. In 2013, Esposito and his colleagues, and in 2014 Cera and his colleagues made a fitting on the data used in this study[32, 33]. Their research aimed to investigate the effect of Modafinil in enhancing FC and fluid intelligence in young, healthy individuals. In Esposito and colleagues study's, 6 brain resting networks called Default Mode Network, the Salience Network, the Fronto Parietal Control Network, the Sensory-Motor Network, Exstriate Visual System, and the Dorsal Attention Network were selected. FC effect was observed in FPC and DAN.

This study demonstrated that the young, healthy individuals' fluid intelligence increased after prescribing Modafinil. In this study, TD hemispheres atlas was employed, which divides the brain volume into seven regions. The main difference between the present study with Esposito and colleagues' research is applying a longitudinal model. In Esposito's and colleagues' study, simpler statistical models were used, compared to the present study. The statistical models applied in Esposito and colleagues' study were independent T-test, one-way ANOVA, and Repeated Measure. A more modern longitudinal model with a more robust statistical power fits the data in the present study[33].

In Cera and his colleagues' study in 2014, Esposito and colleagues' data were used again. This time, Cera and his colleagues analyzed the effect of Modafinil on FC in sub-brain regions. The Insula region had a significant role in Cera and colleagues' study. Their research showed the different functional manner in the front and back of Insula in the Modafinil group. This study demonstrated that after prescribing Modafinil, FC in the putamen left Para hippocampus and left posterior Insula increased. In Cera's and colleagues' study, more straightforward statistical methods were applied[32]. The finding of both studies demonstrated that significant statistical differences in the FC network in both Modafinil and placebo groups.

5. Conclusion

Applying the new longitudinal model presented by Hart and his colleagues in 2018, this study's findings were more documented since the proposed model has more substantial statistical power of test compared with earlier models.

The statistical power of the test in this model was argued in Hart and his colleagues' article. The longitudinal model gained clinical findings using a variance component fitting with no statistically significant difference in functional connectivity between Modafinil and placebo groups. The result did not show a statistically significant difference in both paired-brain regions and the longitudinal and baseline effect before the intervention. Nevertheless, after the intervention, it was

perceived that the functional connectivity during a time in a paired-region called inter-hemispheric and Right-Brainstem in the Modafinil group compared with the placebo group increased, and this rise was statistically significant. However, in general, the results showed that FC in most of the ROI in the Modafinil group compared with the placebo group has decreased. These results can show Modafinil harms ROI selected in this study.

Acknowledgement

Conflict of interest

The authors declare no conflict of interest.

References

1. Meszlényi RJ, Hermann P, Buza K, Gál V, Vidnyánszky Z. Resting state fMRI functional connectivity analysis using dynamic time warping. Frontiers in neuroscience. 2017;11:75.

2. Engels G, Vlaar A, McCoy B, Scherder E, Douw L. Dynamic functional connectivity and symptoms of Parkinson's disease: a resting-state fMRI study. Frontiers in aging neuroscience. 2018;10:388.

3. Lynall M-E, Bassett DS, Kerwin R, McKenna PJ, Kitzbichler M, Muller U, et al. Functional connectivity and brain networks in schizophrenia. Journal of Neuroscience. 2010;30(28):9477-87.

4. Douw L, Schoonheim M, Landi D, Van der Meer M, Geurts J, Reijneveld J, et al. Cognition is related to resting-state small-world network topology: an magnetoencephalographic study. Neuroscience. 2011;175:169-77.

5. Biswal B, Zerrin Yetkin F, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo- planar MRI. Magnetic resonance in medicine. 1995;34(4):537-41.

6. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nature reviews neuroscience. 2007;8(9):700-11.

7. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. Journal of neurophysiology. 2011.

8. Kalcher K, Huf W, Boubela RN, Filzmoser P, Pezawas L, Biswal BB, et al. Fully exploratory network independent component analysis of the 1000 functional connectomes database. Frontiers in human neuroscience. 2012;6:301.

9. van den Heuvel MP, Scholtens LH, Turk E, Mantini D, Vanduffel W, Feldman Barrett L. Multimodal analysis of cortical chemoarchitecture and macroscale fMRI resting- state functional connectivity. Human brain mapping. 2016;37(9):3103-13.

10. Van Den Heuvel MP, Pol HEH. Exploring the brain network: a review on resting-state fMRI functional connectivity. European neuropsychopharmacology. 2010;20(8):519-34.

11. Smith SM, Miller KL, Salimi-Khorshidi G, Webster M, Beckmann CF, Nichols TE, et al. Network modelling methods for FMRI. Neuroimage. 2011;54(2):875-91.

12. Elliott ML, Knodt AR, Cooke M, Kim MJ, Melzer TR, Keenan R, et al. General functional connectivity: Shared features of resting-state and task fMRI drive reliable and heritable individual differences in functional brain networks. NeuroImage. 2019;189:516-32.

13. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. Psychological review. 2001;108(3):624.

14. Egner T. Multiple conflict-driven control mechanisms in the human brain. Trends in cognitive sciences. 2008;12(10):374-80.

15. McTeague LM, Goodkind MS, Etkin A. Transdiagnostic impairment of cognitive control in mental illness. Journal of psychiatric research. 2016;83:37-46.

16. Aron AR, Dowson JH, Sahakian BJ, Robbins TW. Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. Biological psychiatry. 2003;54(12):1465-8.

17. Rock P, Roiser J, Riedel W, Blackwell A. Cognitive impairment in depression: a systematic review and meta-analysis. Psychological medicine. 2014;44(10):2029.

18. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. Neuron. 2011;69(4):680-94.

19. Chamberlain SR, Hampshire A, Müller U, Rubia K, Del Campo N, Craig K, et al. Atomoxetine modulates right inferior frontal activation during inhibitory control: a pharmacological functional magnetic resonance imaging study. Biological psychiatry. 2009;65(7):550-5.

20. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology. 2008;33(7):1477-502.

21. Li J, Yang X, Zhou F, Liu C, Wei Z, Xin F, et al. Modafinil enhances cognitive, but not emotional conflict processing via enhanced inferior frontal gyrus activation and its communication with the dorsomedial prefrontal cortex. Neuropsychopharmacology. 2020;45(6):1026-33.

22. Nguyen TL, Tian YH, You IJ, Lee SY, Jang CG. Modafinil- induced conditioned place preference via dopaminergic system in mice. Synapse. 2011;65(8):733-41.

23. Dawson N, Thompson RJ, McVie A, Thomson DM, Morris BJ, Pratt JA. Modafinil reverses phencyclidine-induced deficits in cognitive flexibility, cerebral metabolism, and functional brain connectivity. Schizophrenia bulletin. 2012;38(3):457-74.

24. Battleday RM, Brem A-K. Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: a systematic review. European Neuropsychopharmacology. 2015;25(11):1865-81.

25. Hart B, Cribben I, Fiecas M, Initiative AsDN. A longitudinal model for functional connectivity networks using resting-state fMRI. NeuroImage. 2018;178:687-701.

26. Finn ES, Constable RT. Individual variation in functional brain connectivity: implications for personalized approaches to psychiatric disease. Dialogues in clinical neuroscience. 2016;18(3):277.

27. Guillaume B, Hua X, Thompson PM, Waldorp L, Nichols TE, Initiative AsDN. Fast and accurate modelling of longitudinal and repeated measures neuroimaging data. NeuroImage. 2014;94:287-302.

28. Xiang J, Guo H, Cao R, Liang H, Chen J. An abnormal resting-state functional brain network indicates progression towards Alzheimer's disease. Neural regeneration research. 2013;8(30):2789.

29. Hafkemeijer A, van der Grond J, Rombouts SA. Imaging the default mode network in aging and dementia. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2012;1822(3):431-41.

30. Roy R. Asymptotic covariance structure of serial correlations in multivariate time series. Biometrika. 1989;76(4):824-7.

31. Gertheiss J, Goldsmith J, Crainiceanu C, Greven S. Longitudinal scalar-on-functions regression with application to tractography data. Biostatistics. 2013;14(3):447-61.

32. Cera N, Tartaro A, Sensi SL. Modafinil alters intrinsic functional connectivity of the right posterior insula: a pharmacological resting state fMRI study. PLoS One. 2014;9(9):e107145.

33. Esposito R, Cilli F, Pieramico V, Ferretti A, Macchia A, Tommasi M, et al. Acute effects of modafinil on brain resting state networks in young healthy subjects. PloS one. 2013;8(7):e69224.