Czech Technical University in Prague
Faculty of Electrical Engineering

Department of Circuit Theory
Study programme: Medical Electronics and Bioinformatics

EEG Changes Assessment after Transcranial Alternating Current Stimulation

BACHELOR THESIS

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BACHELOR'S THESIS ASSIGNMENT

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I declare that the presented work was developed independently and that I have listed all sources of information used within it in accordance with the methodical instructions for observing the ethical principles in the preparation of university theses.

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Jakub Svoboda

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EEG Changes Assessment after Transcranial Alternating Current Stimulation

Název práce:
Vyhodnocení změn EEG po transkraniální stimulaci střídavým proudem

Author:	Jakub Svoboda
Study programme:	Medical Electronics and Bioinformatics
Type of thesis:	Bachelor thesis
Supervisor:	Ing. Petr Ježdík PhD. Department of Measurement, Department of Circuit Theory, LVR
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Abstract: Research on modulating brain activity using electrical currents has been increasingly popular in the last few decades. Brain stimulation techniques have a range of promising applications in therapy and neuroscience. This thesis investigates the effects of transcranial alternating current stimulation (tACS), with the frequency of 7 Hz, on the brain's resting state. We developed a methodology for conducting the study and measured five healthy students' brain activity before and after the stimulation. All of the volunteers were right-handed, their ages ranging from 21 to 26 years. We computed several measures to analyze the neural activity and communication between the regions of the cerebral cortex in the delta, theta, alpha, and beta frequency bands. We registered a few significant shifts in power of neural oscillations and connectivity between some brain areas (notably in the delta and theta rhythms). Most of these changes affected the left hemisphere, which was the stimulation site.

Key words: brain stimulation, electroencephalography, connectivity

Abstrakt: Výzkum modulace mozkové aktivity pomocí elektrického proudu je v posledních desetiletích stále populárnější. Techniky mozkové stimulace mají řadu slibných aplikací v terapii nebo neurovědách. V této práci zkoumáme účinky transkraniální stimulace střídavým proudem (tACS) s frekvencí 7 Hz na klidový stav mozku. Vyvinuli jsme metodiku pro provedení studie a naměřili jsme mozkovou aktivitu pěti zdravých studentů před a po stimulaci. Všichni dobrovolníci měli dominantní pravou ruku a jejich věkový rozsah byl od 21 do 26 let. Bylo spočítáno několik měr pro analýzu neurální aktivity a komunikace mezi regiony mozkové kůry ve frekvenčních pásmech delta, théta, alfa a beta. Zaznamenali jsme několik podstatných odchylek ve výkonu neurálních oscilací a v konektivitě mezi některými oblastmi mozku (zejména v delta a théta rytmech). Většina těchto změn se týkala levé hemisféry, na které byly stimulační elektrody umístěny.

Klíčová slova: mozková stimulace, elektroencefalografie, konektivita

Contents

List of Acronyms

EEG Electroencephalography

tACS Transcranial alternating current stimulation

IC Imaginary coherence

GC Granger causality

DR Difference ratio

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Chapter 1

Introduction

The study of the brain is one of the most complex fields in scientific research. This organ, with its complexity, surpasses all known structures in the universe. It fulfills numerous tasks, from keeping the vital organs functioning to processing the important decisions we make in every waking moment. It presents us with the reality we perceive and lets us transform it.

The possibility of examining brain activity in itself, however, arose only relatively recently. In the first half of the twentieth century, electroencephalography (EEG) came about. This method records the electrophysiological activity of the brain, from which we can infer many conclusions. Since its conception, many developments have been made, like electrode placement standardization for better research comparison or classification of neural oscillation frequencies into frequency bands, historically known as delta, theta, alpha, beta, and gamma. These oscillations have been shown to change their properties, like amplitude and region of prominence, depending on the cognitive or behavioral task at hand.

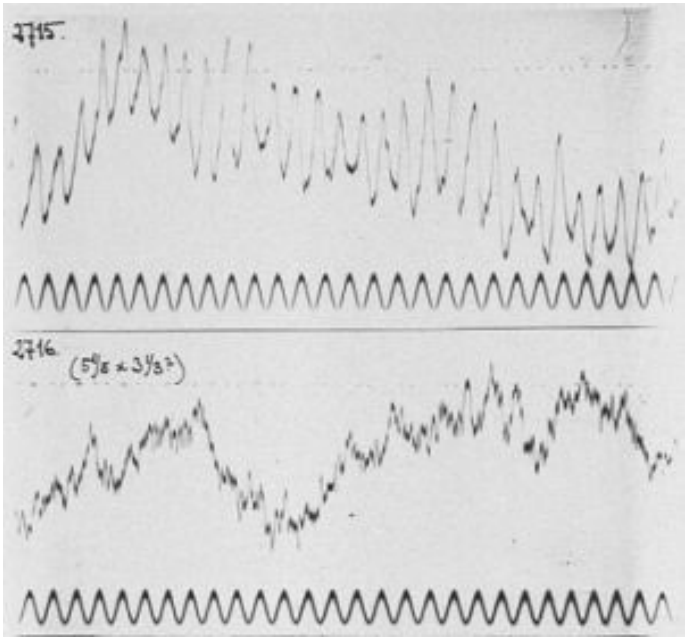

Figure 1.1: Some of the human EEG recordings realized by the pioneer of electroencephalography, Hans Berger. Obtained from [1] and modified.

However, the study of activation of isolated brain regions alone is not sufficient for progress anymore. Tens of billions of neurons in the brain form complicated and interconnected neural networks. Investigating the interactions between these networks is perceived as key to understanding the principles of cognition or psychopathological disorders. In the past few decades, the emphasis has been put on developing methods of the so-called connectivity analysis. These methods provide us with new insights into the interactions between various signals. From these interactions, we can infer a great deal about the brain's functional structure - how different regions communicate to perform tasks.

Besides the fascination with the brain's intrinsic phenomenons, there is the desire to intervene with them directly. Modulation of brain activity is an exciting topic in neuroscience nowadays. There is a variety of neuromodulation methods. Among the least invasive and most accessible are the transcranial electric stimulation methods (TES), including our method of choice, transcranial alternating current stimulation (tACS). Pairs of electrodes are used to deliver electrical current through the scalp. This current then influences the electrical activity in the brain.

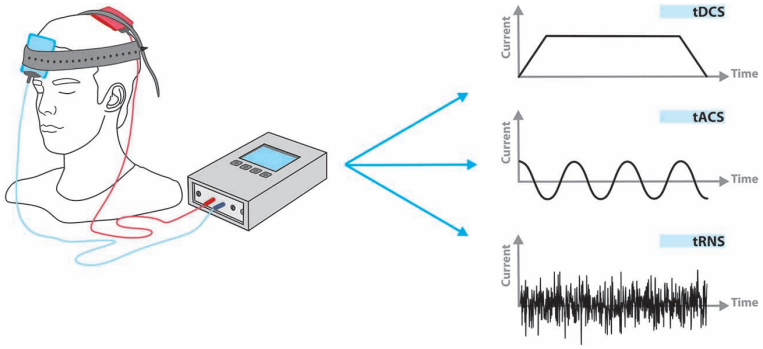

Figure 1.2: Three types of transcranial electric stimulation: direct current, alternating current and random noise stimulation [2]

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Some of the promising applications of transcranial electrical stimulation are, of course, in neuroscience research, psychology, brain function augmentation, or even oncology. By delivering electrical stimuli to the brain, we can observe its response and test various hypotheses. This direct stimulation can be seen as an alternative to performing cognitive and behavioral tasks. Next, the natural idea would be to look for stimulation configurations that, for example, enhance cognitive functions like working memory or attention. Some setups even seem to have mild neuroplastic effects. Finally, tACS stimulation with frequencies around 200 kHz might result in temporary tumor growth inhibition [3].

This thesis explores how the effects of tACS project into the power spectra of neural oscillations and several connectivity measures. We stimulate by the frequency of 7 Hz, which falls into the upper theta range of brain waves. Stimulation electrodes are positioned on the frontal and parietal lobes of the left hemisphere.

In the measurement protocol, the tACS intervention is sandwiched between two EEG recordings of spontaneous brain activity. The first recording tells us approximately what is the normal activity of the brain like. Whereas in the second, we expect to see some changes induced by the stimulation, be it on a local or a global level.

We pose a few questions concerning the activity and connectivity of the brain. For instance, has the connectivity between left and right hemispheres changed? Is there a difference in the power of, e.g., the theta rhythm in the lobes of the cerebral cortex? To answer questions

like these, we performed analysis on both recordings and executed statistical tests to learn if there was a statistically significant change due to the stimulation.

Since the sample size tested is very small, it does not provide any firm evidence. That makes this thesis more of a methodological exercise. However, the value it offers to us is still immense, and it does serve as a valuable lesson for us in future neuroscientific studies. It also provides some insight into brain research for the interested reader.

Chapter 2

Essential Concepts

This chapter familiarizes the reader with basic concepts in neuroscience, providing a better understanding of the subject, the steps we take, and the methods we use.

2.1 The cerebral cortex

Also referred to as the gray matter, the cerebral cortex is the wrinkly outermost layer of the brain. It is a theater of cognitive processes. Anatomically, it is divided into four lobes in each hemisphere: frontal, temporal, parietal, and occipital. It would be wrong to assume that this division also strictly applies to functionality, although some functions tend to be attributed to some lobes more than others. The frontal lobe, for instance, is believed to play a central role in the execution of higher functions such as reasoning, planning, or emotional regulation. [4].

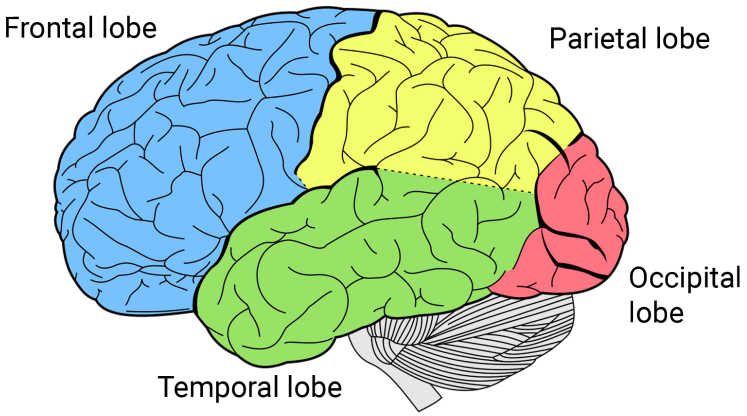


Figure 2.1: The division of the human brain into four lobes: frontal, temporal, parietal and occipital.

2.2 Electroencephalography

Electroencephalography uses electrodes positioned on the scalp of the measured subject. The electrical potentials are taken from the scalp, and their difference against a reference

electrode (placed on the earlobe) is recorded. This principle is identical to other biopotential recording methods, such as electrocardiography (heart activity). Consistent with any other real-world measurement, EEG recordings are plagued with noise. Be it from surrounding electromagnetic fields, the body's own diverse activity, or other factors. In addition to that, the magnitude of the recorded potentials is in the order of microvolts. It is then necessary to understand the pitfalls of the method to be able to avoid them to some extent.

2.3 Electrode positioning standards

To ensure that the results are comparable between studies, a few standard electrode placements have been devised. In this way, researchers have an efficient framework to conduct research or easily navigate in others'. Another reason is a proper electrode naming convention to reflect the four brain lobes in each hemisphere (except the central region, which does not reflect any lobe in particular). The electrode regions for the 10-20 system with their respective electrodes are as follows:

- Frontal-pole: Fp1, Fp2
- Frontal: F7, F3, Fz, F4, F8
- Temporal: T3, T7, T8, T4
- Central: C3, Cz, C4
- Parietal: P3, Pz, P4
- Occipital: O1, O2

The naming convention identifies the brain lobe and the hemisphere. An acronym describing the lobe is followed by a number. Odd numbers indicate the left hemisphere and even numbers the right hemisphere. For the electrodes in the middle, the letter "z" replaces the number. For example, P3 is one of the electrodes located on the parietal lobe of the left hemisphere. EEG caps with prepared electrodes in position exist to alleviate the process of determining anatomical landmarks and measuring skull dimensions (differing by the standard used).

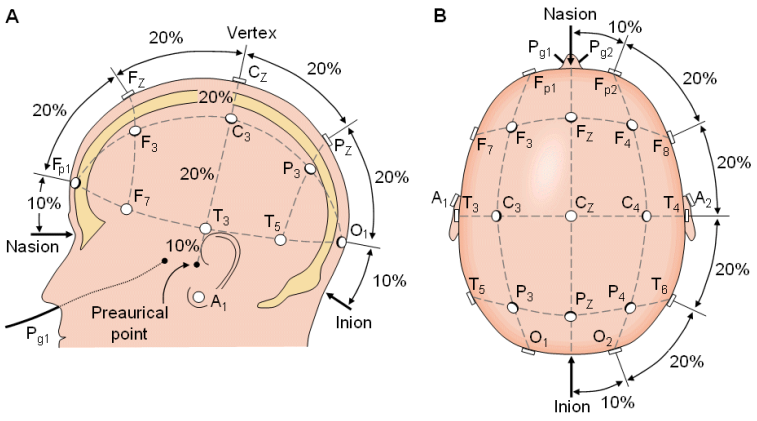


Figure 2.2: Depiction of the electrode placement for the 10-20 system and the required anatomical measurements. Source: [5].

2.4 Sources of artifacts

The most apparent artifact is the power line electromagnetic field. It can be significantly attenuated by properly isolating the room (a Faraday cage). However, it can never be fully avoided, as the recording equipment also has to be powered. This issue can also be partially resolved by filtering out specific frequencies and their multiples - for example, the socket frequency in Europe is 50 Hz, in the Americas, it is 60 Hz. These frequencies, though, are a part of the gamma band of neural oscillations. Therefore, depending on what we want to study, there may be compromises to be made. Then again, frequency filtering is not the only way to filter out artifacts, as mentioned further.

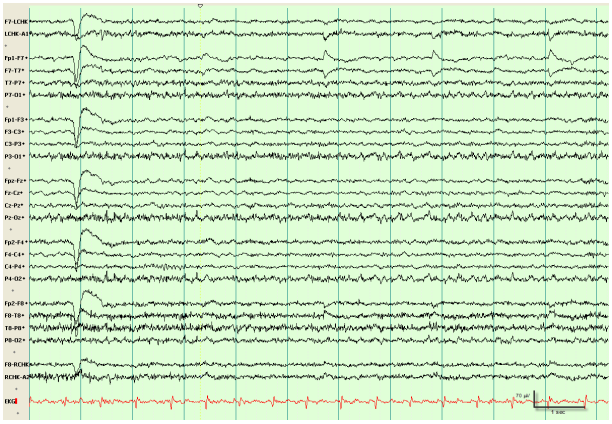


Figure 2.3: Contamination of EEG by lateral eye movement. Source: [6]

The next considerable difficulty is the muscle activity of the body. Heart pumping, eyes blinking, swallowing, and any head muscles moving manifest in the recording noticeably. Some of these we can filter out the same way as with the electrical socket noise. We can also jointly with EEG record electrocardiogram and electrooculogram (eye activity). With such recordings, these particular artifacts can be detected and filtered out with signal-space projection [7] or other methods.

Another source of trouble is the anatomy and physiology of the head itself. Things like intracranial fluid, tissue impedance, or sweating are all factors of distortion but are in practice unavoidable.

Volume conduction (also called field spread) is a significant issue as well. Neuronal clusters generate electromagnetic fields that spread through the surrounding tissue. These fields are then picked up not only by the electrode directly above the source but also by other electrodes around it. The result is that some channels seemingly interacting is merely an illusion created by the source mixing. The remedy is that this mixing appears with almost zero time lag. This fact can be taken advantage of in some cases to minimize the effects of volume conduction [8].

The list of artifact sources does not end with this short overview. However, we deem these few the most prominent ones and a good illustration of the world of EEG measurement pitfalls.

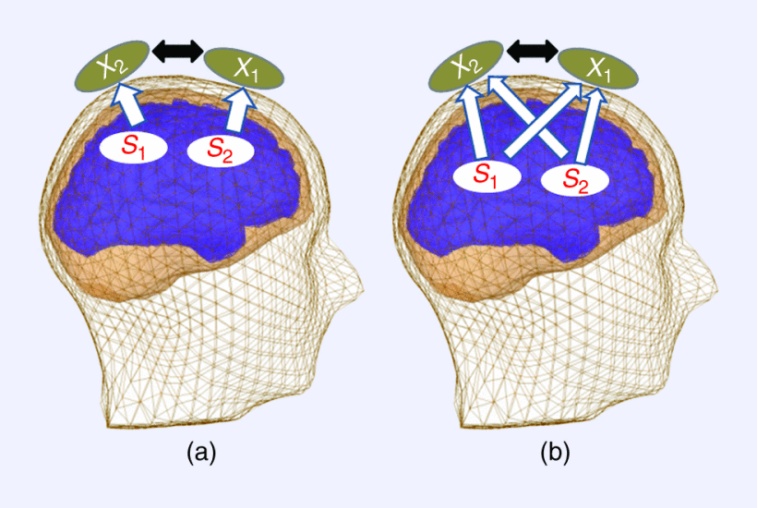


Figure 2.4: Volume conduction. The left side presents an ideal scenario, where each electrode reflects its "desired" source. The right side shows the unfortunate reality: signals from each source get mixed into other channels as well. This might give off the impression that the source networks have some meaningful interaction, while their business might be completely unrelated. Source: [9].

2.5 Neural oscillations

Potentials recorded on the scalp are a summation of the oscillation activity of many neurons. Neurons in the brain are conjoined into complex functional networks. These networks are focused on numerous tasks and oscillate on various frequencies.

Five main frequency bands of neural oscillations named delta, theta, alpha, beta, and gamma are named. These frequencies are generated in many different brain regions, and each rhythm may have contrasting roles depending on context. The definitions of their boundaries differ a little in various texts. Here, we will define them as follows (together with brief descriptions):

- δ (< 4 Hz): Delta has been associated with behavioral inhibition, sleep, or with performing automated activities [10, 11].
- θ ($4-8$ Hz): Theta band is involved in many important cognitive processes connected with memory formation or movement. It plays a part in the creation of associations between time, places, or concepts. These mental maps then support mechanisms like spatial navigation or memory formation and more [12, 13, 14].
- α ($8-13$ Hz): The alpha rhythm is the first recognized of the frequency bands. Its role in neural processing seems to be extensive. The level of cortical activation is believed to be related to the alpha amplitude. Its involvement in processes such as attention and perception are also suggested [13].
- β ($13-30$ Hz): Oscillations in the beta range are primarily excited during motor movements [13]. Similar to alpha, it also has links to cognitive functions, including categorical learning and memory formation [14].
- γ ($30-80$ Hz): Gamma waves are involved in sensory input reception or in cognitive phenomena such as perceptual grouping, attention, working memory, and learning [15]. The gamma band generally has lower amplitudes, making it difficult to distinguish it from noise, especially with noninvasive recording methods.

Note that each of these descriptions is just an excerpt from a large body of research. They serve to give a general idea of each rhythm's part in the "brain orchestra." The functions of these bands may very well overlap.

2.6 Transcranial electrical stimulation principles

The brain is a large-scale network with its own electromagnetic field. The idea of modulating its activity using an external current then comes as natural. Transcranial electrical stimulation (TES) methods are a noninvasive way of brain rhythm modulation using electrical current. The current penetrates the scalp between two stimulation electrodes and modulates the underlying brain networks. Effects of transcranial direct current stimulation (tDCS) are well documented in numerous neurodegenerative disorders such as Parkinson's disease or Lewy body dementia [16]. Research has shown temporary improvements in balance, speech, sleep, attention, and more in patients subjected to tDCS. TES might even impact neuroplasticity, depending on the configuration [16, 3]. With transcranial alternating current stimulation, sinusoidal currents are applied. Entrainment is a phenomenon of directed synchronization of one oscillator by another. Endogenous entrainment happens inside the brain as a way of neural network interaction [14]. TACS exploits exogenous entrainment to synchronize or otherwise modulate desired brain waves. The main parameters of tACS are the intensity, frequency, and mean value. For instance, slow tACS with a DC offset during non-rapid eye movement sleep has been shown to improve retention of a certain type of memories the morning after [3]. The stimulation parameters are chosen

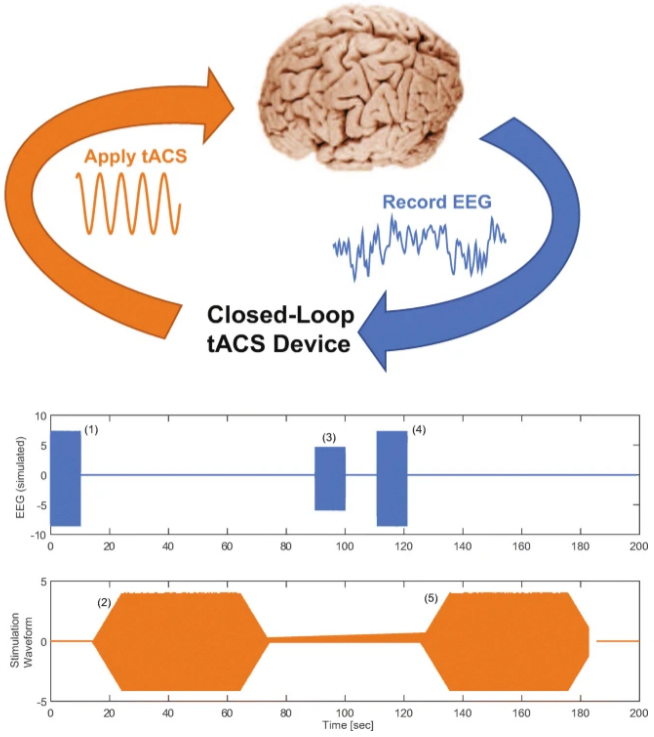


Figure 2.5: A scheme of a closed-loop tACS stimulation adapting to recording. After analyzing the patterns in the recording, we can apply the stimulation reactively. Obtained from [17] and modified.

according to empirical findings, speculations, and intent. If we want to entrain a particular brain rhythm, we may set the stimulation frequency to fall in the corresponding band. We

can also ponder about the location of the stimulation electrodes. If we want to try and force synchronization between some networks, we may place the electrodes above their respective regions. The effects of tACS may also depend on the current activity of the brain [18].

More complicated stimulation waveforms exist. An extension of tACS, transcranial random noise stimulation (tRNS), employs a wide range of frequencies for stimulation. Another method, transcranial pulsed current stimulation (tPCS), uses short pulses. Effects of tRNS and tPCS, however, are not that well documented yet.

The stimulation parameters do not have to be static. There is the idea to adapt the stimulation to the EEG parameters dynamically. This can be either done by alternating epochs of recording and adaptive stimulation, or by performing both in a simultaneous manner. The prospect of concurrent stimulation and recording, though, is as problematic as it is exciting. Decoupling stimulation artifacts from the recording is a challenge in itself, and specialized methods are being developed to address this issue [19].

Chapter 3

State of the Art

In this chapter, we will introduce the current methods used in EEG analysis. By inspecting the frequency spectrum, we can find changes in power in different frequency bands and regions. Increasing traction is gained by connectivity analysis. Insight into the functional coupling between brain networks is paramount in research today. Both symmetric measures (meaning there is no direction of interaction implied) like coherence and directional measures such as Granger causality are presented.

The following formulas are presented in their continuous or discrete variants, depending on convenience.

3.1 Frequency spectrum

Akin to any other time signal, one of the fundamental analyses of EEG remains the spectral analysis. Every signal can be thought of as a summation of many sinusoid signals. The tool for inspection of this decomposition is the frequency spectrum. It can be obtained from the time signal with the Discrete Fourier transform (DFT).

$$\mathrm{DFT}\left\{x[k]\right\} = X[n] = \sum_{k=0}^{N-1} x[k] e^{-j\frac{2\pi}{N}nk},\ n = 0, ..., N-1 \tag{3.1}$$

For every given frequency, the DFT yields a complex number representing a sinusoid. Magnitude of the spectrum $|X[n]|$ gives the amplitude value and the angle $\arg X[n]$ gives the phase shift. The frequency spectrum is an essential tool used by itself and as a component in more complex methods.

3.2 Power spectrum

The total power of a signal is defined as the average value of the signals' magnitude squared.

$$P_x = \lim_{K\to\infty} \frac{1}{2K+1} \sum_{k=-K}^{K} |x[k]|^2 \tag{3.2}$$

The power spectral density (PSD) tells us how the total power of the signal is distributed among its frequency components. An approximation of PSD is often obtained by employing

the Welch's method. We first start by splitting signal x into M (possibly overlaping) segments of length K and shift distance S. First we weigh each segment with a so-called windowing function (such as Hamming or Blackman-Harris window).

$$x_m[k] = x[k + mS] \cdot w[k], \ m = 0, ..., M - 1 \tag{3.3}$$

For every segment, we then compute the periodogram - an estimate of the power spectrum.

$$P_m[n] = \frac{1}{W} \left| \text{DFT} \left\{ x_m[k] \right\} \right|^2 \tag{3.4}$$

where

$$W = \sum_{k=0}^{K-1} w^2[k] \tag{3.5}$$

Then all segments are averaged.

$$\hat{P}_x[n] = \frac{1}{M} \sum_{m=0}^{M-1} P_m[n] \tag{3.6}$$

This is Welch's estimation of power spectral density. In this new averaged spectrum, the noise present in the signal is suppressed to an extent. The PSD is often used to investigate which frequency bands increased or decreased in strength, to identify the so-called individual alpha frequency (the most prominent frequency component in the alpha band), or to construct other measures such as coherence.

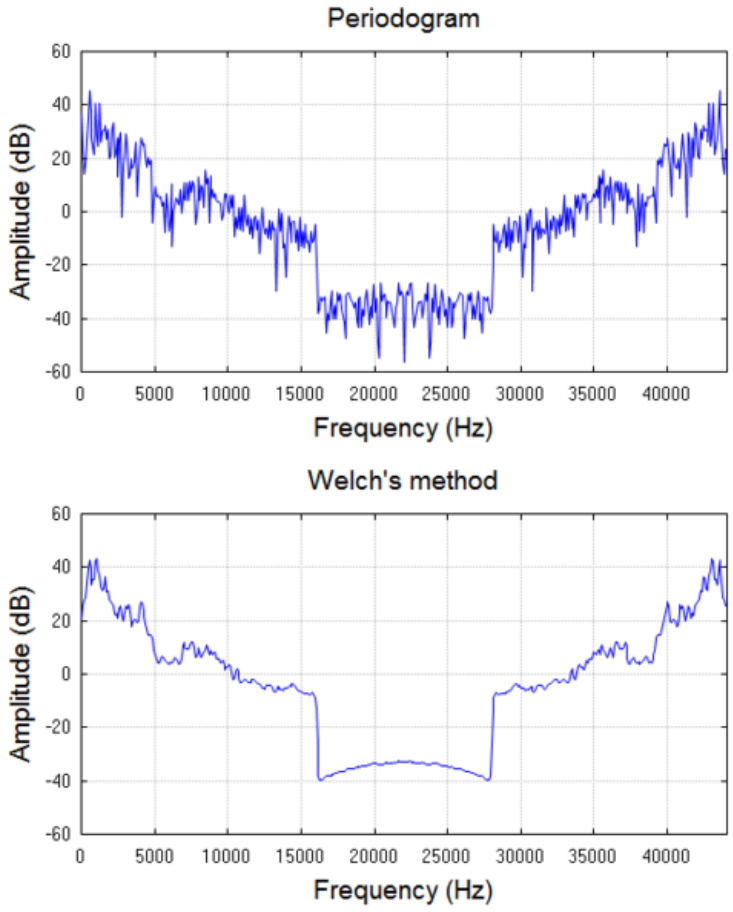


Figure 3.1: An illustration of the readability difference between using just the periodogram versus Welch's estimate. Source: [20].

3.3 Correlation

The most straightforward measure of the relationship between two signals is correlation. It is as simple as a dot product between signals. A greater value of correlation suggests a stronger link.

$$corr_{xy} = \sum_{k=1}^{N} x[k] \cdot y[k] \tag{3.7}$$

Covariance is correlation with the mean value of the signals removed. It reflects the relationship of the signal fluctuations better.

$$cov_{xy} = \sum_{k=1}^{N} (x[k] - \overline{x}) \cdot (y[k] - \overline{y}) \tag{3.8}$$

For multichannel signals, a correlation matrix is assembled. If we, for instance, label this matrix R, then its element r_{ij} represents the correlation between channels i and j [21]. This approach is used for other connectivity measures as well.

In correlation's simplicity lies its disadvantage - it does not address any common issues with recording EEG, such as volume conduction. However, we still mention it, as it is the simplest measure to illustrate connectivity. It is also implemented in many signal processing software packages.

3.4 Coherency

A measure of two signals' spectral relationship is given by a widely used method called coherency. It is defined as the cross-spectral density of two signals normalized by the square root of the product of their individual power spectra.

$$coh_{xy}(\omega) = \frac{X(\omega)Y^*(\omega)}{\sqrt{P_x(\omega)P_y(\omega)}} \tag{3.9}$$

The asterisk marks the complex conjugate of a complex number. The magnitude of coherency is called coherence and ranges from 0 to 1. Its squared value, $|coh_{xy}(\omega)|^2$, "quantifies, as a function of frequency, the amount of variance in one of the signals that can be explained by the other signal, or vice versa" [8]. It is essential to differentiate between coherency and coherence. In general, the former is a complex number, whereas the latter is always real.

Coherence, however, is also susceptible to "false positives" caused by volume conduction. There exists a related measure that can alleviate the issue. When looking at coherency in the complex plane, there is a real and an imaginary component. The zero-lag interactions caused by volume conduction are closely related to the real component. The angle of coherency is equivalent to the phase difference between the signals (at some frequency). If the phase difference (lag) is zero, then the complex number will lie on the real axis. Following this, if we want to render the effect of volume conduction null, we simply omit the real part of the coherency. This related measure we mentioned earlier does just that. It is called the *imaginary part of coherency* (or imaginary coherence (IC) for short) and its name suggests the exact procedure [8].

$$icoh(\omega) = \mathrm{Im}\left(coh_{xy}(\omega)\right) \tag{3.10}$$

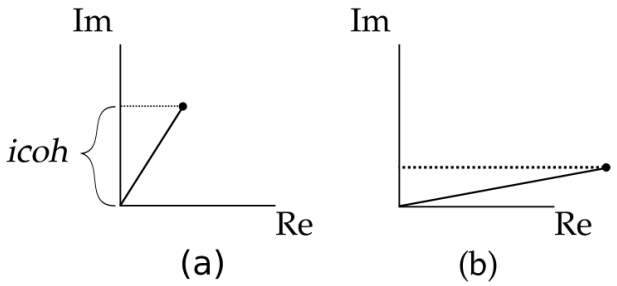


Figure 3.2: Two values of coherency visualized. Note that (a) has a smaller magnitude than (b). On the other side, (b) has a smaller angle (say, close to zero), so its imaginary part is smaller than (a)'s. This illustrates that when two signals only interact by means of volume conduction, their coherency has zero angle (zero lag interaction from volume conduction), and the imaginary coherence will be zero.

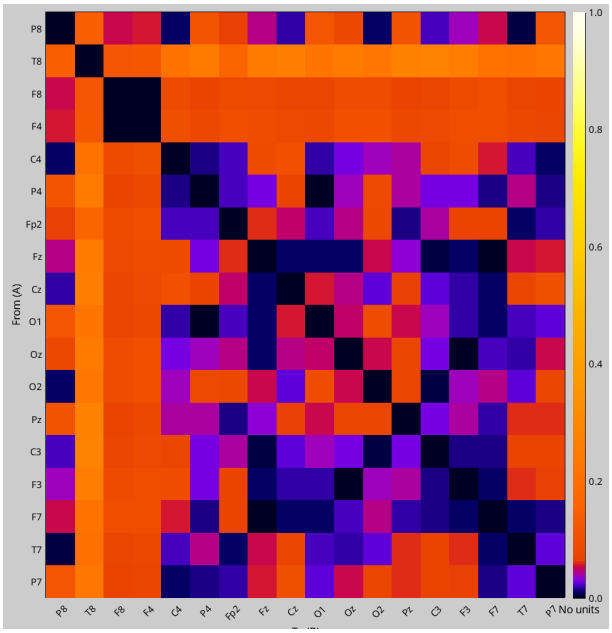


Figure 3.3: An example of an imaginary coherence matrix. It is symmetric with zeros on the diagonal (since the coherency of a signal with itself is real, the imaginary component is zero).

3.5 Granger causality

When investigating the interactions between two regions, we are also interested if the behavior of region A somehow influences region B. Symmetric measures are not helpful in this aspect. That is why several directional measures were introduced. One of these measures is Granger causality (GC). This method was originally developed in the sixties by Clive Granger for the analysis of time series in economics. It has then naturally found its use in neuroscience. GC measures how well signal x predicts signal y.

Granger causality compares two autoregressive models. In an autoregressive (AR) model, a sample of a signal is predicted from a linear combination of its preceding samples.

$$y[k] = \sum_{i=1}^{p} \alpha[i] y[k-i] + \mu[k] \tag{3.11}$$

The model order p is the number of preceding samples in the linear combination, and $\alpha[i]$ are the combinations' coefficients. The residuals $\mu[k]$ represent the deviation of the model from the original signal. In multivariate autoregressive models, linear combinations of past samples of other signals can be added to improve the prediction. We are dealing with interactions between two signals; that's why a bivariate (BVAR) model is used. Let us add a linear combination of x's past samples.

$$y[k] = \sum_{i=1}^{p} \alpha[i]y[k-i] + \sum_{i=1}^{p} \beta[i]x[k-i] + \sigma[k] \tag{3.12}$$

The principle of (bivariate) Granger causality lies in the comparison of a univariate and a bivariate model. More specifically, it compares the variance of residuals for those models.

$$\mathrm{GC}_{x\to y} = \ln\left(\frac{\mathrm{var}(\mu)}{\mathrm{var}(\sigma)}\right) \tag{3.13}$$

If the BVAR's residual variance is smaller than the AR's (meaning that using past samples of x improved the prediction), the fraction inside the logarithm will be greater than one. Then GC will be greater than zero. Since the models are assumed to be optimal, the BVAR residuals' variance will never be greater than AR's. In other words, GC always yields a nonnegative number. One issue with GC is that it does not account for volume conduction [8].

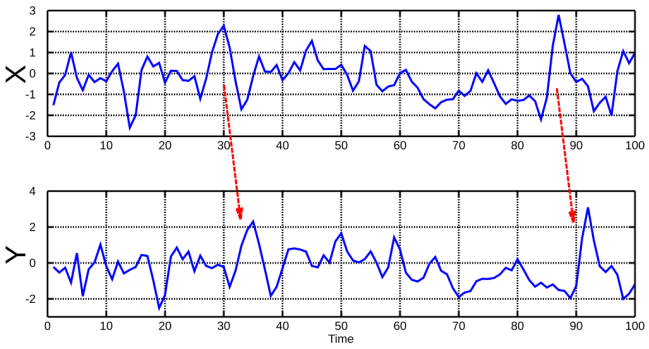


Figure 3.4: Signal X predicting signal Y. Source: [22].

3.6 Spectral Granger causality

The original formulation of GC can provide many hints. However, for each direction of causality, it yields just a single number. In many cases, it is desirable to examine the GC between two signals in the spectral domain. This need again arose in the field of economics. For instance, it is useful to look at the relationship between the macroeconomic situation and electricity consumption on the frequency of the economic cycle. The application in neuroscience is again intuitive since we want to look at the causality between brain regions in various frequency bands. The derivation of spectral GC is more complicated than the time variant. The resulting formula is more complex as well.

$$\mathrm{GC}_{x\to y}(\omega) = \ln\left(\frac{S_{yy}(\omega)}{S_{yy}(\omega) - (\Sigma_{xx} - \frac{\Sigma_{yx}^2}{\Sigma_{yy}})|H_{yx}(\omega)|^2}\right) \tag{3.14}$$

A brief interpretation of the spectral GC formula will suffice. Compared to the time variant that yields a single value, the spectral GC is a function of frequency. The formula again consists of a logarithm of a ratio. In the numerator is the power spectrum of signal y. In the denominator is the difference of that same spectrum and the so-called *causal power*, with which signal x influences signal y on some frequency. If the causal power term is greater than zero, then the denominator will be smaller than the numerator, and GC will be greater than zero [8]. To differentiate better between the original GC and its spectral variant, we will call the former time GC.

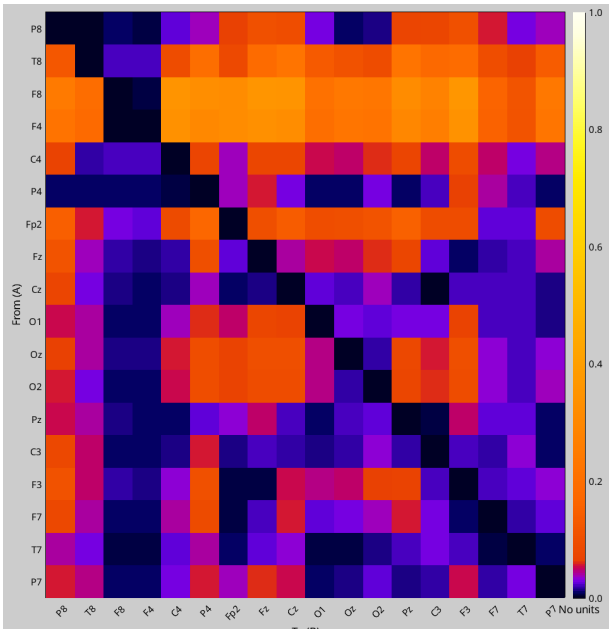


Figure 3.5: An example of a Granger causality matrix. Unlike correlation or coherence matrices, it is not symmetric. The diagonal elements are zero, because $GC_{x\to x} = 0$.

Chapter 4

Methodology

4.1 Means of measurement

The research facility where the measurements took place is situated at the 3rd Faculty of Medicine of Charles University. The EEG recording and tACS were realized using a solution from Neuroelectrics (a company based in Barcelona, Spain). It consists of:

- 2-in-1 EEG + tACS headsest and all hardware needed for recording, stimulation and data transfer,
- Neuroelectrics Instrumentation Controller 2 (NIC2). This software provides the measurement protocol editor, measurement controller, recordings browser, export to various formats, and more.

In the measurement protocol editor inside NIC2, we can tune various parameters. We can, most notably, define:

- The length and order of segments with a specific role (recording, stimulation, or even both),
- which electrodes will be used for recording and stimulation in each segment,
- the type and parameters of the electrical stimulation. For tACS in particular, we can set its amplitude, frequency, and mean value.

4.2 Designing the study

The first thing we had to come up was the framework of the experiment. Once the parameters were decided on, and the measurement sessions had begun, every change of the protocol would mean discarding all previously recorded data (for not being comparable).

We spent a substantial amount of time visiting the laboratory, experimenting with different setups, and acquiring some pilot data. We earned a lot of practical experience this way and gradually devised the idea of the experiment. We tried different lengths of stimulation and recording, various sinusoidal current frequencies, amplitudes, and so on. We also

encountered practical constraints. Recording of the resting state involves no interaction. The subject might become too relaxed or even fall asleep (as one of our pilot subjects did) if left alone for prolonged periods. These states also modulate the recording.

The study is not blinded, meaning both the subject and the researcher know that the tACS intervention has been delivered. A partial or complete blind would be needed in the presence of a placebo (sham stimulation) group, which is not the case in this experiment. The subjects have signed informed consent, and their data is anonymous. Their mean age is 23 years (standard deviation: 1.9 years, range: $21 - 26$ years) and all of them are right-handed.

Comparing the measurement results of one subject across different sessions is called an intrastudy. Comparing conditions across multiple subjects is called an interstudy. This thesis focuses on one subject in an intrastudy across two sessions and five subjects in an interstudy.

After trying out several configurations and protocols and taking numerous variables into account, we settled on the following protocol.

4.3 Measurement protocol

For the entirety of the recording session, the subject is in a resting state. The subject sits with eyes closed. The reason for that is twofold: suppressing eye movement artifacts that are pronounced with eyes open; more effortless relaxation of the subject into the resting state. The measurement consists of three blocks:

1. Resting EEG [5 min] - The so-called baseline is measured. This state is considered a "normal" brain activity. The pre-intervention parameters will be extracted from it.
2. Resting tACS [10 min] - Here the subject is stimulated with tACS. The stimulation frequency is 7 Hz, and the current amplitude is 1 mA. The stimulation electrodes are Fp1 and P3.
3. Resting EEG [10 min] - The potential effects of tACS are observed. This segment is longer than the baseline one because it is desirable to have more data for studying the influence of the intervention. But since the subject is sitting relaxed with their eyes closed, the segment shouldn't be too long. This could cause the subject to fall asleep, which is not a part of the protocol.

4.4 Session protocol

It is imperative to execute every measurement as an exact series of steps. This will ensure the comparability of the results of each measurement. The detailed agenda is as follows:

1. Briefing the subject about the course of the measurement.
2. Preparation and putting the EEG headset on the subject's head. We have to ensure that all the electrodes are placed at their respective locations properly. This can be achieved by correct EEG headset orientation. There are also procedures for

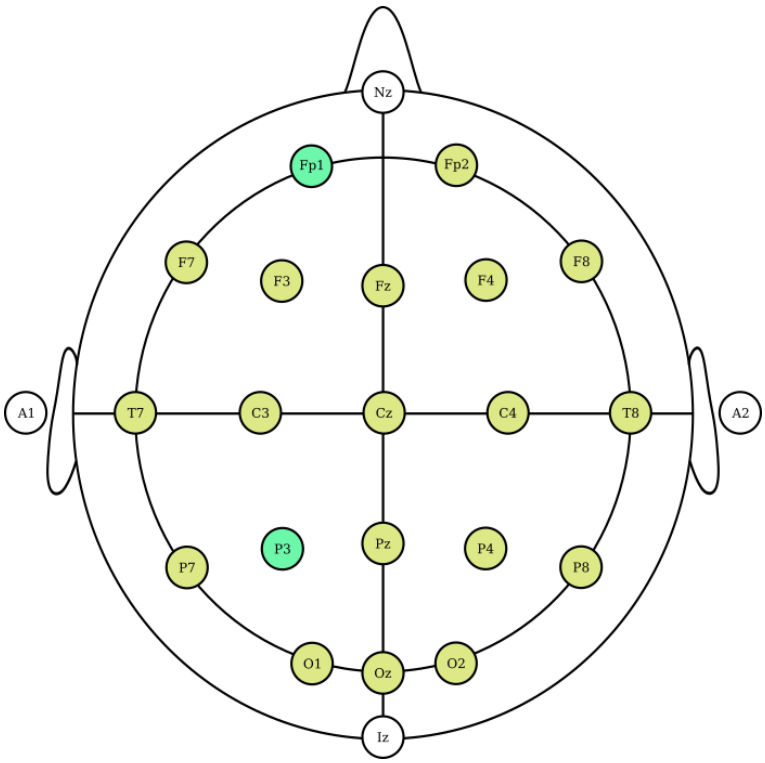


Figure 4.1: The EEG electrode configuration for our experiment. In yellow are electrodes used for EEG recording; in green are stimulation electrodes. Taken from [23] and modified.

exact electrode placement using precise measurements and anatomical landmarks. However, a simple rule will suffice for our case: prefrontal electrodes should be approximately three fingers' width away from the eyebrows.

3. Applying the conductive gel in the area under each electrode. This makes for better conductive contact between the electrode and the scalp. We have to prevent the gel from spilling and creating "bridges" between electrodes. This would mix signals from different sources and invalidate the recording.

4. The subject is prompted to close their eyes and relax. Then, the actual measurement begins. The subject is informed when each block starts. They are also informed roughly 5 minutes before the end of the last block. This is to ensure that the subject doesn't overly relax and fall asleep during the last and longest block.

5. The session is concluded.

4.5 Data processing pipeline

From the data formats available for export in NIC2, we use the European Data Format (EDF). It is freely available without charge, and a de facto standard "format for exchange and storage of multichannel biological and physical signals" [24].

The software used to compute the power spectra and connectivity measures is the Matlab scientific computing environment. Matlab consists of a programming language, an integrated development environment, many toolboxes for different fields, and more. On top of Matlab is built the Brainstorm package. Brainstorm is a collection of many procedures used in the processing and analysis of brain recordings and images. It also provides a

framework for conducting studies, creating processing pipelines or data visualization. It is an open-source project developed in collaboration between research groups at the University of Southern California, McGill University, and Cleveland Clinic [25]. Every subject has

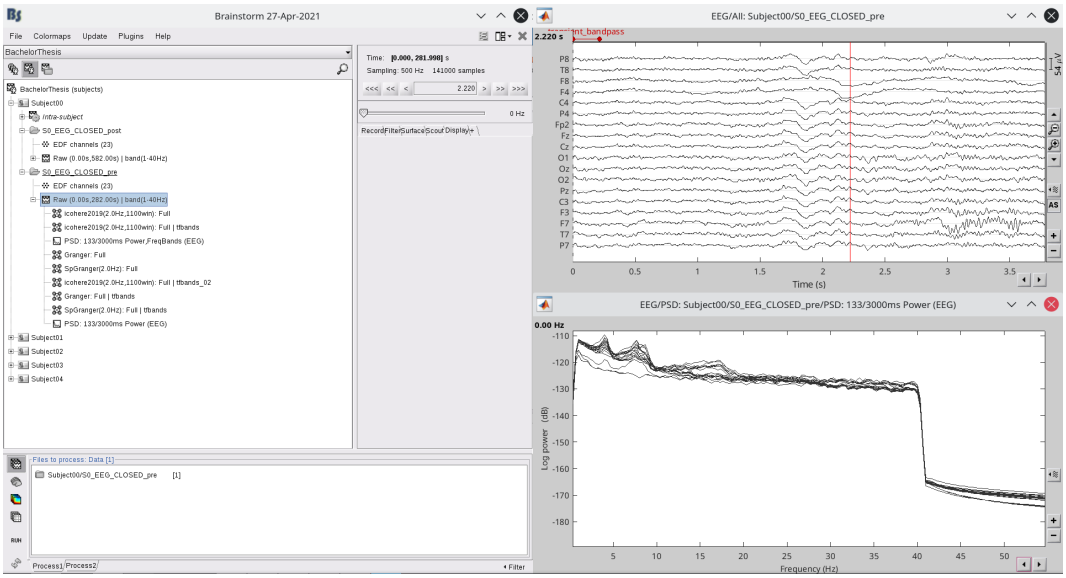


Figure 4.2: The Brainstorm environment. The left side shows the main window, including the database browser. On the right side, an EEG time series with its power spectrum below.

a folder in the Brainstorm database where all data and metadata are stored. We can view these in the Brainstorm browser and directly work with them. Performing processing and analyses is as simple as dragging the desired files or the entire folder into the processing tab. Then, the pipeline editor presents us with a list of procedures we can apply to the files (or we can use Brainstorm's scripting interface to automate the task).

First, as a part of preprocessing, all recordings are filtered in the range of $1 - 40$ Hz. Then the measures such as power or coherency of the recordings are computed.

After we finish the needed procedures, we can export the results into the Matlab workspace as variables for further analysis. In Matlab, we execute more operations on the data and finally perform statistic tests and visualization.

4.6 Statistics

An integral part of every study is some sort of statistic evaluation. Hypothesis testing is based on collecting data, stating the null (H_0) and alternative (H_A) hypotheses, and performing statistic tests on the data to accept or reject the null hypothesis.

We would like to know if some parameters of the brain behavior changed significantly (no matter in which direction) due to the stimulation. This allows us to make more general statements about the effects of tACS on the whole population. One example would be "people's alpha band power changed significantly."

By extracting scores from EEG recordings before and after the stimulation, we constructed two distributions. We then wanted to know if the differences between the distributions were

extreme enough. This leads to the following formulation of the hypotheses:

$$H_0\text{: "The distributions of the data are the same."} \tag{4.1}$$

$$H_A\text{: "The distributions of the data are different."} \tag{4.2}$$

The main output of the test is the p-value. Simply put, assuming the null hypothesis is true, the p-value is the probability of obtaining results at least as extreme as we observed (meaning that the results were a product of chance). The smaller the p, the stronger is the evidence for our findings. The p-value is compared against the *significance level* (α). If p is less than α, we reject the null hypothesis and conclude that the results were significant. Conventionally used is $\alpha = 0.05$, but other thresholds, such as 0.1, 0.025, or 0.01 are also standard.

For our purposes, we choose the Kruskal-Wallis test, implemented in Matlab. The test is nonparametric and consequently does not assume that the measurements come from a Gaussian distribution. It is widely used in experiments where there is a small sample size.

We compute parameters from pre-intervention (group 1) and post-intervention (group 2) recordings. Then, we determine if the medians of these groups are significantly different - and as a consequence, if the stimulation had any discernible effect on these parameters.

Worthy of note is the fact that the p-value is not the end-all of research. Oftentimes it is even a subject of misuse, called *p hacking*, where data patterns that yield significant results are sought after.

Chapter 5

Results

In the interstudy, we looked at the effects of tACS on the population. Meaning, observing great differences in the pre- and post-stimulation activity of a single individual does not tell us about the effects of tACS in general. However, seeing consistent changes in the parameters across measurements means that the changes induced by the stimulation might be significant.

In the intrastudy, we wanted to explore if the application of tACS over multiple sessions would induce some long-term changes in the brain. This could be, for example, used to treat psychological disorders or to enhance brain performance. Since there was just one instrastudy subject, we took a more speculative route of investigation.

5.1 Interstudy

The scores described in this section are extracted from both the pre- and post-intervention recordings. The significance level we decided for is $\alpha = 0.1$. The number of participants that underwent the measurement is $n = 5$. This sample size is small, and any new measured subject can sway the outcome significantly. In each subsection, we describe the score extraction for the particular measure and present the results. More detailed tables are included in the Appendix.

We defined five regions representing the brain lobes:

- Frontal (F) - Fp2, F7, F3, Fz, F4, F8
- Left temporal (LT) - T7, C3
- Right temporal (RT) - C4, T8
- Parietal (P) - P7, Pz, Cz, P4, P8
- Occipital (O) - O1, Oz, O2

5.1.1 Power spectrum

First, the power spectra for all channels are divided into four bands: delta, theta, alpha, and beta. Then, each band is averaged across all channels. This yields four numbers to be

tested. Globally, only the delta power changed (decreased, $p = .028$).

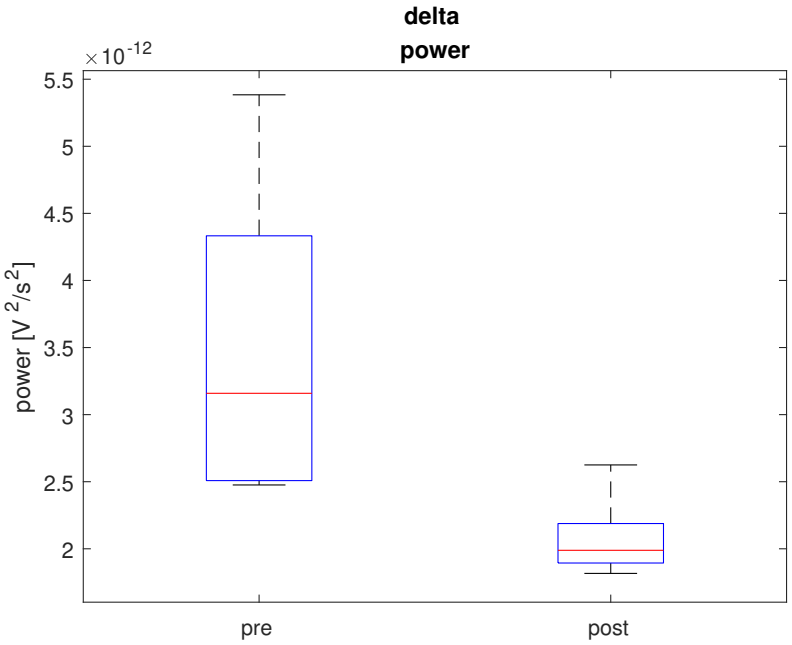


Figure 5.1: Box plot showing two distributions of the global delta power, each distribution constructed from either the pre- or post-stimulation scores. The middle line of the box is the median (50% of data lie below this point) of the distribution, the top and bottom edges are the 3rd and 1st quartiles (the points that have 75% and 25% of the data below them, respectively). The "whiskers" extending from the box are the maximum and minimum. We can see that only the extremes of the two distributions overlap. In this case, the distributions are distinct ($p = .028$).

delta	theta	alpha	beta
0.028	0.347	0.602	0.602

Table 5.1: The p-values for the mean global power in each band.

Next, we take a more granular approach and look at the power in the four bands in each of the brain regions that we defined. Twenty numbers are to be tested. The power only changed in the delta band (all regions, p-values in table 5.2).

	frontal	parietal	temporal left	temporal right	occipital
delta	**0.016**	**0.076**	**0.028**	**0.047**	**0.076**
theta	0.602	0.465	0.602	0.465	0.754
alpha	0.347	0.602	0.602	0.602	0.754
beta	0.754	0.917	0.602	0.347	0.754

Table 5.2: The p-values for the mean power in each band in each region.

5.1.2 Imaginary coherency

Similar to the power spectrum, a global measure of imaginary coherency for each band is to be computed. This means taking an average of all elements of the IC matrix. The diagonal elements of the matrix are zero. These zeroes are influencing the average, but since the

averages before and after are affected the same way, this does not make a difference for testing.

delta	theta	alpha	beta
0.347	0.251	0.251	0.917

Table 5.3: The p-values for the mean global coherence in each band.

As we can see, the mean global IC did not change at all. Let us take a look at the imaginary coherence between the five regions - frontal, parietal, left temporal, right temporal, and occipital. The only pair of regions where the mean IC changed was the F-LT one in the theta band ($p = .076$).

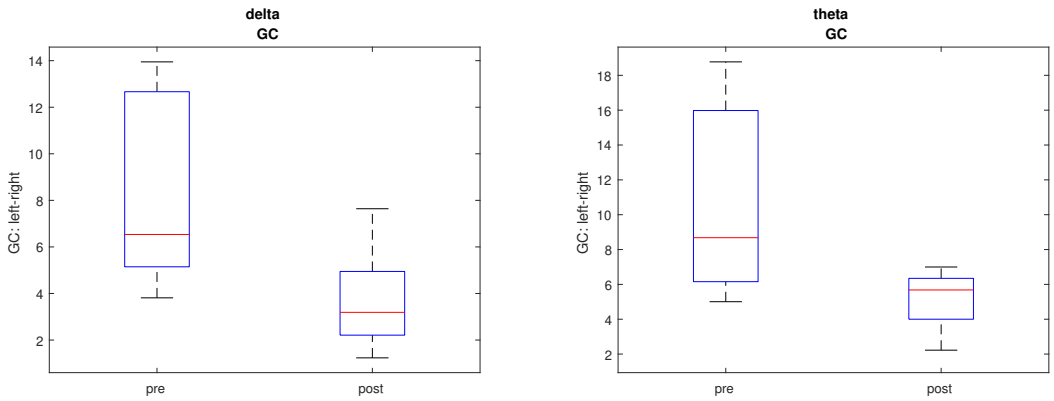
5.1.3 Granger causality

Again, progressing from a more global perspective; first, we will be testing if the directional interactions between the hemispheres changed. The sum of GC from certain right hemisphere electrodes (O2, P4, C4, F4, F8, T8, P8) to the analogous left hemisphere's electrodes is computed and vice versa. No change is found.

A similar idea is used when computing GC between the front (F7, Fz, F8) and back (P7, Pz, P8) sides of the brain. The difference is again null. So are the differences in GC between every pair of regions.

5.1.4 Spectral Granger causality

We will inspect similar aspects as with the time domain GC. The left to right hemisphere GC changed in the delta and theta bands ($p = .076$). GC of the front-back pair did not change.



(a) Left to right hemisphere GC for the delta band. **(b)** Left to right hemisphere GC for the theta band.

Figure 5.2: Left to right hemisphere GC for delta and theta bands. In both plots, we can see a decrease after the stimulation.

While examining the spectral GC between our defined brain regions, a few changes have been observed. We summarize them in the following list:

- **Delta:** The only change was observed from the left temporal to the occipital region ($p = .047$).
- **Theta:** A multitude of changes happened between multiple regions. With $p = .076$, the LT→F and O→P GC changed. A difference was also seen with GC for O→F and O→LT ($p = .047$). Finally, with $p = .028$, a change in P→LT GC was observed.
- **Alpha:** In the alpha band, a single GC difference in P→LT ($p = .047$).
- **Beta:** No shift in GC in the beta band.

5.2 Intrastudy

In the intrastudy, we took a different approach. Since there was just a single subject for the intrastudy, there were no statistic tests. We, therefore, settled on comparing the differences in parameters between sessions in a somewhat speculative manner.

In each session, we extracted the parameters from both recordings. We then subtracted the pre- and post-stimulation parameters for each session.

$$\text{diff}_i = \text{post}_i - \text{pre}_i \tag{5.1}$$

We then compared these differences between the sessions.

$$\text{DR} = \frac{\text{diff}_2}{\text{diff}_1} \tag{5.2}$$

Equation 5.2 gives us a difference ratio (DR) that tells us if the second session difference is less or greater than the first. The measures extracted were the power spectrum and coherence.

First, we looked at the mean of the power spectrum in the regions. Figure 5.3 shows us these relative changes in each region and frequency band. The most notable changes were in the alpha band. The DR in the parietal region was positive, meaning the difference between pre- and post-stimulation was greater in the second session. It was also greater globally, but it had a different direction, which means that the difference was positive in one of the sessions and negative in the other. This could point to the potential randomness of the change since tACS having an opposite effect each time would be inconsistent. In the delta band, the changes in the second session were all, except for the right temporal region, very small compared to the first. To summarize, difference ratios that are either less than one or negative might indicate that the difference is a product of chance.

Next, we examined the mean IC in the regions. We computed the mean IC for each recording and constructed the difference ratios for each region and frequency band. Here we focus on the theta band, as that was the frequency of the stimulation. As shown in figure 5.1, almost all difference ratios showed the same direction of change, with F-RT being the only exception. Only the frontal-occipital pair had a DR greater than one. We could compare these outcomes with a significant result in the interstudy; there was a change in the theta band in the F-LT pair. On the other hand, here, the identical pair had a difference ratio much lower than one. We, however, cannot actually compare the results of a statistical test and analysis of one subject's differences across two sessions.

An extreme case was observed with the alpha band's changes. The mean global imaginary coherence DR was roughly -80. Looking closely at the changes, the first session's difference

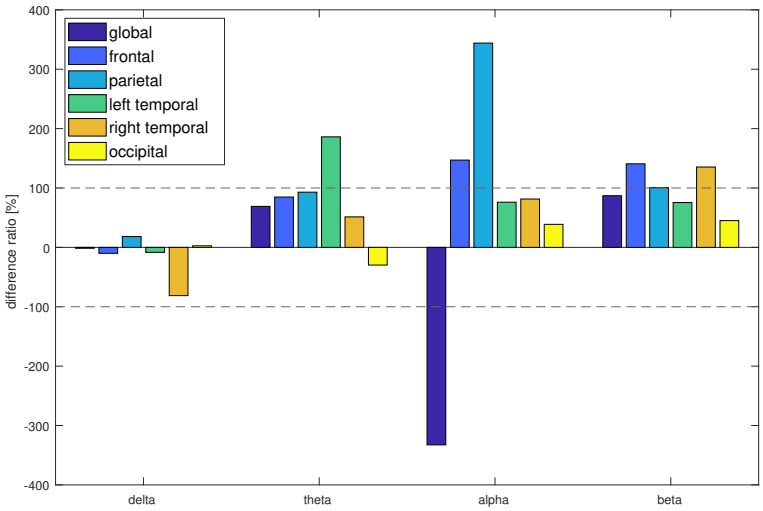
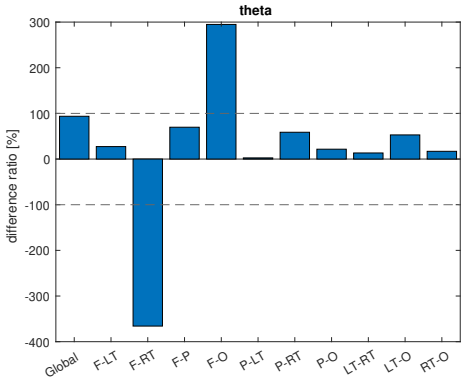
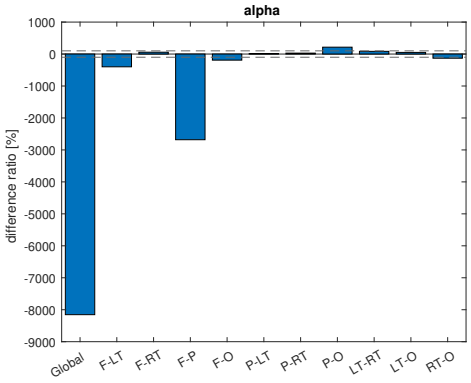


Figure 5.3: The mean power difference ratios for every region in each frequency band.

was $-1.252 \cdot 10^{-5}$, the second session's was 0.001. An unlikely idea would be that there really could be such progression from one session to the other. Since we do not have more subjects' intrastudy data for statistical testing, either difference could be an erroneous one (and in reality, the differences would be much closer).



(a) The mean IC difference ratios for the theta band.



(b) The mean IC difference ratios for the alpha band. Adjusting the vertical axis scale to show the longest bar renders some other bars almost indistinguishable.

Figure 5.4: The mean IC difference ratios for the theta and alpha bands.

Chapter 6

Discussion

The interstudy showed influences of tACS in some measures. To summarize, the most affected frequency bands were delta and theta. This was in part expected since the stimulation frequency of 7 Hz belongs to the theta band. The delta power, for instance, decreased both globally and when tested in each region separately. This goes against our expectations since we thought that the delta power would rise with relaxation (in other words, behavioral inhibition) that the subjects were in. Either that presumption was simply false, or the stimulation was also at play here.

Looking at the imaginary coherence, a decrease was found in IC between the frontal and left temporal regions. A reasonable assumption would be that the synchronization shifted to the fronto-parietal region since those were areas under the stimulation electrodes. The F-P coherence, however, decreased as well in the theta band (although an insignificant change with $p = .117$).

Moving to time Granger causality, there seemed to be no shift. On the other hand, the spectral GC registered multiple changes. In the delta band, with $p = .047$ the GC from left temporal to occipital region decreased. We could associate this change with the global power and IC decrease in the delta band. Corresponding to the frontal - left temporal IC decrease in theta, the LT→F theta GC declined as well. Two measures correlating like this could suggest stronger evidence for the phenomenon (even with a small sample size). Noticing that there also is a change of P→LT GC in the same band, we could interpret this as a P→LT→F "chain of theta GC change," implying some connection. However, we have to keep in mind that both the parietal and left temporal regions include some central electrodes. Meaning, this connection could merely be the result of a source overlap. Contrary to this doubt, there were also changes in O→P and O→LT GC that could be added to this chain somehow. A contribution to this idea could also be the P→LT alpha GC change. Proving that these changes were indeed linked would indicate that the stimulation veritably changed connectivity in the left hemisphere. To connect these speculations to the intrastudy, we could highlight the difference increase in delta P-LT, theta F-O, or beta F-P imaginary coherence.

Chapter 7

Conclusion

This thesis had multiple goals: our introduction into the field of EEG analysis and tACS stimulation, developing some sort of methodology, probing the questions that could be posed, and possibly answering and interpreting some of them.

Initially, this thesis was supposed to be a part of research at the Third Faculty of Medicine at Charles University. The measurement protocol was almost entirely different and also included cognitive tests. These would provide a clue if the stimulation enhanced working memory, for instance. However, due to complicated circumstances, we were forced to diverge from this plan, simplify the protocol, and abandon the cognitive tests altogether.

We investigated the effects of our particular tACS configuration on the EEG parameters and connective measures. We went through the entire process of the experiment, from conducting the measurement sessions to presenting the results. For that purpose, we created an underlying methodology. It consisted of the measurement protocol and a data processing pipeline. This ensured that the measured data were comparable between the subjects.

Since the situation did not allow for the acquisition of a substantial amount of samples, we could not provide strong evidence for the results. We can only speculate what the results would be if the sample size were larger. That is also why it is important to have an exact methodology - potentially, a future experiment following the same design could yield more accurate outcomes.

Working on this thesis provided us with invaluable experience and some ideas about our direction in research going forward. We went through a great deal of literature about the subject, attained a notion of recent progress in neuroscience, and learned about some of the methods used in neuroscientific research.

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Appendix

Here we present detailed p-value tables. The region acronyms are F - frontal, P - parietal, LT - left temporal, RT - right temporal, O - occipital.

The format A-B in the imaginary coherence tables represents the IC between A and B. In the GC tables, it represents the GC from A to B. For example, F-P means the Granger causality from the frontal to the parietal region.

Imaginary coherence										
	F-LT	F-RT	F-P	F-O	P-LT	P-RT	P-O	LT-RT	LT-O	RT-O
delta	0.754	0.175	0.347	0.251	0.251	0.251	0.117	0.251	0.347	0.347
theta	**0.076**	0.465	0.117	0.117	0.917	0.465	0.465	0.602	0.917	0.347
alpha	0.754	0.754	0.602	0.117	0.602	0.754	0.465	0.754	0.175	0.754
beta	0.602	0.602	0.754	0.175	0.917	0.917	0.917	0.754	0.917	0.754

Granger causality									
LT-F	RT-F	P-F	O-F	LT-P	RT-P	O-P	RT-LT	O-LT	O-RT
0.917	0.917	0.917	0.917	0.175	0.754	0.602	0.917	0.347	0.175
F-LT	F-RT	F-P	F-O	P-LT	P-RT	P-O	LT-RT	LT-O	RT-O
0.917	0.251	0.465	0.917	0.347	0.347	0.175	0.251	0.117	0.465

Spectral Granger causality between hemispheres				
	delta	theta	alpha	beta
left to right	**0.076**	**0.076**	0.602	0.917
right to left	0.465	0.465	0.917	0.754

Spectral Granger causality between front and back				
	delta	theta	alpha	beta
front to back	0.347	0.175	0.602	0.602
back to front	0.251	0.251	0.602	0.465

Interregional spectral Granger causality - delta									
LT-F	RT-F	P-F	O-F	LT-P	RT-P	O-P	RT-LT	O-LT	O-RT
0.251	0.917	0.347	0.602	0.117	0.465	0.602	0.465	0.175	0.602
F-LT	F-RT	F-P	F-O	P-LT	P-RT	P-O	LT-RT	LT-O	RT-O
0.347	0.917	0.251	0.251	0.117	0.754	0.117	0.175	**0.047**	0.465

Interregional spectral Granger causality - theta									
LT-F	RT-F	P-F	O-F	LT-P	RT-P	O-P	RT-LT	O-LT	O-RT
0.076	0.917	0.175	**0.047**	0.175	0.465	0.117	0.602	**0.047**	0.175
F-LT	F-RT	F-P	F-O	P-LT	P-RT	P-O	LT-RT	LT-O	RT-O
0.602	0.754	0.347	0.465	**0.028**	0.754	**0.076**	0.117	0.465	0.465

Interregional spectral Granger causality - alpha									
LT-F	RT-F	P-F	O-F	LT-P	RT-P	O-P	RT-LT	O-LT	O-RT
0.347	0.754	0.347	0.251	0.347	0.465	0.602	0.917	0.251	0.754
F-LT	F-RT	F-P	F-O	P-LT	P-RT	P-O	LT-RT	LT-O	RT-O
0.754	0.754	0.602	0.754	**0.047**	0.754	0.602	0.754	0.465	0.754

Interregional spectral Granger causality - beta									
LT-F	RT-F	P-F	O-F	LT-P	RT-P	O-P	RT-LT	O-LT	O-RT
0.754	0.602	0.602	0.917	0.917	0.465	0.917	0.754	0.465	0.251
F-LT	F-RT	F-P	F-O	P-LT	P-RT	P-O	LT-RT	LT-O	RT-O
0.917	0.465	0.465	0.754	0.117	0.602	0.917	0.465	0.917	0.917