



WHAT DOES ELECTROENCEPHALOGRAM CONNECTIVITY ANALYSIS TELL US ABOUT DEPRESSION?

Bachelor's Project Thesis

Ameer Islam, s3410757, a.m.islam@student.rug.nl

Supervisors: Dr Marieke van Vugt & Hang Yang

Abstract: Previous research has shown that functional connectivity of Electroencephalogram (EEG) between different parts of the brain is somewhat predictive of Major Depressive Disorder (MDD). Apart from the functional connectivity also power in various frequency bands (alpha, delta, theta and beta) has been shown to differ between healthy individuals and MDD patients. Specifically, patients with MDD had a significant increase in the theta, alpha and beta frequency bands compared to healthy controls, in the frontal and occipital regions of the brains. This study aimed to investigate whether there was a difference in the functional connectivity and power spectra between more depressed participants compared to less depressed participants who were ranked on a depression spectrum rather than being separated into healthy controls and MDD patients. In addition, this study focused on frontal brain areas represented through 9 electrodes (FP1, FP2, AF3, AF4, F7, F3, FZ, F4, F8) to examine functional connectivity and power spectra. We examined EEG functional connectivity across the frontal brain area during the resting state using the Phase Lag Index (PLI). In addition to functional connectivity, we examined oscillatory power during the resting state, in the 5 frequency bands ; delta (0.5 to 4Hz); theta (4 to 7Hz); alpha (8 to 12Hz) and beta (13 to 30Hz). The results showed that less depressed individuals had higher frontal theta power than more depressed individuals. All other frequency bands and the PLI failed to show any significant difference in the two groups. Future research with a larger data set and more measures of EEG functional connectivity would give a more detailed functional connectivity analysis with groups on both end of the depression spectrum by providing more information on how different brain areas relate to each other for the two groups.

1. Introduction

Depression is a common yet serious medical mental disorder that negatively effects how an individual feels and acts. (Torres, 2020). Conservative estimates put us at 350 million patients worldwide suffering from this illness. In addition, it is one of the leading causes of disabilities worldwide (Caan, 2015). Depression causes sadness and loss of interest amongst several other mood changes. In the United States alone, 20% of the population is said to suffer from some form of depression (Blazer, 2000).

Depression is associated with specific changes in brain activity measured with Functional Magnetic Resonance Imaging (fMRI) and Electroencephalogram (EEG). Leuchter et al. (2012) observed that major depressive disorder (MDD) can be associated with dysfunctions in the brain networks linking the limbic system and cortical regions. They observed altered

functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and subcortical limbic structures. Several other studies have backed up this finding including Pandya et al. (2012) who showed that the DLPFC could be central to the understanding of MDD. Typically, those with MDD show deficits in emotional and cognitive information processing. In addition, the most common region to manifest anatomic abnormalities in MDD is the frontal lobe, hence this area is of importance for EEG research and should be studied (Zhang et al., 2018). Further fMRI research also showed the anterior cingulate cortex (ACC) has increased functional correlations with the DLPFC and the amygdala in MDD patients (Zhang et al., 2018).

In order to get these useful insights from fMRI individuals are observed while in resting-state. In the resting-state participants do not have active task demands (Stevens, 2016). This enables researchers to block out any external activity that interferes with brain functioning as the brain is

not performing any extra activity. Analysis of resting-state EEG is commonly used for clinical research purposes (Bai et al., 2017). Biswal et al. (1995) were the first to understand the importance of taking measurements in the resting-state. Resting-state fMRI recordings can prove to be more beneficial for research as they can provide analysis and topographical maps which are highly consistent and reproducible across multiple subjects and sessions (Rosazza et al., 2014). In the resting-state the human brain is fully operational (Smitha et al., 2017). The brain is still functioning regularly, and all states can still be observed. Taking fMRI recordings in the resting-state requires least effort from individuals and can even be done with unconscious patients while being cost effective and convenient (Bai et al., 2017). However, resting-state recordings cannot be used to study specific brain areas. It is also not yet clear whether there are individual differences in sleep state and wake state (Daliri, 2014).

fMRI studies are known to be very costly. Previous studies concluded that EEG analysis has been proved to be more cost effective, easier to perform and requires the least expertise (Olbrich & Arns, 2013). Recent studies have also shown that EEG recordings are of particular importance for measuring cognitive functioning and hence could help understand depression at a deeper level in terms of brain activity and different brain areas involved in this disorder. The study by Leuchter et al. (2012) looked at how EEG can be used to examine depression. It was established that patterns of alpha asymmetry fluctuated over the span of a week in patients with MDD as compared to other individuals. This could suggest that distributed synchrony in MDD may be reflected by a broadly distributed dysregulation. Frontal EEG alpha asymmetry showing increased relative right hemispheric activity has been frequently linked with depression and anxiety (Sun et al., 2017). Ferdek et al. (2016) showed that in a group that was more prone to ruminative thoughts, seen through the Ruminative Response Scale (RSS) questionnaire, there was decreased activation of the left DLPFC and increased activation of the left temporal lobe structures (Ferdek et al., 2016). Ruminative thoughts have been identified as one

of the most problematic cognitive symptoms associated with depression. These negative thoughts interfere with an individual's thinking, problem solving and adaptive behaviours (Alderman et al., 2015). MDD clinical diagnosis reflects a cluster of observable behaviour which can be seen through EEG. (Olbrich & Arns, 2013).

Fingelkurts et al. (2007) found increased synchronization in the EEG alpha and theta bands in patients with MDD, with increases reported over the frontal or parietooccipital regions, either on the right or left side. The study used a *structural synchrony* (SS) approach to measure the synchronization between different brain areas. Synchronization was seen when applying the rapid transition processes (RTP's) between different EEG channels (Fingelkurts, 2007). Leuchter et al. (2012) recently reported an increased EEG coherence between frontal brain areas in MDD in the EEG alpha, beta and theta bands. For this study different frequencies in the EEG spectrum were observed in order to see differences between both groups. EEG waveforms can be characterized based on their location, amplitude, frequency, morphology, continuity (rhythmic, intermittent or continuous), synchrony, symmetry, and reactivity. The most frequently used method for clinical research is to classify EEG waveforms by frequency. The most commonly studied waveforms include delta (0.5 to 4Hz); theta (4 to 8Hz); alpha1 (8 to 10Hz); alpha2 (10 to 13Hz) and beta (13 to 25Hz) (Nayak & Anilkumar, 2020).

Most studies focus on comparing healthy controls to patients who have been diagnosed with MDD. It is not known yet whether these differences in functional connectivity and oscillatory power can also be observed for individuals who are not necessarily clinically depressed but placed on a depression spectrum from low to high. This study focuses on analysing the functional connectivity and oscillatory power of different brain areas to see whether there is a difference in connectivity and power between the resting state of low and high depressed participants.

2. Methods

We examined whether functional connectivity differed between individuals in a normally functioning group that varied in their self-reported depression scores.

2.1 Participants

Forty participants with normal or corrected-to-normal vision and having proficiency in English were recruited for the experiment through a Facebook group and by word of mouth. All participants were between the ages of 18 and 35 years. Participants were subdivided into groups with low and high self-reported depression like thinking. Data from 39 participants was used for this study as data from one participant was not usable. In order to get a detailed insight of the participants depression-like thinking a number of questionnaires were used. These further helped in putting the participants into low and high depression groups. The questionnaires include Perseverative Thinking Questionnaire (PTQ) measuring repetitive negative thinking (Ehring et al., 2011), Rumination Response Scale (RRS) for accessing depressive rumination (Nolen-Hoeksema & Morrow, 1991) and CES-D indicating the severity of depression (Radloff, 1977). Participants within the criterion of the top and bottom 25% of the distribution on the total score were selected for the current study. All participants signed an informed consent before the experiment was started. The study was approved by the local Ethics Committee.

2.2 Equipment and Procedure

Each participant was invited to the EEG laboratory (Room 209) located at the University of Groningen Zernike Campus, Nijenborgh 4, 9747 AG, Groningen. Participants had to sit quietly for five minutes while EEG was being recorded – a resting state scan. Each participant was invited to enter the room and take part in the resting state task that had been set up. All equipment had been used according to international standards and was cleaned properly to ensure hygiene and to ensure minimum interference from electrode sensors when recording. Participants were also instructed to follow certain instructions in order to proceed with the experimental task. During

the experiment, participant pairs sat on two chairs in a room behind two monitors which were set to the same resolution. To avoid the possibility of verbal or nonverbal communication, their view of each other was obstructed by a barrier in between them. An interface to record the resting state scan was created in the programming software Python, which provided instructions. Once the participants sat on the chairs with all the EEG equipment attached, they had to open the program in python which contained the resting-state scan experimental information. After opening the program, audio was played asking the participants to turn on the speakers and test the audio equipment, along with on-screen text instructions. The instructions were played through the computer speakers, stating that a rest period of five minutes would shortly start. Upon pressing the space key on the computer, a timer would count down from 5 minutes to 0. This would be the resting-state period which would then be examined for further analysis. Participants would hear a beep after 5 minutes indicating that the time period is over. In the case of an interruption by something or someone, participants could open their eyes and press the 'space' key again and immediately close their eyes to restart the 5 minutes rest session. Once the 5 minutes of rest were over another instruction played. This stated: "Now several statements will follow regarding potential feelings and thoughts you may have experienced during the resting period." Participants had to indicate to what degree they agreed with the statements that followed (Completely Disagree, Disagree, Neither Agree nor Disagree, Agree, Completely Agree).

Participants were hooked up to a Biosemi electroencephalography (EEG) system. The stimulus presentation machine displayed the behavioural computer-based task to two separate screens and sent EEG triggers via parallel ports to the USB receiver. These EEG caps had 32 electrodes for the scalp and 6 external electrodes. The electrodes were placed according to the layout in Figure 2.1 and EEG recordings were carried out in the ActiView program. Each resting-state task lasted for two minutes and was recorded with the BioSemi 32-channel system

and six facial electrodes: two on the mastoids, one below and above the eye and one to the left and the right of the eyes, as shown in Figure 2.1. Mastoid electrodes were used for referencing, whilst those around the eyes were placed for catching the eye-movement artifacts. Initially, the Cz electrode was used as the reference signal, however after pre-processing it was the average reference computed in MATLAB. The sampling rate was 512 Hz and the impedance was below 40 k Ω .

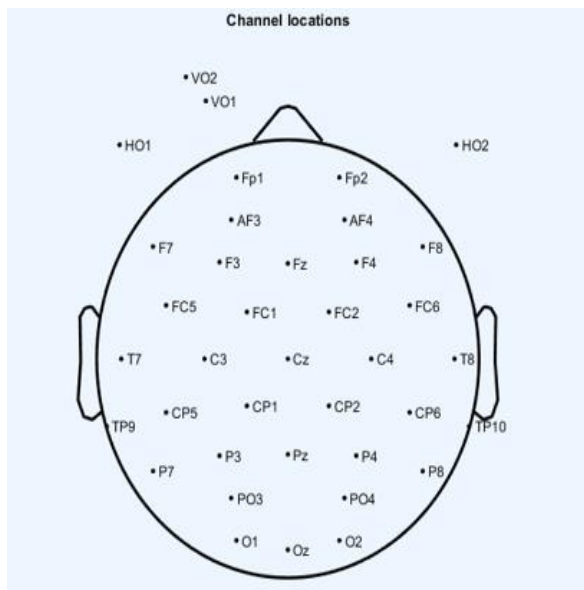
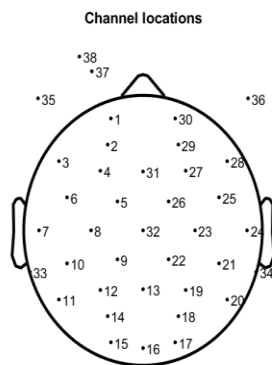


Figure 2.1: Placement of electrodes for the current study including all 38 electrodes.



38 of 38 electrode locations shown

Figure 2.2: Channel locations represented by numbers from 1 to 38

2.3 EEG Pre-Processing

Continuous EEG data were imported into EEGLAB (Delorme and Makeig, 2004) for analysis. The EEG data was then pre-processed using the EEGLAB toolbox (Delorme and Makeig, 2004) and custom scripts running on MATLAB (MATLAB, 2020). Channels with excessive artifacts such as eye blinks, eye movements, body movements, and muscle contractions were removed. The EEG data were digitally filtered (0.5-30 Hz band-pass filter), down sampled to 512 Hz, and segmented into 2-s long epochs after re-referencing to the average of all scalp channels. The data from the participants was then converted to 148 artifact free epochs of 2-s per epoch, each containing 512 frames per epoch. This data was then saved in plain text files. These steps were carried out by a Matlab script created to perform these specific steps.

To examine functional connectivity and oscillatory power, subsequent analyses was performed separately for the delta (0.5-4 Hz), theta (4-8 Hz), alpha1 (8- 10 Hz), alpha2 (10-13Hz) and beta (13-25 Hz) bands. The analysis was carried out in the BrainWave software developed by Cornelis Jan Stam (version 0.9.76; freely available from <http://home.pn.nl/stam7883/brainwave.html>).

2.4 EEG Data Analysis

After the data had been processed in MATLAB, it was converted to text files using EEGLAB (Delorme and Makeig, 2004). This was then imported to BrainWave to get the various metrics for analysis of functional connectivity and power spectra analysis. Fast Fourier Transform (FFT) Power Analysis had been conducted on delta (0.5-4 Hz), theta (4-8 Hz), alpha1 (8- 10 Hz), alpha2 (10-13Hz) and beta (13-25 Hz) frequency bands. In addition, the Phase Lag Index (PLI) was also calculated for all channels. In order to measure the connectivity of the frontal brain only 9 electrodes had been considered (FP1, FP2, AF3, AF4, F7, F3, FZ, F4, F8) as seen in Figure 2.1. All 32 channels were also analysed to get the mean power value across each of the 4 frequency bands and the PLI value.

2.4.1 Spectral Power

Spectral power was calculated for all EEG channels in Brainwave, with a frequency resolution of $1/2 \text{ s} = 0.5 \text{ Hz}$. The relative power values were calculated for the following frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13Hz), beta (13–25 Hz) and gamma (25–49 Hz). The gamma power has a high frequency range which was not required for this study. In addition, research has showed that gamma activity is a by-product of other network activity and hence not useful to analyse (Jia & Kohn, 2011). Thus, this frequency band was not examined for the current study. Mean power values from each of the 9 channels over 148 epochs were calculated for each frequency band. An averaged power value was calculated for each frequency band and the PLI for each subject. This was done for each depression group (“high” and “low”) (see Appendix B). Mean power for each frequency band was calculated by taking the power value for each channel (Ch1, Ch3, Ch3, Ch4, Ch27, Ch28, Ch29, Ch30 and Ch31) (see Figure 2.2) adding it then dividing it by the total number of channels.

2.4.2 Functional Connectivity

The phase lag index (PLI) was used to calculate functional connectivity between all 32 electrodes for each frequency band and across all epochs. The PLI measures phase synchronization based on the asymmetry of the distribution of instantaneous phase differences between two signals, which is determined using the analytical signal based on the Hilbert transformation (Stam et al., 2007). Furthermore, the PLI quantifies the relative phase distribution’s asymmetry; that is, that the likelihood that the phase difference $\Delta\varphi$ will be in the interval $-\pi < \Delta\varphi < 0$ is different from the likelihood that it will be in the interval $0 < \Delta\varphi < \pi$. This implies the presence of a consistent, nonzero phase difference (‘lag’) between two time series. The distribution is expected to be symmetric if there is no coupling or if the median phase difference is equal to or centres around a value of $0 \text{ mod } \pi$. The PLI is obtained from time series of phase differences $\Delta\varphi(t_k)$, $k = 1 \dots N$ by means of:

$$\text{PLI} = |\langle \text{sign}[\sin(\Delta\varphi(t_k))] \rangle|$$

Here sign is the signum function. The PLI ranges between 0 and 1. A PLI of zero indicates either no coupling or coupling with a phase difference centered around $0 \text{ (mod } \pi)$. A PLI of 1 indicates perfect phase locking at a value of $\Delta\varphi$ different from $0 \text{ (mod } \pi)$. The stronger this nonzero phase locking is, the larger PLI will be. Mean PLI was calculated by getting the PLI between the various channels (Ch1, Ch2, Ch3, Ch4, Ch27, Ch28, Ch29, Ch30 and Ch31) and then dividing it by the total number of channels.

2.4.3 Statistical Analysis

After performing power spectrum analysis and obtaining PLI values from the Brainwave software, unstructured data (see Appendix C) and had to be converted into structured data for further analysis. All the data was imported in Microsoft Excel (Office 365, 2012) for creation of a data set. This data set was then imported into RStudio (RStudio Team, 2020) for statistical analysis. To compare the mean power values of the two groups of more and less depressed participants, a Two-Sample t-test was used. Each group’s (“high” and “low”) mean power in each frequency band and mean PLI was compared to one another. The assumptions made to use this test were; the data are continuous (not discrete), the data follow the normal probability distribution and the variance of the two population are equal. In addition, $p < 0.05$ was the significance threshold.

3. Results

To examine whether depression differentiated EEG signals, power in all the frequency bands (delta, alpha1, alpha2, beta and theta) and PLI values were examined for any significant differences between low and high depression groups.

3.1. Mean power and PLI in the frontal brain regions

In order to see if a difference existed between more and less depressed participants, the mean power for each frequency band; delta (0.5 to 4Hz); theta (4 to 8Hz); alpha1 (8 to 10Hz); alpha2

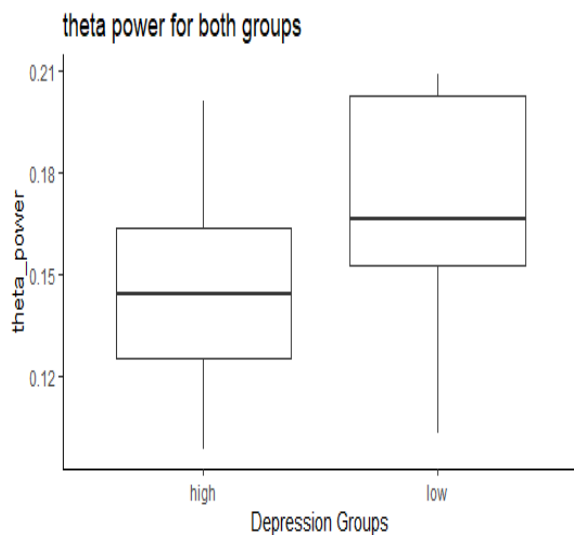


Figure 3.1: Box plot showing differences in oscillatory power (in the theta band) for more (“high”) and less (“low”) depressed groups.

(10 to 13Hz) and beta (13 to 25Hz) was computed across 9 channels (Fp1, Fp2, F3, F4, F7, F8, AF3, AF4, FZ). Along with this, the PLI was calculated across all the 9 channels as well. The results can be seen in Table 3.1(see Table 3.1).

Only the theta band showed a significant difference in the mean values between both groups ($t_{(37)} = -2.52$; $p = 0.016$; Table 3.1) with the low depressed group having a higher average theta power in the chosen set of frontal channels (see Figure 3.1). In other frequency bands and the PLI no significant differences were seen to be found (see Table 3.1).

3.2 Topographical Analysis

In order to extract meaningful data from EEG analysis, topographical maps are also used. For the purposes of this study two subjects representing each group (low depression and high depression) were examined. The 2 subjects were chosen based on how closely the mean theta oscillatory power for each subject was related to the mean theta oscillatory power for each group the subject belonged too. These maps show the power spectrum at the particular frequency band chosen. To observe the theta band (4 – 7Hz) where a significant difference was observed, the various frequencies were examined; 4Hz, 6Hz and 7 Hz. A difference in oscillatory power across the frontal brain areas can be observed in Figure 3.2 and Figure 3.3. The

comparison between both subjects shows a difference in oscillatory power when visualized in a topographical map. The top portion of the head in each figure, representing the frontal brain areas can be seen to have different values for both individuals.

4. Discussion and Conclusion

This study aimed to examine whether there was a difference in oscillatory power and functional connectivity between two groups of individuals ranked along a depression spectrum. Fingelkurts et al. (2007) previously showed differences in connectivity between those who had been diagnosed with MDD and healthy controls. In order to perform this analysis oscillatory power and functional connectivity had been calculated for all 39 participants who belong to a group of low depression or high depression.

When looking at the 9 electrodes representing the frontal brain areas, a significant difference ($t_{(37)} = -2.52$; $p = 0.016$; Table 3.1) was seen in oscillatory power for the theta band however all other frequency bands showed no significant difference. In addition, the PLI which measured functional connectivity did not show any significant difference either. The theta frequency band could be representative of the functional connectivity in the limbic system and Anterior Cingulate Cortex (ACC) (Fingelkurts et al., 2007). This is area is believed to be important for emotional and behavioural control (Palleiro et al., 2019). A lower mean connectivity value in this study for the high depressed group could be explained by functional impairments in participants’ limbic system and ACC which are related to theta activity in the human brain. (Pizzagalli et al., 2003). This further motivates a single electrode analysis across frequency bands to show differences in oscillatory power in groups with depression and those who have no depression. In addition to this, oscillatory power and functional connectivity had been examined for the whole brain however no significant results were observed. When averaging power across all electrodes individual electrode differences are washed out and hence no significant results are obtained (Appendix D)

	Depression (low)	Depression (high)	Statistical Values (t-test)		
			p	t	df
	n = 19	n = 20			
Relative Power					
Delta (mean)	0.451978136	0.433086033	0.5934	-0.5386	37
Theta (mean)	0.168534443	0.143017532	0.01629 *	-2.517	37
Alpha 1 (mean)	0.063018079	0.063144234	0.9910	0.01140	37
Alpha 2 (mean)	0.174690782	0.223006508	0.2245	1.235	37
Beta (mean)	0.132781673	0.128805249	0.7523	-0.3180	37
Connectivity					
PLI (mean)	0.259428638	0.258157704	0.9172	-0.1047	37

Table 3.1: Table with the mean values of each frequency bands (delta, theta, alpha1, alpha2, beta) and mean PLI, averaged across the 9 channels (Fp1, Fp2, AF3, AF4, F7, F3, Fz, F4, F8) representing the frontal brain areas. These values are calculated for both groups ("low" and "high"). A p-value for each "Measure" is also given.

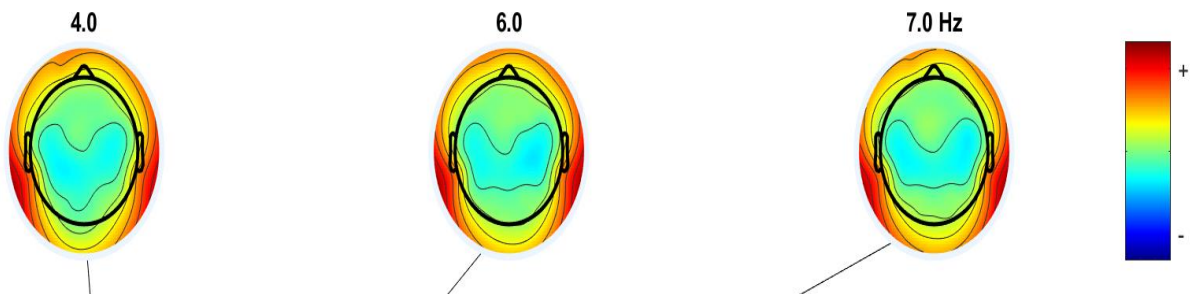


Fig 3.2: Topographical map at 4Hz, 6Hz and 7Hz for subject 15 in the high depression group

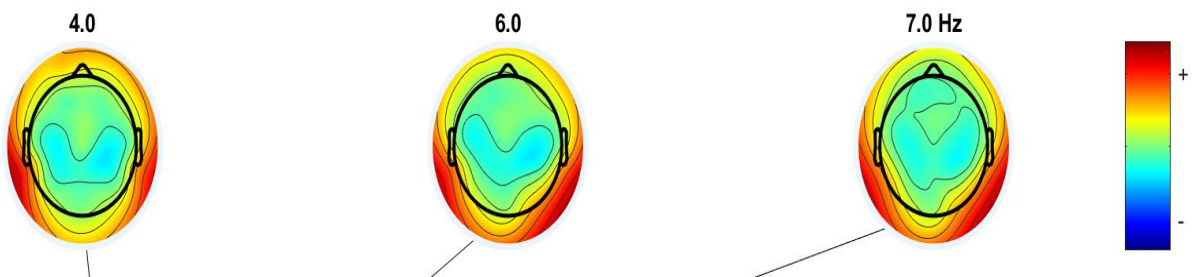


Fig 3.3: Topographical map at 4Hz, 6Hz and 8Hz for subject 37 in the low depression group

A number of potential problems have been identified with the current study. Firstly, previous research has focussed on groups which have been diagnosed with MDD compared to healthy controls. This allows for more significant results already supported by prior research. This study was carried out with individuals who had some form of depression but ranked differently on a spectrum. However, the motivation behind this study was to see whether these differences could be observed in individuals on a depression spectrum and possibly in the future allow for more such studies to be carried out. Secondly, in order to measure functional connectivity several other measures such as the Phase Locking Value, Phase Slope Index, Coherence, Pair Phase Consistency, Minimum Spanning Trees and Granger Causality were not used in this study. Amor et al., (2005) explained that phase synchrony suffers from two major problems. This could lead to phase synchronization methods being insensitive to very brief periods of synchronization because of their use of a time integration window (Amor et al., 2005). Other methods to measure functional connectivity could provide more reliable results. Thirdly and finally, EEG coherence in the form of oscillatory power or functional connectivity like any metric derived from electrical recordings of the scalp does not directly measure brain activity.

Future research could build upon single electrode analysis in various frequency bands and perform further connectivity analysis in order to examine differences between depressed and non-depressed participants. This would allow for a more focussed analysis on specific brain areas making an MDD diagnosis easier to perform. This research could have practical application since, current methods of determining whether individuals have MDD or not are inefficient as several questionnaires and diagnosis from certified therapists or medical professionals is required to provide a diagnosis for MDD. This usually takes quite some time. It would be useful to employ an Artificial Neural Network to diagnose MDD or help trained professionals and hence make this process more efficient and faster (Rostamabad et al., 2013). Research by Li et al., (2020) showed that a Convolutional Neural Network (CNN) built to

categorize mild depression obtained a classification accuracy of 80.74%. Future research to aid clinical diagnosis of MDD would enable those with this disorder to be diagnosed and treated at a much faster rate if relevant data could be collected.

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References

- Alderman, B. L., Olson, R. L., Bates, M. E., Selby, E. A., Buckman, J. F., Brush, C. J., ... Shors, T. J. (2015). Rumination in major depressive disorder is associated with impaired neural activation during conflict monitoring. *Frontiers in Human Neuroscience*, 9, 269–269. <https://doi.org/10.3389/fnhum.2015.00269>
- Bai, Y., Xia, X., & Li, X. (2017). A review of resting-state electroencephalography analysis in disorders of consciousness. *Frontiers in Neurology*, 8, 471–471. <https://doi.org/10.3389/fneur.2017.00471>
- Biswal, B., Zerrin Yetkin, F., Haughton, V.M. and Hyde, J.S. (1995), Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magn. Reson. Med.*, 34: 537-541. doi:10.1002/mrm.1910340409
- Blazer, D. G., & Koenig, H. G. (1996). *Mood disorders*. In E. W. Busse & D. G. Blazer (Eds.), *The American Psychiatric Press textbook of geriatric psychiatry* (p. 235–263). American Psychiatric Association.
- Caan, W. (2015). The global crisis of depression: the low of the 21st century? *Perspect. Public Health* 135:62. doi: 10.1177/1757913915569958
- Chaturvedi, M., Bogaarts, J. G., Kozak (Cozac), V. V., Hatz, F., Gschwandtner, U., Meyer, A., ... Roth, V. (2019). Phase lag index and spectral power as qeeg features for

identification of patients with mild cognitive impairment in parkinson's disease. *Clinical Neurophysiology*, 130(10), 1937–1944. <https://doi.org/10.1016/j.clinph.2019.07.017>

Cristina, R., Domenico, A., Ludovico, D. I., Roberto, C., Adrian, A., Domenico Zacà, ... Ludovico, M. (2014). Preoperative mapping of the sensorimotor cortex: comparative assessment of task-based and resting-state fmri. *Plos One*, 9(6). <https://doi.org/10.1371/journal.pone.0098860>

Cristina, R., Domenico, A., Ludovico, D. I., Roberto, C., Adrian, A., Domenico Zacà, ... Ludovico, M. (2014). Preoperative mapping of the sensorimotor cortex: comparative assessment of task-based and resting-state fmri. *Plos One*, 9(6). <https://doi.org/10.1371/journal.pone.0098860>

Ehring, T., Zetsche, U., Weidacker, K., Wahl, K., Schönfeld, S., & Ehlers, A. (2011). The perseverative thinking questionnaire (ptq): validation of a content-independent measure of repetitive negative thinking. *Journal of Behavior Therapy and Experimental Psychiatry*, 42(2), 225–232. <https://doi.org/10.1016/j.jbtep.2010.12.003>

Ferde, M.A., van Rijn, C.M. & Wyczesany, M. Depressive rumination and the emotional control circuit: An EEG localization and effective connectivity study. *Cogn Affect Behav Neurosci* 16, 1099–1113 (2016). <https://doi.org/10.3758/s13415-016-0456-x>

Fernández-Palleiro P, Rivera-Baltanás T, Rodrigues-Amorim, D., Fernández-Gil S, Del, C. V.-C. M., Álvarez-Ariza M, ... Spuch, C. (2020). Brainwaves oscillations as a potential biomarker for major depression disorder risk. *Clinical Eeg and Neuroscience*, 51(1), 3–9. <https://doi.org/10.1177/1550059419876807>

Fingelkurts, A.A., Rytälä, H., Suominen, K., Isometsä, E. and Kähkönen, S. (2007), Impaired functional connectivity at EEG alpha and theta frequency bands in major depression. *Hum. Brain Mapp.*, 28: 247–261. <https://doi.org/10.1002/hbm.20275>

Fischer, N. L., Peres, R., & Fiorani, M. (2018). Frontal alpha asymmetry and theta oscillations associated with information sharing intention. *Frontiers in Behavioral Neuroscience*, 12, 166–166. <https://doi.org/10.3389/fnbeh.2018.00166>

Grabowski B. (2016). "P < 0.05" Might Not Mean What You Think: American Statistical Association Clarifies P Values. *Journal of the National Cancer Institute*, 108(8), djw194. <https://doi.org/10.1093/jnci/djw194>

Leuchter, A. F., Cook, I. A., Hunter, A. M., Cai, C., & Horvath, S. (2012). Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. *PloS one*, 7(2), e32508. <https://doi.org/10.1371/journal.pone.0032508>

Lv, H., Wang, Z., Tong, E., Williams, L. M., Zaharchuk, G., Zeineh, M., Goldstein-Piekarski, A. N., Ball, T. M., Liao, C., & Wintermark, M. (2018). Resting-State Functional MRI: Everything That Nonexperts Have Always Wanted to Know. *AJNR. American journal of neuroradiology*, 39(8), 1390–1399. <https://doi.org/10.3174/ajnr.A5527>

Ma, X., Liu, J., Liu, T., Ma, L., Wang, W., Shi, S., Wang, Y., Gong, Q., & Wang, M. (2019). Altered Resting-State Functional Activity in Medication-Naive Patients With First-Episode Major Depression Disorder vs. Healthy Control: A Quantitative Meta-Analysis. *Frontiers in behavioral neuroscience*, 13, 89. <https://doi.org/10.3389/fnbeh.2019.00089>

MATLAB. (2010). *version 7.10.0 (R2010a)*. Natick, Massachusetts: The MathWorks Inc.

Nayak CS, Anilkumar AC. EEG Normal Waveforms. [Updated 2020 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK53980> 5/

Ng, W. B., Saidatul, A. A., Chong, Y. F., Lim, C. C., & Ong, Z. Y. (2019). A study of informative eeg channel and brain region for typing activity, 1372(1). <https://doi.org/10.1088/1742-6596/1372/1/012008>

- Nolen-Hoeksema, S., & Morrow, J. (1991). A prospective study of depression and posttraumatic stress symptoms after a natural disaster: The 1989 Loma Prieta earthquake. *Journal of Personality and Social Psychology*, 61(1), 115–121. <https://doi.org/10.1037/0022-3514.61.1.115>
- Olbrich, S., & Ams, M. (2013). EEG biomarkers in major depressive disorder: discriminative power and prediction of treatment response. *International review of psychiatry (Abingdon, England)*, 25(5), 604–618. <https://doi.org/10.3109/09540261.2013.816269>
- Pandya, M., Altinay, M., Malone, D. A., & Anand, A. (2012). Where in the brain is depression? *Current Psychiatry Reports*, 14(6), 634–642. <https://doi.org/10.1007/s11920-012-0322->
- Pizzagalli, D. A., Oakes, T. R., & Davidson, R. J. (2003). Coupling of theta activity and glucose metabolism in the human rostral anterior cingulate cortex: an eeg/pet study of normal and depressed subjects. *Psychophysiology*, 40(6), 939–949.
- Porz, S., Kiel, M., & Lehnertz, K. (2014). Can spurious indications for phase synchronization due to superimposed signals be avoided? *Chaos (Woodbury, N.y.)*, 24(3), 033112–033112. <https://doi.org/10.1063/1.4890568>
- Reza Daliri, M. (2014). Advantages and disadvantages of resting state functional connectivity magnetic resonance imaging for clinical applications. *Omic Journal of Radiology*, 3(1). <https://doi.org/10.4172/2167-7964.1000e123>
- Rolls, E.T. The cingulate cortex and limbic systems for emotion, action, and memory. *Brain Struct Funct* 224, 3001–3018 (2019). <https://doi.org/10.1007/s00429-019-01945-2>
- RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL <http://www.rstudio.com/>.
- Smitha, K. A., Akhil Raja, K., Arun, K. M., Rajesh, P. G., Thomas, B., Kapilamoorthy, T. R., & Kesavadas, C. (2017). Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. *The neuroradiology journal*, 30(4), 305–317. <https://doi.org/10.1177/1971400917697342>
- Stevens, M. C. (2016). The contributions of resting state and task-based functional connectivity studies to our understanding of adolescent brain network maturation. *Neuroscience and Biobehavioral Reviews*, 70, 13–32. <https://doi.org/10.1016/j.neubiorev.2016.07.027>
- Sun, L., Peräkylä J, & Hartikainen, K. M. (2017). Frontal alpha asymmetry, a potential biomarker for the effect of neuromodulation on brain's affective circuitry-preliminary evidence from a deep brain stimulation study. *Frontiers in Human Neuroscience*, 11, 584–584. <https://doi.org/10.3389/fnhum.2017.00584>
- Sun, S., Li, J., Chen, H., Gong, T., & Li, X. (2020). A study of resting-state EEG biomarkers for depression recognition. Retrieved from : <https://arxiv.org/abs/2002.11039v1>. (arXiv:2002.11039v1)
- Torres, F. (2020). What Is Depression? Retrieved October 07, 2020, from <https://www.psychiatry.org/patients-families/depression/what-is-depression>
- Xiaoxuan, J., & Adam, K. (2011). Gamma rhythms in the brain. *Plos Biology*, 9(4). <https://doi.org/10.1371/journal.pbio.1001045>
- Yasin, S., Hussain, S., Aslan, S., Raza, I., Muzammel, M., & Othmani, A. (2020). Neural Networks based approaches for Major Depressive Disorder and Bipolar Disorder Diagnosis using EEG signals: A review. *ArXiv, abs/2009.13402*.
- Zhang, F. F., Peng, W., Sweeney, J. A., Jia, Z. Y., & Gong, Q. Y. (2018). Brain structure alterations in depression: Psychoradiological evidence. *CNS neuroscience & therapeutics*, 24(11), 994–1003. <https://doi.org/10.1111/cns.12835>

Zhuo, C., Li, G., Lin, X., Jiang, D., Xu, Y., Tian, H., ... Song, X. (2019). The rise and fall of mri studies in major depressive disorder. *Translational Psychiatry*, 9(1), 335–335. <https://doi.org/10.1038/s41398-019-0680-6>

1 Appendix A

Subject 3 averaged across 148 epochs , 9 channels representing frontal brain areas					
0.080792042	alpha1_power				
0.420469219	alpha2_power				
0.121362613	beta_power				
0.269713213	delta_power				
0.239234985	PLI				
0.098043544	theta_power				

Each subject has an average power value for each frequency band and a PLI value. The PLI was calculated between 9 channels for 148 epochs. Power values for each frequency band were averaged over all epochs.

2 Appendix B

Subjects	alpha1_p ower	alpha2_pow er	beta_power	delta_powe r	PLI	theta_p ower	Depre ssion
2	0.0447755 26	0.424653904	0.126105105	0.292884384	0.244784 535	0.103638 889	high
3	0.0807920 42	0.420469219	0.121362613	0.269713213	0.239234 985	0.098043 544	high
7	0.0254684 68	0.09650976	0.17215991	0.550984985	0.264579 58	0.132460 961	high
8	0.0959249 25	0.266802553	0.09959009	0.363028529	0.236805 556	0.167094 595	high
9	0.0435840 84	0.20171021	0.146278529	0.474368619	0.289142 643	0.125635 886	high
11	0.1418647 93	0.118222222	0.080827979	0.489482597	0.257986 613	0.163727 577	high
13	0.1841163 66	0.281066817	0.089436186	0.301165916	0.234469 97	0.137882 883	high
15	0.0404744 74	0.101581832	0.219061562	0.450402402	0.236988 739	0.177547 297	high
17	0.0402079 58	0.279508258	0.150438438	0.372855105	0.229056 306	0.146930 931	high
18	0.0312929 29	0.06666936	0.10630303	0.637131313	0.307731 987	0.151381 145	high
19	0.0472685 19	0.340456553	0.123930199	0.381623219	0.224081 909	0.101563 39	high
23	0.0631820 68	0.191647415	0.109949945	0.483789329	0.232270 627	0.144609 461	high
25	0.0380330 33	0.143152402	0.162022523	0.502251502	0.266161 411	0.144084 835	high
26	0.0338138 14	0.263054805	0.075587838	0.485112613	0.253512 763	0.136372 372	high
33	0.0332845 35	0.058756757	0.106095345	0.633680931	0.371569 069	0.158678 679	high
39	0.0576997 96	0.165623344	0.133234964	0.450459225	0.282519 878	0.177125 382	high
40	0.1216704 2	0.255168919	0.067584084	0.349042793	0.225457 958	0.201087 087	high
41	0.0453723 72	0.083731231	0.138886637	0.558497748	0.301509 009	0.163631 381	high
42	0.0598521 02	0.374707207	0.167566066	0.268749249	0.208120 12	0.123906 907	high
43	0.0342064 56	0.326637387	0.179683934	0.346496997	0.257170 42	0.104947 447	high
4	0.0617590 09	0.141074324	0.114292793	0.466771772	0.239709 459	0.209187 688	low
5	0.0502297	0.15868018	0.185036787	0.42739039	0.225606	0.166455	low

	3				607	706	
10	0.0688611 11	0.281676426	0.180608108	0.311692943	0.193734 985	0.148867 868	low
12	0.1174121 62	0.139267267	0.088593844	0.462825826	0.234259 76	0.184216 967	low
14	0.0563828 83	0.093039039	0.089096847	0.54649024	0.283783 033	0.207972 222	low
16	0.0946516 52	0.356246997	0.097737988	0.332253754	0.230162 913	0.114077 327	low
20	0.0812597 6	0.143424174	0.119993243	0.490854354	0.250983 483	0.157690 691	low
24	0.0710743 24	0.056265015	0.206968468	0.454674174	0.232155 405	0.194870 12	low
27	0.0484617 12	0.095818318	0.10809985	0.534915165	0.290457 958	0.204117 117	low
28	0.0606509 01	0.071755255	0.17943994	0.470583333	0.247366 366	0.207556 306	low
29	0.0638340 84	0.305148649	0.086338589	0.425925676	0.288026 276	0.111199 7	low
30	0.0383881 38	0.14584009	0.183548799	0.455312312	0.228319 069	0.161205 706	low
31	0.0357852 85	0.278801051	0.118825826	0.426631381	0.264219 97	0.131295 796	low
32	0.0360454 78	0.063557623	0.157544703	0.570059432	0.269519 38	0.163883 204	low
34	0.0425442 94	0.067286787	0.140345345	0.565088589	0.336346 096	0.174753 003	low
35	0.0424887 39	0.061477477	0.117358108	0.565448949	0.305487 237	0.203491 742	low
36	0.0396298 57	0.044099523	0.115088616	0.589685072	0.323843 217	0.202005 453	low
37	0.0818213 21	0.327637387	0.148259009	0.278568318	0.215629 129	0.156049 55	low
38	0.1060630 63	0.488029279	0.085674925	0.212412913	0.269533 784	0.103258 258	low

An average power and PLI value was calculated for each subject over 148 epochs. After this individuals were separated into the two groups.

3. Appendix C

Example of unstructured data for Subject 33 obtained after performing analysis in Brainwave.

Subject 33 FFT & PLI - Notepad

File Edit Format View Help

Filename:	Epoch:	Measure:	Mean	Ch. 1	Ch. 2	Ch. 3	Ch. 4	Ch. 5	Ch. 6	Ch. 7	Ch. 8	Ch. 9	Ch. 10	Ch. 11	Ch. 12	Ch. 13	Ch. 14
Subject 33	1	total_power	813	20997	1377	320	60	25	2	15	39	10	19	87	72	36	50
Subject 33	1	delta_power	0.823	0.770	0.965	0.975	0.872	0.848	0.205	0.740	0.800	0.860	0.905	0.933	0.912	0.910	0.910
Subject 33	1	theta_power	0.074	0.149	0.030	0.017	0.059	0.041	0.233	0.098	0.030	0.032	0.044	0.038	0.018	0.036	0.030
Subject 33	1	alpha1_power	0.020	0.022	0.001	0.003	0.015	0.026	0.101	0.027	0.022	0.007	0.012	0.005	0.018	0.015	0.010
Subject 33	1	alpha2_power	0.019	0.019	0.000	0.001	0.004	0.011	0.004	0.010	0.025	0.024	0.001	0.007	0.018	0.006	0.000
Subject 33	1	beta_power	0.059	0.032	0.003	0.004	0.043	0.071	0.368	0.112	0.111	0.074	0.032	0.015	0.032	0.030	0.010
Subject 33	1	gamma_power	0.005	0.009	0.000	0.000	0.006	0.004	0.009	0.012	0.011	0.003	0.006	0.001	0.002	0.003	0.000
Subject 33	1	peak_freq	5.281	4.000	4.000	4.000	5.000	4.000	5.000	5.000	12.000	6.000	6.000	4.000	9.000	6.000	4.000
Subject 33	1	PLI	0.356	0.244	0.463	0.404	0.491	0.388	0.077	0.270	0.225	0.217	0.332	0.792	0.280	0.382	0.310
Subject 33	1	dPLI	0.000	0.484	0.455	0.448	0.435	0.448	0.495	0.539	0.486	0.487	0.494	0.631	0.538	0.483	0.510
Subject 33	2	total_power	670	20997	80	9	15	8	5	15	49	3	2	14	6	4	3
Subject 33	2	delta_power	0.462	0.770	0.840	0.479	0.619	0.481	0.596	0.704	0.668	0.491	0.426	0.700	0.303	0.661	0.410
Subject 33	2	theta_power	0.203	0.149	0.091	0.313	0.117	0.292	0.180	0.110	0.072	0.116	0.098	0.127	0.153	0.041	0.210
Subject 33	2	alpha1_power	0.030	0.022	0.011	0.024	0.019	0.058	0.036	0.006	0.013	0.023	0.005	0.018	0.062	0.031	0.000
Subject 33	2	alpha2_power	0.060	0.019	0.012	0.054	0.031	0.008	0.053	0.018	0.011	0.074	0.053	0.036	0.163	0.064	0.000
Subject 33	2	beta_power	0.228	0.032	0.043	0.114	0.163	0.158	0.130	0.156	0.222	0.290	0.317	0.112	0.310	0.201	0.210
Subject 33	2	gamma_power	0.018	0.009	0.004	0.016	0.051	0.003	0.005	0.005	0.014	0.006	0.021	0.007	0.009	0.002	0.010
Subject 33	2	peak_freq	4.906	4.000	4.000	4.000	6.000	4.000	4.000	6.000	4.000	4.000	8.000	5.000	4.000	12.000	4.000
Subject 33	2	PLI	0.291	0.425	0.324	0.369	0.228	0.421	0.386	0.326	0.340	0.276	0.260	0.434	0.234	0.302	0.210
Subject 33	2	dPLI	0.000	0.540	0.478	0.425	0.493	0.413	0.434	0.478	0.491	0.481	0.451	0.564	0.532	0.520	0.410
Subject 33	3	total_power	732	20997	225	21	29	11	4	8	18	3	7	7	11	6	6
Subject 33	3	delta_power	0.587	0.770	0.879	0.752	0.835	0.751	0.439	0.626	0.484	0.455	0.754	0.533	0.525	0.694	0.510
Subject 33	3	theta_power	0.138	0.149	0.037	0.125	0.042	0.149	0.126	0.170	0.209	0.223	0.087	0.259	0.249	0.142	0.110
Subject 33	3	alpha1_power	0.058	0.022	0.033	0.061	0.030	0.008	0.062	0.030	0.032	0.074	0.049	0.060	0.069	0.031	0.110
Subject 33	3	alpha2_power	0.042	0.019	0.011	0.014	0.023	0.016	0.066	0.012	0.022	0.040	0.028	0.013	0.005	0.033	0.000
Subject 33	3	beta_power	0.162	0.032	0.038	0.045	0.068	0.074	0.299	0.145	0.244	0.188	0.072	0.120	0.128	0.082	0.110
Subject 33	3	gamma_power	0.014	0.009	0.002	0.004	0.001	0.002	0.009	0.017	0.009	0.019	0.010	0.015	0.024	0.017	0.000
Subject 33	3	peak_freq	5.688	4.000	8.000	4.000	4.000	5.000	5.000	5.000	4.000	4.000	4.000	4.000	4.000	4.000	8.000
Subject 33	3	PLI	0.337	0.311	0.307	0.329	0.575	0.563	0.431	0.380	0.342	0.350	0.316	0.273	0.145	0.284	0.310
Subject 33	3	dPLI	0.000	0.584	0.582	0.566	0.637	0.620	0.519	0.598	0.557	0.515	0.415	0.530	0.486	0.489	0.410
Subject 33	4	total_power	668	20997	12	15	67	18	3	29	14	6	2	20	31	2	3
Subject 33	4	delta_power	0.582	0.770	0.429	0.901	0.935	0.878	0.656	0.891	0.576	0.764	0.346	0.754	0.660	0.173	0.210
Subject 33	4	theta_power	0.154	0.149	0.283	0.017	0.022	0.036	0.142	0.050	0.093	0.080	0.273	0.127	0.261	0.444	0.210
Subject 33	4	alpha1_power	0.037	0.022	0.064	0.009	0.007	0.018	0.040	0.007	0.005	0.007	0.023	0.023	0.019	0.060	0.000
Subject 33	4	alpha2_power	0.068	0.019	0.031	0.020	0.010	0.023	0.027	0.009	0.050	0.024	0.134	0.039	0.023	0.077	0.110
Subject 33	4	beta_power	0.137	0.032	0.140	0.044	0.023	0.042	0.120	0.042	0.243	0.116	0.169	0.053	0.033	0.166	0.110
Subject 33	4	gamma_power	0.022	0.009	0.052	0.009	0.004	0.003	0.015	0.001	0.032	0.009	0.055	0.004	0.004	0.080	0.000
Subject 33	4	peak_freq	5.531	4.000	4.000	5.000	4.000	5.000	6.000	4.000	4.000	6.000	6.000	5.000	4.000	4.000	4.000

4. Appendix D

	Total Group	Depression(low)	Depression (high)	T-test (p value)
	n = 39	n = 19	n = 20	
Relative Power				
Delta (mean)	0.4422898 79	0.321635 528	0.323898542	0.9495
Theta (mean)	0.1554488 48	0.158311 014	0.142082424	0.1662
Alpha 1 (mean)	0.0630827 74	0.085795 918	0.085763655	0.9986
Alpha 2 (mean)	0.1994680 77	0.246463 231	0.273345326	0.5032
Beta (mean)	0.1307424 81	0.180457 767	0.169005463	0.43
Connectivity				
PLI (mean)	0.2587768 77	0.244524 916	0.250062886	0.5973

Results obtained when performing t test on average power and PLI values for all 32 channels for each group. No significant values were obtained.