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EEG alpha band instantaneous frequency

Master's thesis

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PhD

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TALLINNA TEHNIKAÜLIKOOL
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EEG signaali alfa rütmi hetksagedus

Magistritöö

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Marietta Gavriljuk

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Abstract

The present study investigates the fluctuations in the oscillatory alpha frequency of the EEG signal within the depressive and healthy subjects. The frequency of an alpha oscillation is assumed to represent the degree of inhibition in the thalamocortical system, as well as to characterize individual differences in cognitive functioning and managing the speed of information processing.

The 5 minutes of EEG data from the occipital channel Oz of 13 healthy and 13 medication-free outpatients diagnosed with major depressive disorder was used to obtain the instantaneous frequency changes. The applied algorithm is based on the Hilbert transform and correction for the aperiodic component was performed through the polynomial fitting.

The results indicate a statistically significant difference between the two groups, demonstrating a higher amount of instantaneous frequency spikes registered for the depressive group. The sum of instantaneous frequency fluctuations averaged over the subgroups is equal to 62 ± 9.8 for the control group and 76 ± 10.5 for the depressive group. The level of significance revealed through the Wilcoxon rank-sum test is 0.0044 ($p < 0.05$). The result strengthens the idea that depressive subjects have a more complex character of the EEG signal.

This thesis is written in English and is 26 pages long, including 6 chapters, 15 figures.

Annotatsioon

EEG signaali alfa rütmi hetksagedus

Käesoleva töö eesmärk oli selgitada, kas elektroentsefalograafilise (EEG) signaali alfa rütmi hetksageduse põhjal on võimalik eristada depressiooni diagnoosiga gruppi ja kontrollgruppi. Töö eesmärk tulenes uuest tunnuse ekstraheerimise meetodist nimega *in-phase matrix ptofile* (pMP), mille puhul võis oletada, et just alfa hetksagedus mängib efektiivsel gruppide eristamise olulist rolli. Alfa riba sagedus esindab eeldatavalt talamokortikaalse süsteemi inhibeerimise astet, samuti iseloomustab individuaalseid erinevusi kognitiivses toimimises ja teabetöötluse kiiruse juhtimises. Autori teadmisel käsitleb käesolev töö esmakordselt puhkeoleku EEG hetksagedust tervete ja depressiooni diagnoosiga uuritavate eristamiseks.

Hetksageduse analüüsimiseks kasutati 5-minutilisi EEG signaale kuklakanalist Oz, mis olid eelnevalt salvestatud 13 tervelt uuritavalt ja 13 ravimivabalt depressiooni diagnoosiga patsiendilt. Rakendatud hetksageduse algoritm põhineb Hilberti teisendusel, millele eelnes aperioodilise komponendi korrigeerimine polünoomi sobituse teel.

Käesoleva töö tulemused näitavad statistiliselt olulist erinevust kahe grupi vahel, kus depressiooni diagnoosiga grupi puhul registreeriti rohkem hetksageduse hüppeid (62 ± 9.8) kui kontrollgrupi puhul (76 ± 10.5). Wilcoxoni astaksummatesti olulisuse tasemeks saadi 0.0044 ($p < 0.05$). Tulemus tugevdab ideed, et depressiooni diagnoosiga isikutel on keerukam EEG signaali iseloom

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 26 leheküljel, 6 peatükki, 15 joonist.

List of abbreviations and terms

CNS	Central Nervous System
CoG	Center of Gravity Frequency
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Eyes closed EEG recording
EEG	Electroencephalography
EO	Eyes open EEG recording
EOG	Electro-Oculograms
FFT	Fast Fourier Transform
FIR	Finite Impulse Response
IAF	Individual Alpha Frequency
ICD	International Classification of Diseases
IF	Instantaneous Frequency
PAF	Peak Alpha Frequency
PSD	Power Spectral Density
TF	Transition Frequency
WHO	World Health Organization

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1 Introduction

Depression is a common illness worldwide with an estimated 4.4% of the population affected according to the World Health Organization (WHO). It can be long-lasting or recurrent limiting or completely impairing an individual's ability to cope with daily life, as well as being a major contributor to suicide [1]. The global prevalence of anxiety and depression increased by 25% in the first year of the COVID-19 [2] and is projected to rank as the first cause of burden disease worldwide by 2030 [3].

The diagnosis of depression and its further treatment and management often poses challenges for clinicians due to its various presentations, unpredictable course and prognosis, and variable response to treatment [4]. Nowadays, the diagnosis of depression is based mainly on the identification of key symptoms and results from the questionnaires that are prone to professionals' and patients' subjectivity. Non-invasive EEG biomarkers for depression may lead to more objective diagnosis [5] as well as allow better planning and management of the treatment [6]. The physiological changes in the brain neuronal activity caused by the illness are expected to be reflected in the brain bioelectrical activity [7].

Over the years, research groups have studied biomarkers to better differentiate the depressive and control groups based on EEG signals [5], [7]–[11]. Lately, a Ph.D. student Tuuli Uudeberg from the brain bioelectrical signals research group at Tallinn University of Technology has introduced a novel feature extraction method, the in-phase matrix profile (pMP), specifically adapted for EEG signals [12] (publication under review). The method characterizes the general self-similarity of EEG signals and outperforms all other previously applied methods. The researchers implied that while pMP excludes amplitude information, the frequency fluctuations of the alpha frequency band might play a considerable role. Therefore, the current Master's thesis studies the EEG alpha band instant frequency to check whether instant frequency alone is able to differentiate depressive and control groups.

Depression presents high comorbidity with other neurological disorders, especially anxiety which may lead to different results in similar experiments. Researchers highlight the importance of understanding each characteristic of depression [5] and the utilization of multimodal shreds of evidence not limited to mood disorders but also psychomotor and cognitive functions [13]. In reviewing the literature, no data was found on the association between resting-state instantaneous frequency of EEG and depression.

The frequency of an alpha oscillation is assumed to represent the degree of inhibition in the thalamocortical system [14]. Alpha frequency has been linked to characterize individual differences in cognitive functioning and managing the speed of information processing [15], [16]. Fluctuations of neural oscillators around their mean frequency and power are often assumed to be spontaneous [17]. However, several studies have discovered the state and stimulus dependent changes in oscillatory activity [17]–[19]. The instantaneous frequency has been employed as a feature for the detection of the oscillatory type of seizures [20], [21]. Different methods have been proposed for estimation and analysis of instantaneous frequency in EEG data [22]–[24]. A suitable method for resting-state analysis has been introduced by Cohen [24] and then further investigated in a later study [25] to obtain the ground-truth properties of the signal. The results highlighted the systematical underestimation of the true oscillation frequency caused by the presence of aperiodic component in the signal as well as the choice of filter bandwidth.

The main aim of this study is to investigate the alpha oscillations in terms of instantaneous frequency changes taking into account the individual differences and aperiodic broadband activity of the EEG signal. The methodological approach taken in this study utilizes a Hilbert transform-based algorithm for instantaneous frequency estimation that had been widely applied for the investigation of neural data. To the best of the author's knowledge, this is the first study to apply the instantaneous frequency method to explore differences between healthy and depressive subjects. The reader should bear in mind that the following study employs only one of the several possible methods for instantaneous frequency quantification.

The main part of this work begins with an introduction that highlights the importance of the topic and states the purpose of the current study. The second section of the thesis is a literature review that provides a theoretical background for the periodic and aperiodic broadband activity of the EEG signal, common frequency bands, and a more detailed

description of the alpha band, as well as depression and its diagnosis with EEG biomarkers. The third chapter is concerned with the methodology used for this study. The fourth chapter provides an overview of the findings - differences in instantaneous frequency fluctuations within healthy and depressive groups. The fifth chapter discusses the results and offers a potential explanation for the findings. The main part of the work ends with a summary.

2 Literature overview

2.1 Neural oscillations

Neural oscillations, which are also known as brainwaves refer to the rhythmic and/or repetitive electrical activity generated spontaneously and in response to stimuli by neural tissue in the central nervous system (CNS) [26]. Neurons possess electrical excitability, which is the ability to respond to a stimulus, and convert it into an action potential. The stimuli can be described as any change in the environment that is strong enough to initiate an action potential which is an electrical signal that propagates along the surface of the membrane of a neuron [27]. Single neurons act as oscillators as far as they respond to a constant input current by repetitive firing of action potentials at a certain frequency [28].

Three main parameters for characterizing a single oscillating signal are frequency, amplitude, and phase [29]. A neural oscillator can be represented by the Hopf-Andronov (HA) bifurcation where a two-dimensional system has a stable fixed point and is described by the frequency of infinitesimal oscillations and the dependence of frequency on amplitude for larger amplitude oscillations. HA bifurcation takes place when, by continuously increasing or decreasing a parameter, the system switches from a damped oscillatory regime where oscillations fade away with time to sustained oscillations where periodic oscillations are maintained [30], [31].

Oscillatory activity originates either from individual neurons or from inter-neural interactions [32]. The general model of neuronal communication is that a neuron sends its message encoded in e.g. action potential rate or in the degree of action potential synchronization down its axons to all neurons to which it is anatomically connected. The receiving neurons combine all the different inputs that they acquired from all neurons to which they have connections [33]. This functional groups of neurons are organized into complicated networks called neural circuits (Figure 1) [27].

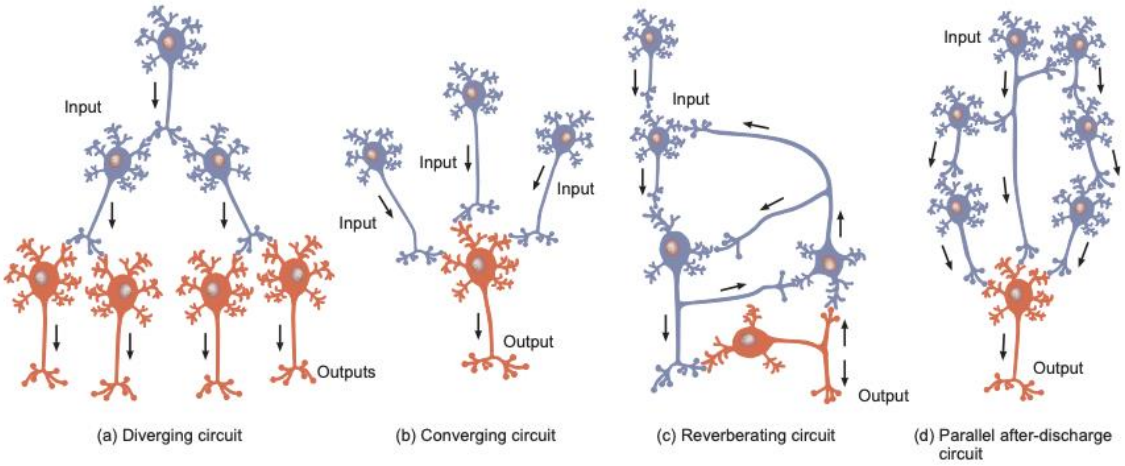

Figure 1. Neural circuits in different arrangements [27].

The electric potentials generated by single neurons are too small to be recorded outside the scalp whereas large-scale neural oscillations can be studied using electroencephalography (EEG) [32]. The rhythmic fluctuations in EEG signals primarily reflect the rhythmic synchronous firing of populations of pyramidal neurons, which are a common class of neurons found in areas of the brain including the cerebral cortex, the hippocampus, and the amygdala. The amplitude of the oscillation that defines the strength of the signal depends on the absolute number of firing pyramidal cells, their synchronicity, and periodicity. The rhythmic nature of individual neuronal firing bursts which leads to a population-level activity follows a sinusoidal pattern representing the high and low levels of activity [29]. Associations between various neurons can cause oscillations among different frequencies with respect to different situations [32].

2.2 Electroencephalography and common frequency bands

EEG was invented by German scientist Hans Berger in 1924. This recording technique measures electrical fields generated in the brain by groups of pyramidal cells of neurons that are modeled as micro dipole when they produce synchronized electric fields. EEG provides a high temporal resolution compared to other neuroimaging techniques. The recording procedure involves the placement of the electrodes that are generally made up of Ag/AgCl on the scalp. The location of each electrode is defined in compliance with the electrode placement systems such as the International 10-20 system, Maudsley system, and 10-10 system [34].

EEG signal is decomposed into component frequency bands, each of which has different functional characteristics (Figure 2).

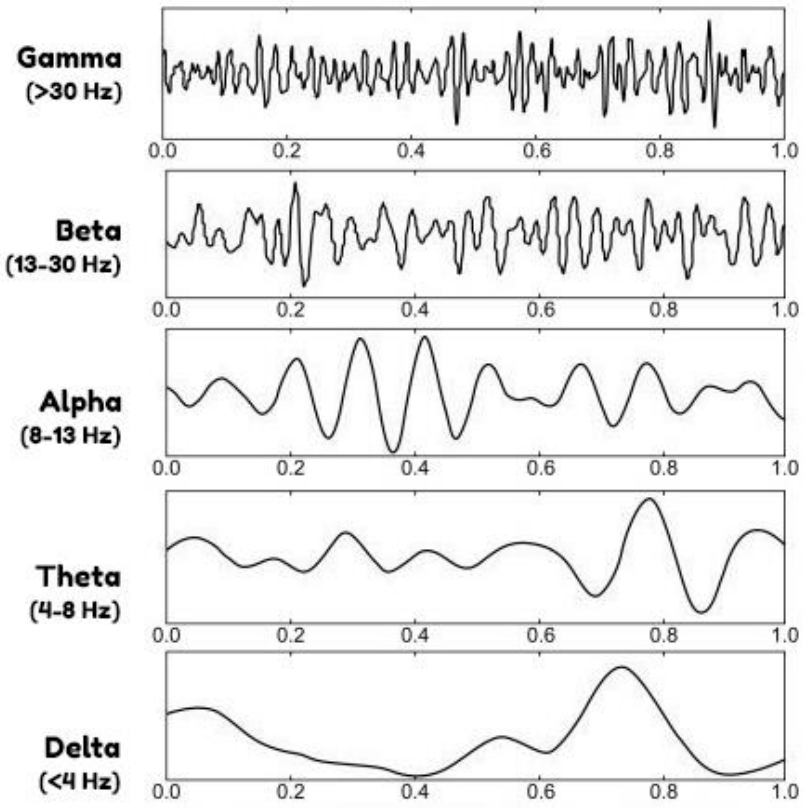

Figure 2. Classification of EEG signal in different frequency bands [35].

Delta rhythms (<4 Hz) are the slowest rhythm but with the higher amplitude. Delta waves have been associated with idling and sleep with higher values being observed when the subject is in deep sleep [34]. However, delta also plays an important role in cognition [36].

Theta rhythms (4-8 Hz) are often observed during the transition from wakefulness to sleep in adults. In the awake state, an increase in theta band occurs during memory-related tasks [37], [38] and has also been associated with the processing of emotional information [39] including the correlation of infant theta activity with the expression of positive and negative emotions [40], [41].

Alpha rhythms (8-13 Hz) are considered to be the dominant EEG frequency measured from the human scalp of adults [42]. They are commonly found over the occipital region of the brain and in the posterior half of the head with a higher power during eyes closed (EC) compared to eyes open (EO) conditions [34]. The properties of the alpha rhythm include the dominative behavior during relaxed wakefulness [42], strong genetic control [43] and stability over time [44].

Beta rhythms (13-30 Hz) are low-amplitude signals that are normally found in adults. They are associated with thinking, active attentions, solving concrete problems, or focusing on the outside world [34].

Gamma rhythms (>30 Hz) are mainly connected to perceptual and cognitive processes, linking the gamma waves to attention [45], object perception [46] and language related processes [47].

2.3 1/f neural electrophysiological noise

The human EEG signal is a mix of brain oscillations, i.e., periodic activity and non-oscillations i.e., aperiodic broadband activity or noise of uncertain origin [48]. These components of a signal stand in contrast to oscillations. An example of non-oscillatory component is white noise that is uniformly distributed across frequencies. In neural data, the aperiodic activity has an inverse power-frequency relation and is characterized by $1/f^x$ function where x is referred as the aperiodic exponent [49]. The case where the exponent equals 1 is the canonical case and is referred to as pink noise [50]. The presence of pink and white noise is greater across the scalp during EC state recording than EO [48].

Variability in oscillation features within predefined bands is often ignored leading to the misinterpretations of parameters such as narrowband power differences. An example of white and pink noise (1/f) presented in Figure 3 illustrates the result of narrowband filtering where an illusory oscillation occurs despite the absence of periodic features [49].

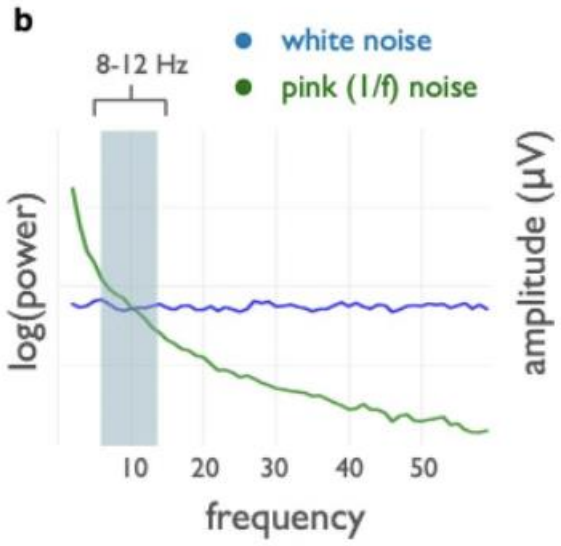

Figure 3. White and pink (1/f) noise examples [49].

The 1/f noise factor accounts for between-person variability in the magnitude of the broadband EEG activity while the alpha factor accounts for between-person variability in the amplitude of pure alpha oscillations [51]. Oscillatory (alpha) and non-oscillatory (1/f) activity components are mixed in recorded brain signals making the process of correcting for the aperiodic component problematic as pink noise also reflects physiological information [49].

Studies have revealed a relationship between a marker of neural noise and cognitive performance. Voytek and colleagues [52] found a higher presence of 1/f noise among older adults while performing a specific visual working memory task, which as a result indicates cognitive decline. Furthermore, Dave and colleagues [53] addressed the age-related changes in 1/f slope during language comprehension and effect on neural indices of accurate prediction of words during discourse comprehension. According to the study 1/f noise revealed high within-subject correlations and was a significant age predictor.

Overall, these studies highlight the need for understanding the functional role of the 1/f noise and its effect on oscillation features within predefined bands. Compared to white noise, pink (1/f) noise does not reflect meaningless unstructured noise but instead indicates valuable information about brain functioning and information processing.

2.3.1 Individual alpha frequency (IAF)

The traditional alpha range is about 8-13 Hz. However, the use of fixed frequency bands does not seem to be justified due to the large variety of the alpha frequency caused by brain volume, task demands, memory performance, age, and neurological diseases, raising the importance of interindividual variability in resting alpha activity [42]. The quantification of the spectral distribution variations within the alpha range can be done via peak alpha frequency (PAF) and individual alpha frequency (IAF). IAF is based on the center of gravity frequency (CoG) which depends on the shape of the power distribution. Compared to PAF which measures the frequency with the highest magnitude, IAF reflects the activity of the alpha population in a more adequate way taking into consideration the possibility of the multiple peaks' appearance [54].

In a study conducted by Klimesch [54] the proposed method for calculating the CoG utilized the selection of the individual's alpha bandwidth rather than employing a fixed range (8-13 Hz). This method allows capturing the entire range of an individual's alpha-

band activity taking into account the interindividual differences. Klimesch and colleagues [55] obtained the CoG (further denoted as IAF) by initially applying a Fast Fourier Transform (FFT) to each of the selected epochs to obtain the Power Spectral Density (PSD). Further averaging of the spectra improves the accuracy of spectral estimates. The IAF was calculated individually for each subject according to the formula:

$$IAF = \frac{\int_{f1}^{f2} PSD(f) \cdot f \, df}{\int_{f1}^{f2} PSD(f) \, df} \quad (1)$$

where f_1 and f_2 are individually determined frequency window based on visual inspection of the individual alpha activity.

In a later work Klimesch [42] proposed a less subjective method for defining the individual alpha band windows. The method focuses on exploiting the transition between theta and alpha band in order to define the lower frequency limit of the alpha band. The anticorrelation between theta and alpha band oscillatory dynamics is observed in response to task demands. The frequency in the power spectra which marks the transition is defined as individual transition frequency (TF). The initial procedure was firstly utilized for the mental stimuli, however later proposed to be applied for the resting-state EEG where the shift from alpha to theta band activity is evoked by the visual stimulation experienced upon opening the eyes [56].

A new promising line of research with a focus on quantification of the spectral feature of EEG attempts to quantify spectral peaks through statistical curve-fitting techniques. One of the methods was developed by Chiang and colleagues [57] addressing the need for unbiased and robust quantification of alpha power, frequency, and topography. The general approach is to fit parametric functions to the spectra from each recording site and then combine the parameters from all sites to produce topographically informative summary of the size and shape of each alpha peak. In order to identify and obtain peaks' associated parameters such as frequency, amplitude, and width, the spectra are fitted using a nonlinear algorithm with a series of criteria. Another automated spectral analysis technique was proposed by Lodder and van Putten [58] utilizing a three-component curve-fitting technique for dominant peaks in the EEG spectra during eyes-closed states.

An alternative curve fitting method has been demonstrated by Hinrikus and colleagues [8], in which the parabolic approximation was applied to the spectrum band determined

by the PAF value and bandwidth of 2 Hz from the central point. In a more recent study Corcoran and colleagues [56] described automated method for deriving PAF and CoG. The PSD of each channel was employed smoothened with Savitzky-Golay filter (SGF) to reduce the noise artifacts. The peaks within each channel were then extracted and averaged based on their peak quality to obtain the final estimate of IAF.

Despite the advantages that come from automated analysis methods, the curve fitting techniques are not widely implemented. The possible reasons might be the potential complexity of these methods for the studies where IAF is only an intermediate step within a broader analysis framework. Alternatively, researchers might be simply unaware of the existence of such approach for the quantification of alpha frequency [56].

2.4 Instantaneous frequency

Oscillatory neural dynamics are highly non-stationary making it more challenging to understand neural function. In order to quantify time-resolved changes in oscillatory activity, new methods are required [25]. Instantaneous frequency (IF) is applied to understand the detailed mechanisms for non-linear and non-stationary processes [59]. The frequency of the wave motion is defined as the number of waves which pass by any fixed point per unit time. Stationary signals can be represented as the weighted sum of sine and cosine waves with defined frequencies, phases, and amplitude. However, things are not so definite in the non-stationary case. The definition of instantaneous frequency is controversial, application-related and requires empirical assessment. For a dynamical oscillating system, it can be expressed as the change in the phase per unit time [60].

In terms of EEG time series instantaneous frequency can be defined as the first temporal derivative of the phase angle time series [24]. In the literature, different methods have been proposed for estimating and analysing changes in instantaneous frequency of EEG e.g. empirical mode decomposition [22] and frequency flow analysis [23]. However, the proposed methods have limitations when used for frequency band-limited analysis, thus a more robust solution that is also more suitable for resting-state investigations developed by Cohen [24] offers a computationally efficient approach based on the initially proposed definition of instantaneous frequency [60] and the Hilbert transform. The algorithm is described in more detail in the following chapter.

2.4.1 The algorithm based on the analytic signal

For any real valued signal *s(t)*, an analytical signal *z(t)* is corresponding to complex valued signal defined as

$$z(t) = s(t) + jH[s(t)] \quad (2)$$

where *H* is the Hilbert transform of the received signal *s(t)*, and *j* is the complex imaginary number. The Hilbert transform is defined as

$$H[s(t)] = p.v. \int_{-\infty}^{+\infty} \frac{s(t-\tau)}{\pi\tau} d\tau \quad (3)$$

where *p.v.* denotes the Cauchy principal value of the integral (i.e., to account for the $t = \tau$ situation) [60]. In other words, the Hilbert transform can be evaluated through computing the Fourier transform *S(t)* of the signal *s(t)* and multiplying *S(t)* by *-j* for positive frequencies, by *+j* for negative frequencies and by zero for DC component. After that the inverse Fourier transform is obtained [61].

It is then possible to define the instantaneous frequency $f_i(t)$ as

$$f_i(t) = \frac{1}{2\pi} \frac{d\ arg(z(t))}{dt} \quad (4)$$

where *z(t)* is the analytical signal given by (2) [60].

The following method for estimating instantaneous frequency of a signal is integrated inside the MATLAB (The MathWorks, Inc.) function instfreq.m as 'Hilbert' method.

2.4.2 Alternative causes of estimated frequency modulation in neural data

The instantaneous frequency and phase provide information about the speed and timing of neural network communication helping to understand the evolvement of information processing across the cortex and over time [62]. This approach (also termed as frequency sliding for Hilbert method) has been applied in a number of experiments e.g. to analyse visual task demands [63], as well as response to the visual stimuli [64] and predict observed sensory inputs [65]. Despite the utilization in the field, the frequency sliding has not been extensively tested to recover the ground-truth oscillatory frequency of simulated data until the new study conducted by Samaha and Cohen [25].

In a recent study by Donoghue and colleagues it has been noted that the aperiodic component of the signal, particularly 1/f (pink) noise can confound measurements such as oscillatory power or band-power ratios [49]. Samaha and Cohen [25] analysed simulated data wherein an oscillation of 10 Hz with varying amplitude was embedded within a $1/f^x$ signal with a varying exponent. The results presented in Figure 4 indicate the increased bias with an increase of aperiodic exponent, as well as the dependence on the oscillation amplitude, leading to a reduced bias and nearly absent impact of the aperiodic component for oscillations with larger amplitude. The dependency can be explained by a changing contribution of the aperiodic component to the signal, whereas the increase in the amplitude of the periodic component makes $1/f^x$ noise less influential.

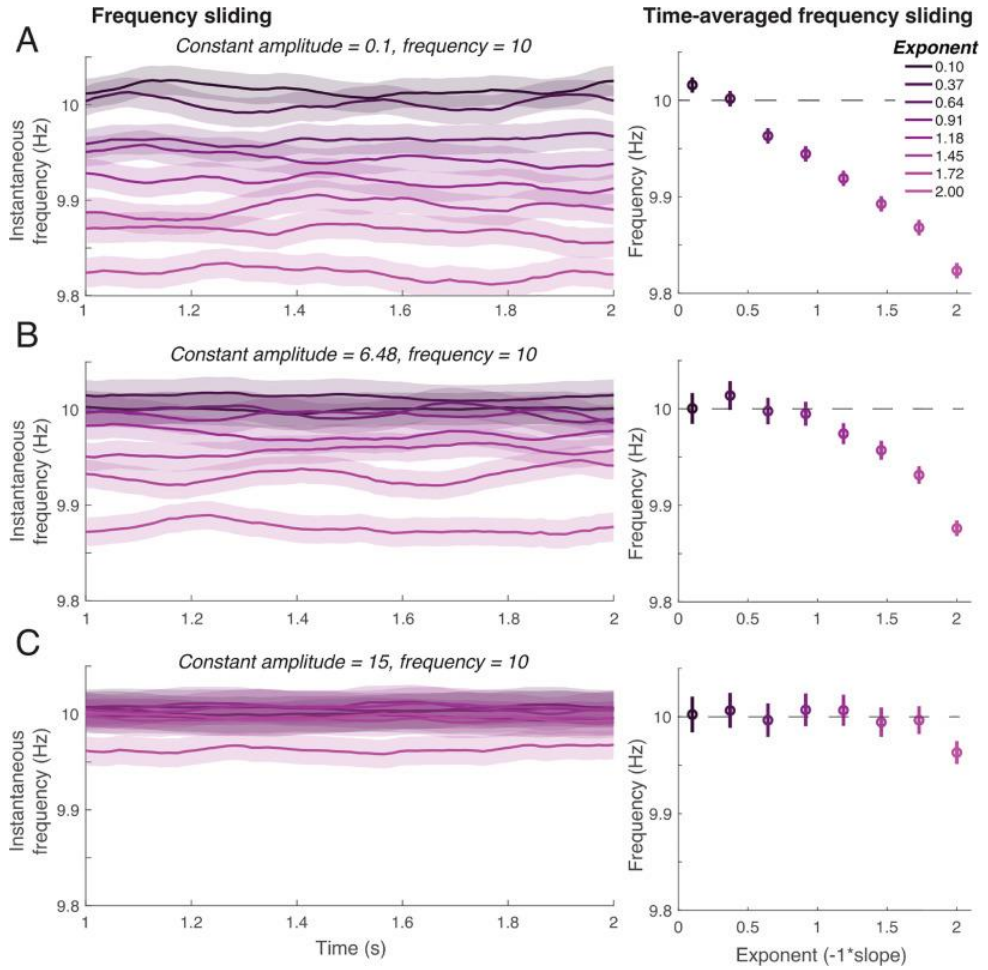

Figure 4. Accuracy of recovering the simulated frequency via frequency sliding. A) At low amplitudes the frequency bias is greater and increases as the slope of the aperiodic component of the power spectrum increases. B) At medium amplitudes the underestimation is notable at larger exponents and is attenuated at small ones. C) The impact of the aperiodic component is nearly absent at large amplitudes. Oscillation amplitudes are measured in microvolts and approximate the range of peak-to-peak amplitudes of single trial alpha oscillations observed in EEG [25].

Besides the influence of the aperiodic component, researchers also explored the impact of filter bandwidth and location on the relationship between oscillation amplitude, aperiodic slope, and estimated frequency, particularly for the alpha band (Figure 5). A filter placed below or above the alpha peak leads to frequency sliding estimates that either strongly underestimates (if below) or strongly overestimate (if above). A filter with a large bandwidth attenuates the simulated frequency, while a very narrowband filter strongly attenuated the underestimation, however it limits the possibility to recover meaningful variations in frequency [25].

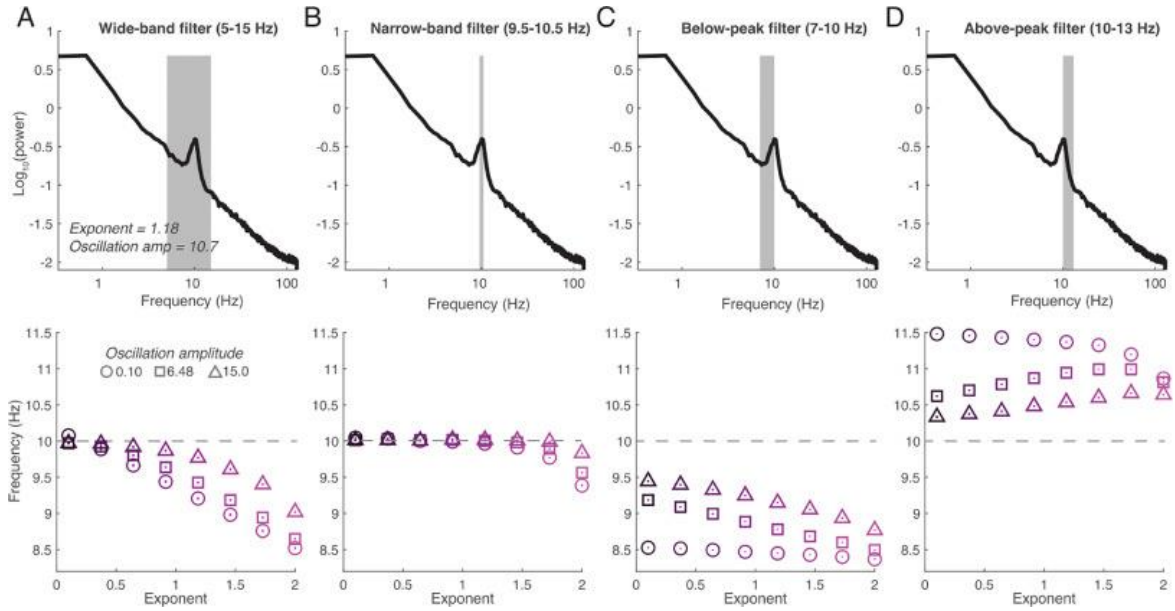

Figure 5. The impact of filter bandwidth and location on estimated frequency. A) Example of a wide-band filter that is centered on the true oscillation peak (10 Hz) but extends substantially below and above the peak increasing of the influence of the aperiodic component. B) Example of overly narrow filter that suppresses the aperiodic component but is insensitive to any fluctuations in frequency. A filter placed below (C) or above (D) the true oscillation peak leads to strong, amplitude-dependent underestimation [25].

2.5 Quantitative EEG biomarkers for depression

The debates around EEG valuableness in the clinical diagnostics of psychiatric diseases have been arising for a long time [66]. The detection rate was declared to be relatively low to provide sufficient information for further diagnosis or patient management [67]. EEG was also concluded to not be a suitable diagnostic tool for ADHD highlighting the need for further development in the analytical and technological domains to anticipate future progress in its utility [68]. On the other side, the sensitivity of the pathological EEG findings in patients with mild Alzheimer's dementia was sufficient for the diagnosis of the disease [69].

Despite the dispute, the findings in recent years indicate the potential of EEG for patients suffering from depressive disorders for diagnostic [7], [9], [13] and planning of the optimized treatment option [6], [70]. The recent advancements in EEG make it a powerful tool for non-invasive investigation of the brain with a high potential towards objective measures of complex illnesses such as depression.

2.5.1 Assessment and diagnosis of depression

Depression is a common illness worldwide with an estimated 4.4% of the population affected according to the World Health Organization (WHO) which results in approximately 322 million people in the world. The illness is considered to be the leading cause of disability and a major contributor to the overall global burden of disease. According to the report, the number of people in the world living with depression has increased by 18.4% between 2005 and 2015 [1], whereas the global prevalence of anxiety and depression increased by 25% in the first year of the COVID-19 [2] and is projected to rank as the first cause of burden disease worldwide by 2030 [3].

In clinical practice, the diagnosis of depression and its further treatment and management often pose challenges for clinicians due to its various presentations, unpredictable course and prognosis, and variable response to treatment [4]. The two main classificatory diagnostic systems Diagnostic and Statistical Manual of Mental Disorders (DSM) [71] and the International Classification of Diseases (ICD) [72] are based on identifying a number of key symptoms. Depression is often diagnosed using questionnairies that are prone to professionals' and patients' subjectivity. Finding non-invasive EEG biomarkers for depression may help to diagnose the disorder more objectively [5] as well as allow diagnostic tests that predict treatment response and minimize patients' suffering [6].

2.5.2 Biomarkers

The term biological marker (biomarker) is defined as "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [73]. Biomarkers can be used in disease screening, diagnosis, characterization, and monitoring, as well as for the development of individualized therapeutic interventions, prognostic indications, prediction, and treatment of adverse drug reactions. Good biomarkers should be measurable with little or no variability and have a sizable signal to noise ratio [74].

The common depression biomarker types using EEG are classified as: various absolute or relative band powers, alpha asymmetry, functional connectivity, different nonlinear measures etc.

Band power derived from the frequency has been widely studied and applied in order to distinguish depressive from healthy subjects [5]. For example, a study by Lee and colleagues reported a higher alpha power originating from the central areas of the left hemisphere for depressed compared to control subjects [75]. Alpha asymmetry measures the relative alpha-band activity between the brain hemispheres at the location of frontal electrodes. Previously mentioned study by Lee and colleagues indicates the increase in alpha activity at the left side of the brain, however, the study does not compare the activity with the right side [5]. Several studies outlined that alpha asymmetry may predict specific symptoms and treatment outcome [10], [76]. However, the conflicting findings within the literature [11], [77] indicate the unknown impact of gender in alpha asymmetry.

In a study conducted by Guo and colleagues [78] authors observed the functional connectivity abnormal via the superior and middle frontal gyrus in depression patients compared to healthy subjects. Another method giving promising results utilizes Higuchi's fractal dimension to measure fractal dimension of EEG signal and seems to be greater in depressed patients [7]. Lately, a Ph.D. student Tuuli Uudeberg from the brain bioelectrical signals research group at Tallinn University of Technology has introduced a novel feature extraction method, the in-phase matrix profile (pMP), specifically adapted for EEG signals [12] (publication under review). The method characterizes the general self-similarity of EEG signals and outperforms all other previously applied methods. The researchers implied that while pMP excludes amplitude information, the frequency fluctuations of the alpha frequency band might play a considerable role.

3 Method

3.1 EEG data collection and pre-processing

The study was conducted using pre-collected EEG data recorded in the Department of Health Technologies from a group of medication-free right-handed outpatients with major depressive disorder and a control group with matching age, gender, and handedness characteristics. Both groups consisted of 13 subjects (5 male and 8 female) with a mean age of 38.7 and a standard deviation of 15.8 years. Patients underwent a clinical interview and were diagnosed with a single (9 patients) or recurrent (4 patients) depressive episode based on ICD-10 criteria.

The data was acquired using Neuroscan Synamps2 system (Compumedics, NC, USA) and 30 electrodes positioned according to the international 10-20 extended system (Figure 6). In addition, reference electrodes on each mastoid as well as horizontal and vertical electro-oculograms (EOG) were used. Electrode impedances were kept below 10 kΩ and sampling frequency was 1000 Hz.

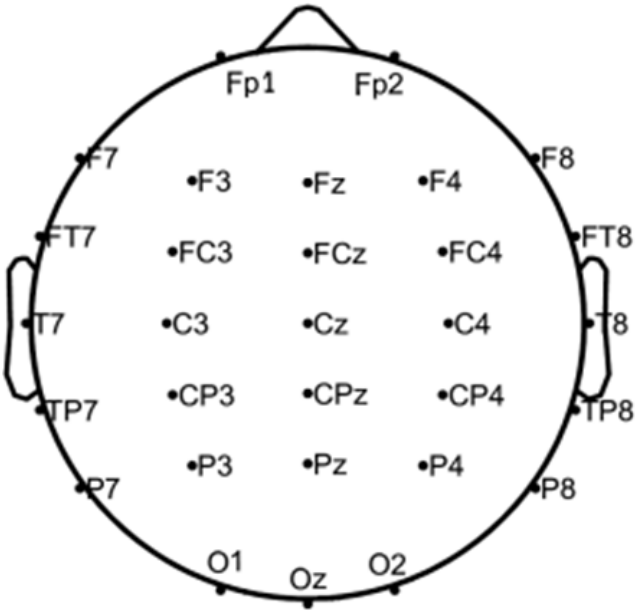

Figure 6. International 10-20 extended system with 30 electrodes [79].

Further analysis was performed on 5-minute eyes closed Oz single channel signal obtained from 0-10 minutes section of the EEG recording and cut into 100 epochs with a length of 3 seconds each. The epochs were visually inspected and segments with artefacts were replaced. The selection of the channel was based on the high presence of alpha waves in the occipital region during the eyes-closed state [80]. All signal preprocessing and calculations were done in MATLAB software.

3.2 Removal of 1/f noise and signal demodulation

In order to investigate and minimize frequency sliding bias caused by 1/f (pink) noise the method proposed by Samaha and Cohen [25] was employed. Compared to other solutions [49], [81], [82], it allows to invert the spectrum back into the time domain overcoming the issues with producing a demodulated spectrum with negative amplitude values at any frequency. The workflow of the algorithm for the attenuation of 1/f (pink) noise and demodulation of the signal is presented in Figure 7.

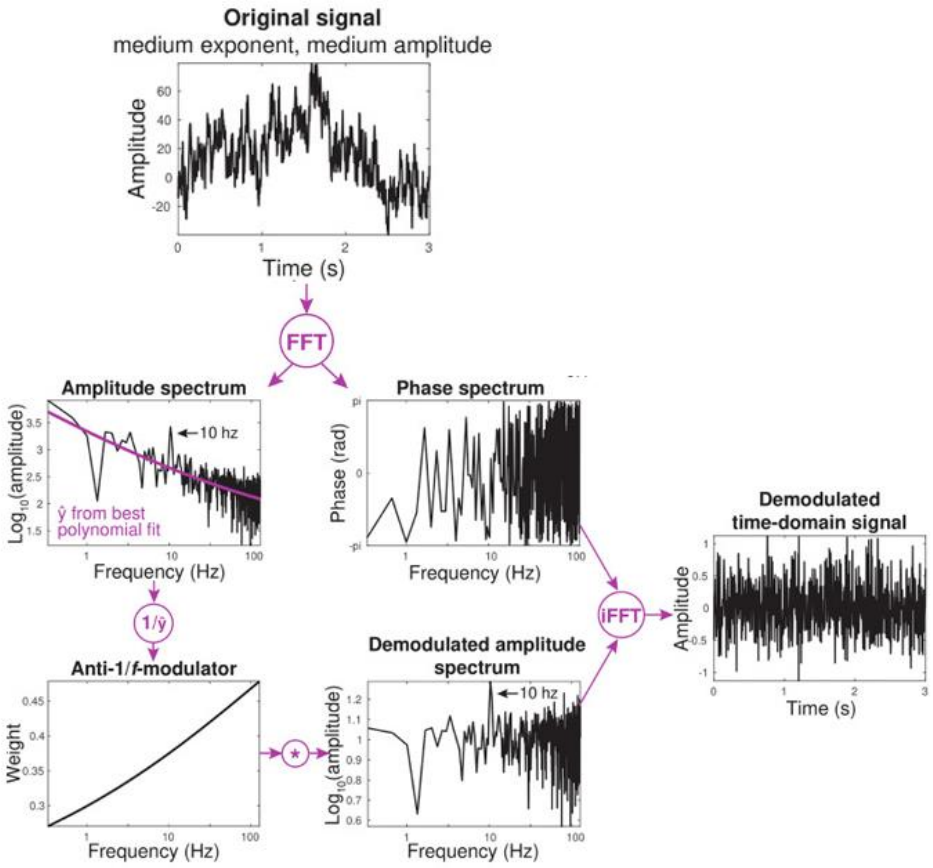

Figure 7. The workflow of the algorithm for the reconstruction of the time-domain signal with attenuated 1/f [25].

In current study, the 1-st degree polynomial fitting (MATLAB polyfit function) was computed for the power spectrum with a frequency band of 1 to 50 Hz in $\log_{10}$-$\log_{10}$ space as the distribution of 1/f (pink) noise is expected to be linear. The power spectrum was obtained through FFT. Examples of the curve fitting are presented in figure Figure 8.

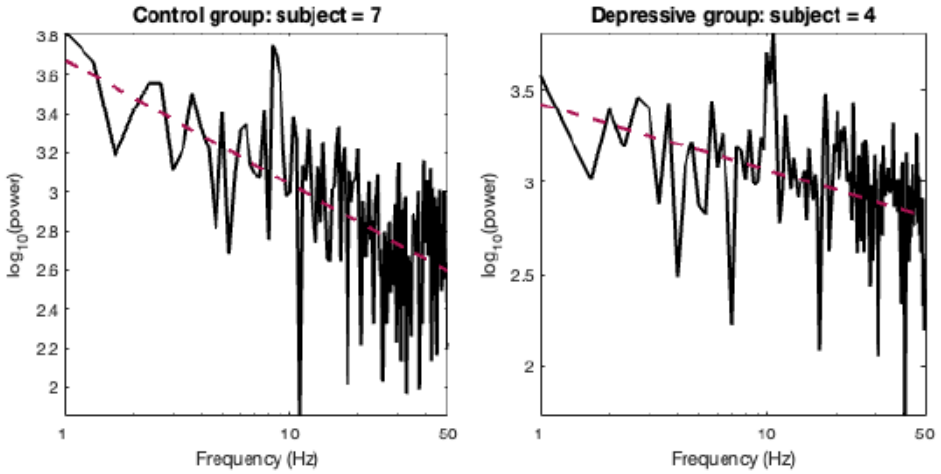

Figure 8. 1-st degree polynomial fitting for the power spectrum obtained through FFT.

The best-fit model was evaluated using MATLAB function polyval. The inverse of the best-fit model was multiplied by the empirical power spectrum (frequency wise) and then combined with the original phase spectrum. The signal was reconstructed back to the time-domain by obtaining the inverse FFT. The attenuation and reconstruction of the signal were performed for each epoch (Figure 9).

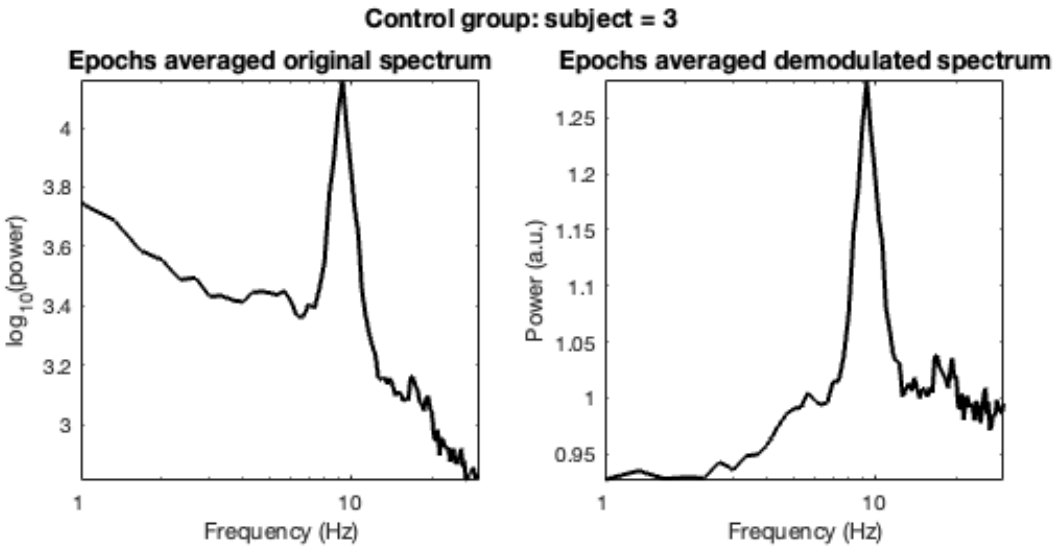

Figure 9. Comparison of original and demodulated (1/f noise removed) signal spectrums.

3.3 Estimation of IAF

An essential aspect of the frequency sliding evaluation is the presence of the alpha oscillation peak in the power spectrum and the consideration of inter-individual differences. The quantification of the spectral feature of alpha band utilized the curve fitting method proposed by Hinrikus and colleagues [8].

At first, the PAF was estimated by obtaining the maximum power value in the region of alpha band 7-14 Hz using trials (epochs) averaged demodulated spectrum (1/f removed) obtained through FFT. Thereafter the parabolic approximation was applied to the predefined spectrum band (in $\log_{10}$-$\log_{10}$ space) with a width of ± 2 Hz from the central point defined by the PAF value. Using the MATLAB polyfit function, the coefficients of a polynomial function that fit the data in a least-square sense were obtained. The maximum value of the fitted parabola was taken as IAF of the subject (Figure 10).

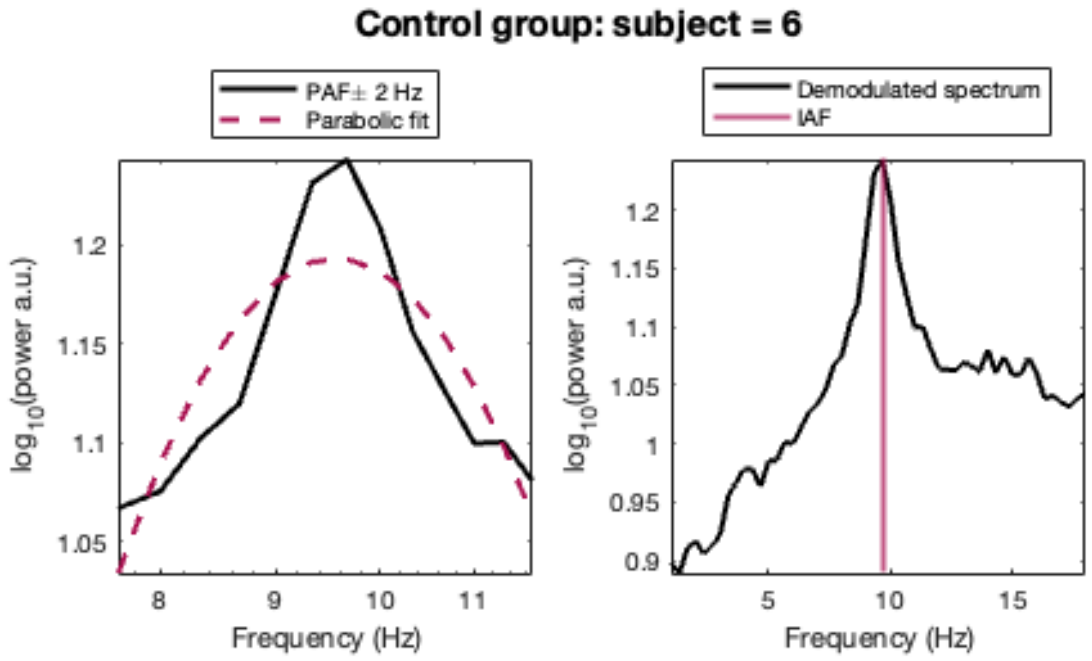

Figure 10. Example of IAF estimation. The parabolic approximation is applied to PAF defined alpha band spectra. The maximum value of the fitted parabola is taken as IAF.

Alpha oscillation peaks as well as IAF results were visually inspected for each individual. In case of non-defined alpha oscillation peak the IAF was obtained through CoG frequency (Formula 1, Chapter 2.3.1).

3.4 IAF based narrowband filtering

According to the studies [24], [25] a filter with a plateau-shaped frequency response centered on the oscillation peak can help to minimize or eliminate the biases. Thus, the filter was designed on subject-by-subject level with a center point corresponding to individual IAF. The filter bandwidth was selected as ± 2 Hz from the central point. A window-based FIR filter (MATLAB function fir1) with small transition bandwidths (Figure 11) was applied to each 3 seconds epoch. Filter order was selected as 950.

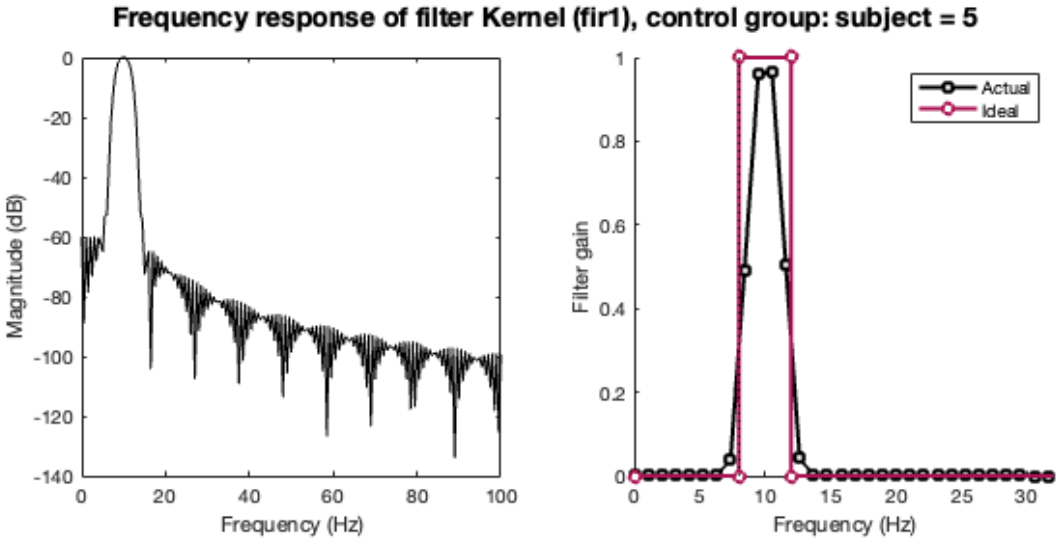

Figure 11. Frequency response of the IAF FIR based filter.

3.5 Instantaneous frequency calculations and analysis

Instantaneous frequency and phase were calculated for each epoch using MATLAB function instfreq and the method was selected as Hilbert. The algorithm is described in detail in chapter 2.4.1.

The obtained instantaneous frequency was further analyzed to investigate the oscillations in the alpha frequency of each subject, particularly to investigate the intensity of abrupt instantaneous frequency fluctuations. For this purpose, the instantaneous frequency of each segment was compared to the IAF value in order to obtain the changes that do not fit within the selected frequency range. To avoid the sharp spikes caused by the Hilbert transform only the middle part of the segment was investigated. The examples of healthy subjects are illustrated in Figure 12. The range defined as IAF ± 3.6 Hz, was calculated individually, where 3.6 Hz was selected based on the observation of frequency response

of the designed filter where the attenuation reached 40 dB. The result was represented through vectors of binary digits, where 1 indicated the values outside the range. After that, the difference between the adjacent elements of the vectors was computed to detect the beginnings of the periods where the instantaneous frequency would rise outside the defined range. In addition, the first value of each vector was checked to consider the case where the beginning of the segment started with values outside of the range. The sum of all fluctuations that exceeded the predefined range was computed.

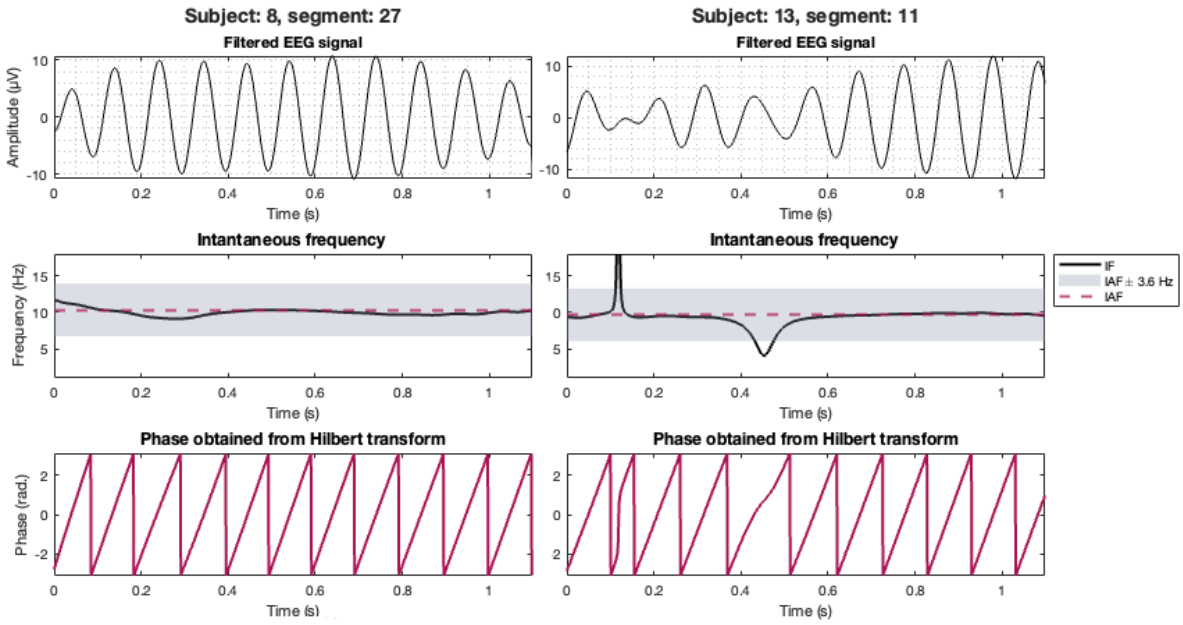

Figure 12. Examples of instantaneous frequency and phase of healthy subjects' segments. The first graph illustrates the raw EEG signal after applying a window-based filter with a bandwidth of 7-14 Hz. The second graph shows the instantaneous frequency fluctuations around IAF (purple line), whereas the grey area indicates the acceptable range defined from the filter response.

3.6 Statistics

Statistical analysis was performed using the Wilcoxon rank-sum test which is used to compare two independent samples. To assess whether the resulting sum of all fluctuations indicating the out-of-range frequency activity is statistically significant between depressive and control groups, the p-value (between 0 and 1) is computed. It describes the probability of the rejection of the null hypothesis that indicates the absence of difference between the two groups. The significance level alpha α which is the probability of making the wrong decision when the null hypothesis is true is set to 0.05. Thus, if $p < \alpha$, then the null hypothesis is not valid and there is a statistically significant difference between the two groups, whereas if $p > \alpha$, then the null hypothesis is true.

4 Results

The first set of analyses of the alpha oscillations after the elimination of the aperiodic 1/f noise component was performed to obtain the IAF value for each subject. Figure 13 presents the spectrum of the 3rd subject from the depressive group for whom the polynomial fitting method was not suitable, thus the IAF value was computed through CoG using Formula 1 (Chapter 2.3.1).

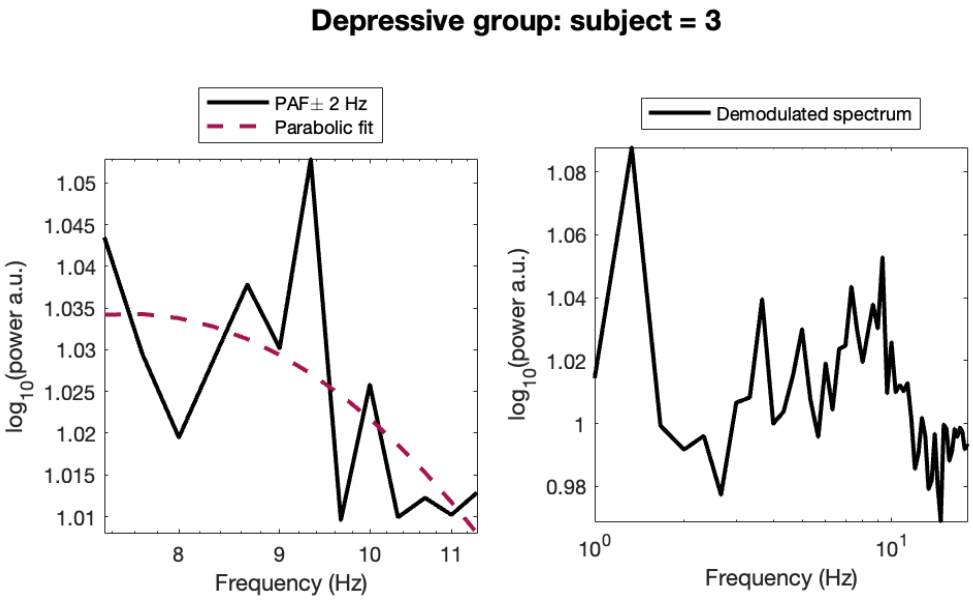

Figure 13. Spectrum of 3rd subject from the depressive group.

Now turning to the investigation of the intensity of the abrupt instantaneous frequency fluctuations, the sorted IF values for depressive and control groups are presented in Figure 14, where the total sum of abrupt fluctuations is reported for each subject.

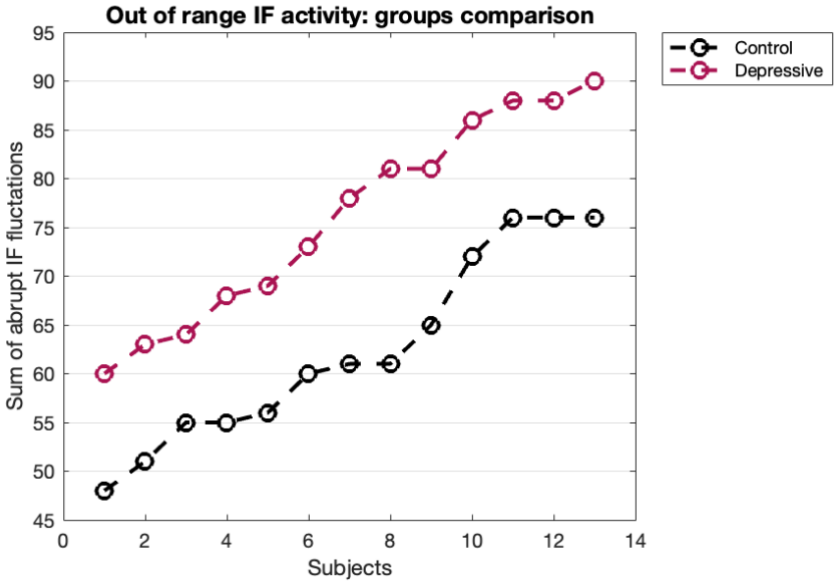

Figure 14. The sum of abrupt IF fluctuations of each subject from control and depressive groups.

The average number of abrupt instantaneous frequency fluctuations for control and depressive groups are presented in Figure 15. There was a significant difference between the two groups. On average depressive subjects were shown to have a higher number of instantaneous frequency fluctuations compared to the control group. The Wilcoxon rank-sum test revealed a significance level of 0.0044 leading to a rejection of the null hypothesis. The result is significant at the p = 0.05 level.

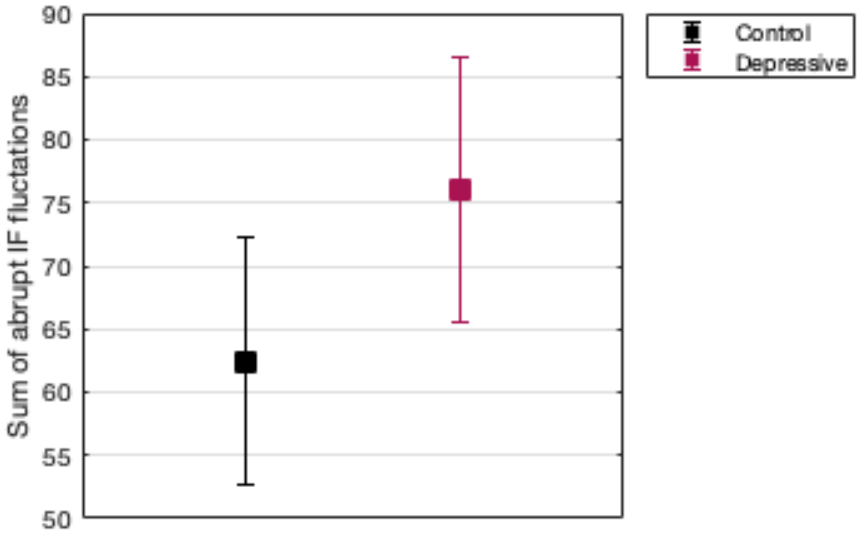

Figure 15. The average number of abrupt IF fluctuations for control and depressive groups. Vertical bars denote the standard deviation. The difference is statistically significant at the level of p = 0.05.

5 Discussion

The present study was conducted to investigate the changes in the oscillatory frequency of depressive and healthy control subjects. The results indicate that the instant frequency abrupt fluctuations in the EEG alpha band can differentiate the depressive group from the controls. There was a statistically significant difference between the two groups, demonstrating a higher amount of instantaneous frequency spikes registered for the depressive group. Those fluctuations are most probably partially causing the effectiveness of the newly developed pMP method. Still, not all of the pMP effectiveness can be explained by the abrupt changes in instant frequencies, and the mPM method needs further studies to be thoroughly explained.

The obtained result is in accordance with previous results where the EEG signals of depressive subjects have shown increased sample entropy and Lempel Ziv Complexity [83] and a positive correlation between the severity of depression and EEG alpha band complexity measures [84] as the increased number of abrupt changes could also indicate the more complex character of the EEG signal.

One can speculate on the cause of those abrupt frequency changes. In his work Cohen [24] explained the cause of the non-physiological frequency fluctuations as the noise-driven jumps and removed them, whereas the current work interpreted the jumps as possible physiological processes carrying useful information. Although the EEG alpha band has a clear dominant frequency for most of the subjects, it does not consist of exclusively the dominant frequency. Therefore, the seemingly abrupt changes could be caused by the interflow of several frequencies present in the alpha band. An alternative explanation of the current findings could be that the resting state networks go through some phase transitions which are detected. For example, it has been argued, whether event-related potentials are generated by the evoked response or produced by the result of a phase reset [85]. During the resting state condition, the alpha band frequency has the highest power but cannot be considered as a stable background activity, thus the different phase transitions can be expected.

In the current work, only the abrupt fluctuations of instantaneous frequency were considered since they have a higher effect on pMP method. Additionally, the small frequency shifts of the alpha dominant frequency might be of interest as the frequency of an alpha oscillation is assumed to represent the degree of inhibition in the thalamocortical system [14].

The main source of limitation of the current study is the small sample size. In addition, these findings are somewhat limited by the assumption that the physiological processes that underline oscillation amplitude and frequency modulation are independent of those that generate the aperiodic activity [25]. Besides that, the fitting of the line for the 1/f component was performed in a fixed mode [49], where the 'knee' parameter *k* controlling the bend in the aperiodic component was set to *k=0*.

Due to the limited scope of the Master's thesis, several questions remain unanswered at present. To develop a full picture of the potential physiological processes behind the instantaneous frequency fluctuations, additional studies are needed utilizing the data collected across all EEG channels. Also, the aperiodic component of the alpha band should be explored in future studies. Additionally, the stability of the 1/f (pink) noise over time could be investigated.

6 Summary

The present study was conducted to investigate the changes in the oscillatory alpha frequency of depressive and healthy control subjects taking into account the individual differences and aperiodic broadband activity of the EEG signal. The methodological approach taken in this thesis utilizes a Hilbert transform-based algorithm for instantaneous frequency estimation that had been widely applied for the investigation of neural data. The correction for the aperiodic component was performed through the 1st degree polynomial fitting.

The results of the study indicate a statistically significant difference between the control and depressive groups, demonstrating a higher amount of instantaneous frequency spikes registered for the depressive group. The study strengthens the idea that depressive subjects have a more complex character of the EEG signal.

This study has been one of the first attempts to thoroughly examine the difference in instantaneous frequency between healthy and depressive subjects. The main source of limitation is the small sample size of the study. The study is limited by the lack of information regarding the aperiodic component and the assumption that the physiological processes that underline oscillation amplitude and frequency modulation are independent of those that generate the aperiodic activity. Additionally, the possible changes of the aperiodic component over time and its influence on the frequency estimations were not investigated. Further research needs to examine more closely the links between the aperiodic component and depression, as well as investigate the possible physiological processes that could explain the fluctuations of alpha oscillations.

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