Signals and Systems Project

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Analysis of Phase Locking Value during Olfactory Stimulation as a Biomarker for Alzheimer's Disease in EEG Signals

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Contents

1 Introduction **2**
1.1 Neurodegenerative Diseases . . . 2
1.2 Olfactory Dysfunction . . . 2
1.3 Goal of the Project . . . 2

2 Electroencephalography (EEG) **3**
2.1 What is EEG? . . . 3
2.2 Alzheimer's Disease . . . 5
2.3 Frequency Bands of EEG . . . 5
2.3.1 Gamma Waves . . . 6
2.3.2 Beta Waves . . . 6
2.3.3 Alpha Waves . . . 7
2.3.4 Theta Waves . . . 7
2.3.5 Delta Waves . . . 7
2.4 Sampling frequency . . . 8

3 EEG Signal Processing **9**
3.1 Task Definition . . . 9
3.2 Data Description . . . 9
3.3 Pre-Processing . . . 10
3.4 Phase Locking Value (PLV) . . . 15

4 Results **16**
4.1 Values . . . 16
4.2 Distributions . . . 16
4.3 Statistical Significance . . . 17
4.4 Phase Difference . . . 17
4.5 Heatmaps . . . 19

5 *Bonus **20**
5.1 Mild Cognitive Impairment (MCI) . . . 20
5.1.1 Additional Information . . . 20
5.1.2 MCI Data Processing . . . 20
5.2 Phase-Amplitude Coupling (PAC) . . . 21
5.2.1 Metrics . . . 21
5.2.2 Implementation . . . 21

6 Conclusion **21**

1 Introduction

1.1 Neurodegenerative Diseases

Neurodegenerative diseases, including Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI), pose significant challenges to individuals, families, and healthcare systems worldwide. These conditions are characterized by progressive deterioration of cognitive functions, leading to severe impairment and loss of independence. Understanding the importance of these diseases and the urgency to find reliable biomarkers for their early detection and accurate diagnosis is critical for effective intervention and disease management and has become a priority in the field of neurodegenerative research.

Alzheimer's disease, the most common form of dementia, affects millions of individuals globally, and its prevalence is expected to rise with the aging population. MCI, often considered a transitional stage between normal aging and AD, is characterized by subtle cognitive decline that does not severely impact daily functioning. Scientists recognize that the combination of a person's genes and environment contributes to their risk of developing a neurodegenerative disease. For example, someone might have a gene that makes them more susceptible to Parkinson's disease, but their environmental exposures can affect whether, when, and how severely they are affected. [3]

1.2 Olfactory Dysfunction

The sense of smell is today one of the focuses of interest in aging and neurodegenerative disease research. In several neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease, the olfactory dysfunction is one of the initial symptoms appearing years before motor symptoms and cognitive decline which manifests as a decreased ability to detect, identify, or differentiate odors and thus, being considered a clinical marker of these diseases' early stages and a marker of disease progression and cognitive decline. [5]

One of the primary reasons olfactory dysfunction is prominent in neurodegenerative diseases is the presence of pathological changes in the olfactory system. In AD, for example, amyloid plaques and neurofibrillary tangles, the hallmark pathological features of the disease, are found not only in brain regions associated with memory and cognition but also in areas involved in olfaction, such as the olfactory bulb and olfactory cortex.

1.3 Goal of the Project

Understanding the significance of olfactory dysfunction in neurodegenerative diseases is important as it can serve as a potential biomarker for early detection and help unravel underlying disease mechanisms. The study of olfactory dysfunction in neurodegenerative diseases is an active area of research. Researchers are investigating the potential of olfactory testing as a diagnostic tool and exploring the mechanisms underlying olfactory dysfunction. They are also examining the role of olfactory dysfunction in disease progression and exploring therapeutic interventions targeting the olfactory system.

In this project, we want to identify early biomarkers for related brain disorders through olfactory stimulus.

2 Electroencephalography (EEG)

2.1 What is EEG?

There are different tools for collecting data from the brain. One of the methods of capturing brain signals is called Electroencephalography (EEG). These signals are changes in voltage level caused by changes in brain signals captured by some electrodes. These voltages are microVolt-level, so they can be sensitive to small noises.

One of the EEG advantages compared to other methods is its high temporal accuracy (i.e. high sampling frequency) while it suffers from low spatial accuracy. Another benefit of EEG devices is their smaller size compared to other devices like fMRI (functional Magnetic Resonance Imaging). While fMRI devices occupy the whole room, you can use EEG via portable devices.

EEG headsets are devices built to save EEG signals. These headsets could contain many electrodes. One internationally recognized electrode placement method is the **10-20 system**. This method was developed to maintain standardized testing methods ensuring that a subject's study outcomes (clinical or research) could be compiled, reproduced, and effectively analyzed and compared using scientific methods. It is called 10-20 because the distance between adjacent electrodes is 10% or 20% of the skull's total front–back or right–left distance.

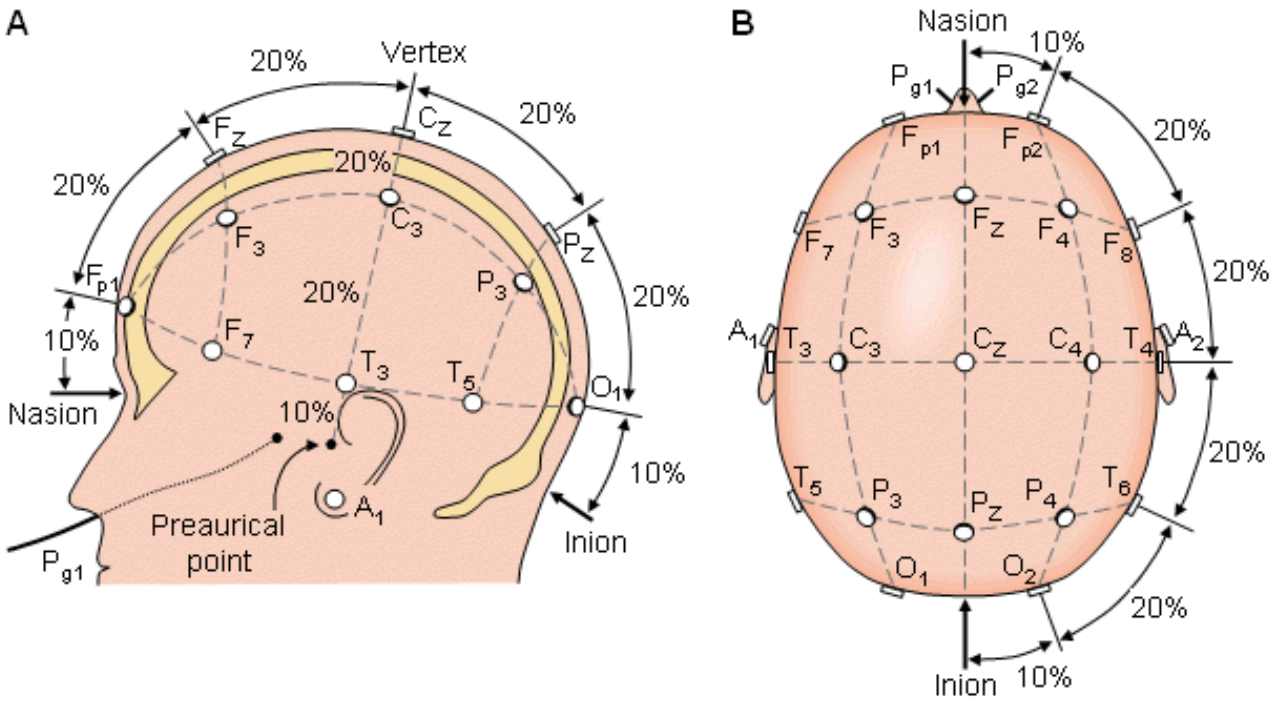


Figure 1: EEG 10-20 Electrode Placement System

Based on the picture above, What does each electrode's name stand for? Explain the naming method used in the 10-20 EEG system.

In the 10-20 system, the electrode names are determined based on the relative distances between specific anatomical landmarks on the head. The "10" and "20" refer to the fact that the actual distances between adjacent electrodes are either 10% or 20% of the total front–back or right–left distance of the skull. For example, a measurement is taken across the top of the

head, from the nasion to inion. Most other common measurements ('landmarking methods') start at one ear and end at the other, normally over the top of the head. Specific anatomical locations of the ear used include the tragus, the auricle and the mastoid.

Each electrode placement site has a letter to identify the lobe, or area of the brain it is reading from: pre-frontal (Fp), frontal (F), temporal (T), parietal (P), occipital (O), and central (C). Note that there is no "central lobe"; due to their placement, and depending on the individual, the "C" electrodes can exhibit/represent EEG activity more typical of frontal, temporal, and some parietal-occipital activity, and are always utilized in polysomnography sleep studies for the purpose of determining stages of sleep.

There are also (Z) sites: A "Z" (zero) refers to an electrode placed on the midline sagittal plane of the skull, (FpZ, Fz, Cz, Oz) and is present mostly for reference/measurement points. These electrodes will not necessarily reflect or amplify lateral hemispheric cortical activity as they are placed over the corpus callosum, and do not represent either hemisphere adequately. "Z" electrodes are often utilized as 'grounds' or 'references,' especially in polysomnography sleep studies, and diagnostic/clinical EEG montages meant to represent/diagnose epileptiform seizure activity, or possible clinical brain death. Note that the required number of EEG electrodes, and their careful, measured placement, increases with each clinical requirement and modality.

Even-numbered electrodes (2,4,6,8) refer to electrode placement on the right side of the head, whereas odd numbers (1,3,5,7) refer to those on the left; this applies to both EEG and EOG (electrooculogram measurements of eyes) electrodes, as well as ECG (electrocardiography measurements of the heart) electrode placement. Chin, or EMG (electromyogram) electrodes are more commonly just referred to with "right," "left," and "reference," or "common," as there are usually only three placed, and they can be differentially referenced from the EEG and EOG reference sites.

The "A" (sometimes referred to as "M" for mastoid process) refers to the prominent bone process usually found just behind the outer ear (less prominent in children and some adults). In basic polysomnography, F3, F4, Fz, Cz, C3, C4, O1, O2, A1, A2 (M1, M2), are used. Cz and Fz are 'ground' or 'common' reference points for all EEG and EOG electrodes, and A1-A2 are used for contralateral referencing of all EEG electrodes. This EEG montage may be extended to utilize T3-T4, P3-P4, as well as others, if an extended or "seizure montage" is called for.

2.2 Alzheimer's Disease

Alzheimer's Disease (AD) is a progressive and irreversible neurological disorder that affects the brain, primarily causing problems with memory, thinking, and behavior. It is the most common cause of dementia, a general term for a decline in cognitive ability severe enough to interfere with daily life.

The exact cause of Alzheimer's disease is not yet fully understood, but it is believed to involve a combination of genetic, lifestyle, and environmental factors. The staging of the AD is associated with the accumulation of Amyloid- beta ($A\beta$) proteins in the brain. These depositions cause synaptic and neuronal loss, which leads to major cognitive dysfunction in the advanced levels of the disease.

While EEG is not currently used as a primary treatment for Alzheimer's disease, it can be a valuable tool in the diagnosis and monitoring of the disease. EEG can help in the diagnosis of Alzheimer's by detecting abnormal patterns of brain activity that are characteristic of the disease. In individuals with AD, EEG often shows changes such as a reduction in certain brainwave frequencies and an increase in others. These patterns can aid in differentiating Alzheimer's from other types of dementia or cognitive disorders.

2.3 Frequency Bands of EEG

In the frequency domain, EEG signals are divided into 5 bands. [2]

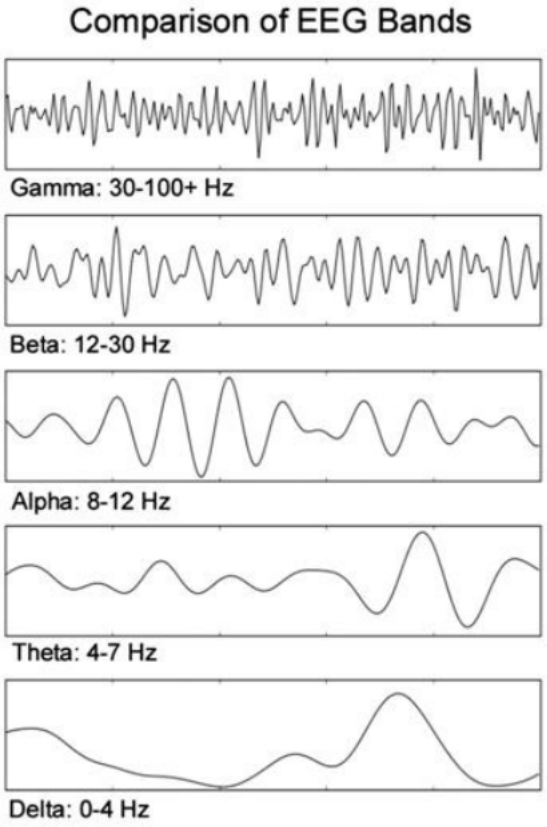


Figure 2: EEG Frequency Bands

Determine the activities each frequency band is associated with.

Understanding brain waves involves recognizing five distinct frequencies. It is essential to acknowledge that when referring to a specific brain wave, it implies its prevalence. Throughout wakefulness, an electroencephalogram (EEG) captures all five brain wave types simultaneously. However, the dominant brain wave depends on the particular state of consciousness.

For instance, during wakefulness, individuals with severe ADHD might exhibit heightened slow wave (alpha and/or theta) activity as opposed to beta waves. As for sleep, various combinations of slower frequencies are commonly observed, even with gamma waves found to be engaged during rapid-eye movement (REM) sleep. The subsequent section provides a succinct delineation of each brain wave state.

2.3.1 Gamma Waves

These are involved in higher processing tasks as well as cognitive functioning. Gamma waves are important for learning, memory and information processing. It is thought that the 40 Hz gamma wave is important for the binding of our senses in regards to perception and are involved in learning new material. It has been found that individuals who are mentally challenged and have learning disabilities tend to have lower gamma activity than average.

- **Frequency Range:** 40 Hz to 100 Hz (Highest)
- **Too much:** Anxiety, high arousal, stress
- **Too little:** ADHD, depression, learning disabilities
- **Optimal:** Binding senses, cognition, information processing, learning, perception, REM sleep
- **Increase gamma waves:** Meditation

2.3.2 Beta Waves

These are known as high frequency low amplitude brain waves that are commonly observed while we are awake. They are involved in conscious thought, logical thinking, and tend to have a stimulating affect. Having the right amount of beta waves allows us to focus and complete school or work-based tasks easily. Having too much beta may lead to us experiencing excessive stress and/or anxiety. The higher beta frequencies are associated with high levels of arousal. When you drink caffeine or have another stimulant, your beta activity will naturally increase. Think of these as being very fast brain waves that most people exhibit throughout the day in order to complete conscious tasks such as: critical thinking, writing, reading, and socialization.

- **Frequency Range:** 12 Hz to 40 Hz (High)
- **Too much:** Adrenaline, anxiety, high arousal, inability to relax, stress
- **Too little:** ADHD, daydreaming, depression, poor cognition
- **Optimal:** Conscious focus, memory, problem solving
- **Increase beta waves:** Coffee, energy drinks, various stimulants

2.3.3 Alpha Waves

This frequency range bridges the gap between our conscious thinking and subconscious mind. In other words, alpha is the frequency range between beta and theta. It helps us calm down when necessary and promotes feelings of deep relaxation. If we become stressed, a phenomenon called "alpha blocking" may occur which involves excessive beta activity and very little alpha. Essentially the beta waves "block" out the production of alpha because we become too aroused.

- **Frequency Range:** 8 Hz to 12 Hz (Moderate)
- **Too much:** Daydreaming, inability to focus, too relaxed
- **Too little:** Anxiety, high stress, insomnia, OCD
- **Optimal:** Relaxation
- **Increase alpha waves:** Alcohol, marijuana, relaxants, some antidepressants

2.3.4 Theta Waves

This particular frequency range is involved in daydreaming and sleep. Theta waves are connected to us experiencing and feeling deep and raw emotions. Too much theta activity may make people prone to bouts of depression and may make them "highly suggestible" based on the fact that they are in a deeply relaxed, semi-hypnotic state. Theta has its benefits of helping improve our intuition, creativity, and makes us feel more natural. It is also involved in restorative sleep. As long as theta isn't produced in excess during our waking hours, it is a very helpful brain wave range.

- **Frequency Range:** 4 Hz to 8 Hz (Slow)
- **Too much:** ADHD, depression, hyperactivity, impulsivity, inattentiveness
- **Too little:** Anxiety, poor emotional awareness, stress
- **Optimal:** Creativity, emotional connection, intuition, relaxation
- **Increase alpha waves:** Depressants

2.3.5 Delta Waves

These are the slowest recorded brain waves in human beings. They are found most often in infants as well as young children. As we age, we tend to produce less delta even during deep sleep. They are associated with the deepest levels of relaxation and restorative, healing sleep. They have also been found to be involved in unconscious bodily functions such as regulating heart beat and digestion. Adequate production of delta waves helps us feel completely rejuvenated after we wake up from a good night's sleep. If there is abnormal delta activity, an individual may experience learning disabilities or have difficulties maintaining conscious awareness (such as in cases of brain injuries).

- **Frequency Range:** 0 Hz to 4 Hz (Slowest)

- **Too much:** Brain injuries, learning problems, inability to think, severe ADHD
- **Too little:** Inability to rejuvenate body, inability to revitalize the brain, poor sleep
- **Optimal:** Immune system, natural healing, restorative\deep sleep
- **Increase alpha waves:** Depressants, sleep

2.4 Sampling frequency

Based on frequency bands and Nyquist criterion, which sampling frequencies are preferred for EEG signals?

In EEG signal preprocessing and processing, we are mainly concerned with frequencies up to 100 Hz, or maybe a bit higher. According the Nyquis criterion, sampling frequency must higher than the maximum signal frequency that we are working with. Therefore this conclusion could be drawn that the sampling frequency must at least be 200 Hz in EEG signal processing.

$$\omega_s > 2\omega_m = 2(100)Hz \implies \omega_s > 200Hz$$

3 EEG Signal Processing

In this section, firstly you would get familiar with the task and the structure of the data.

3.1 Task Definition

[12] To identify the effect of olfactory dysfunction among different brain health states, the following task was performed to collect the data. The same sequence of stimuli was presented to all participants. The stimulation sequence was composed of two different odors, one occurring frequently (standard) with a probability of 0.75 and the other presented rarely (deviant) with a probability of 0.25. Each trial consisted of a 2s stimulus presentation followed by 8s of rest (pure water vapor). The odors were delivered to the participants using a laboratory olfactometer. The experiment involved 120 trials in which 90 frequent and 30 rare stimulation cycles were presented in a predetermined, randomized order. Lemon essence was used as the frequent odorant and rose essence was used as the rare odorant. These odors were selected to avoid trigeminal system activation as the olfactory and trigeminal systems are interconnected and may interact with each other during exposure to certain stimuli [13]. The duration of odor presentation was set at 2s to enable regular breathing cycles for the participants.

3.2 Data Description

[12] The dataset consists of three files as follows:

- `AD.mat`: Contains data for Alzheimer's disease patients.
- `Normal.mat`: Contains data for healthy elderly participants.
- `MCI.mat`: Contains data for mild cognitive impairment patients. (Described in part 5.1)

The structure of the files is the same. Each file is organized as a structure array, in which each row contains information of one participant and the three columns correspond to the "epoch", "odor" and "noisy" fields as described in Table 1.

Field	Description
epoch	This is a 3D array structured as 4 × 600 × Num_trials. The first dimension indicates EEG channels respectively from the first column as Fp1, Fz, Cz, and Pz. The second dimension contains EEG samples from 1 s pre stimulus to 2 s post stimulus, which at a 200 Hz sampling rate amounts to 600 samples. The last dimension shows the number of trials. This could be different for each participant as some trials were deleted during preprocessing.
odor	This is a 2D binary array shaped as Num_trial × 1. This array shows the odorant type (lemon/rose) the participant was exposed to in each trial. The value = 1 indicates the rose odor and the value = 0 indicates the lemon odor.
noisy	This is a 2D array with the size 1 × Num_noisy. This array indicates noisy trials identified based on comparing the instantaneous and average trial amplitudes. These noisy trails can be ignored in processing and were included for the dataset completeness.

Table 1: Description of each structure array (.mat file) in the dataset.

3.3 Pre-Processing

Using a standard pipeline in EEG signal preprocessing is crucial for ensuring consistency, reproducibility, and objectivity in research. It reduces bias, enhances the reliability of results, and provides established best practices for addressing common challenges. A popular and widely used pipeline for EEG signal preprocessing is Makoto's pipeline (Makoto's preprocessing pipeline - SCCN).

The collected raw data from all participants were preprocessed following the full pipeline of Makoto with the use of EEGLAB and posted as a dataset, as described in the following steps:

1. Apply 1 Hz high pass filter to remove baseline drifts.
2. Apply relevant notch filter to remove the 50 Hz line noise.
3. Reject bad channels as a critical step before average referencing with the use of `clean_rawdata()` EEGLAB plugin.
4. Interpolate the removed channels.
5. Re-reference the data to the average of all channels to obtain a good estimate of referenceindependent potentials.
6. Apply `clean_rawdata()` for cleaning the data by running artifact subspace reconstruction(ASR).
7. Re-reference the data to the average again to compensate for any potential changes in the data caused by the previous step.

8. Run independent component analysis (ICA) to identify EEG sources as well as the sources associated with noise and artifacts.

9. Fit single and bilateral (if available) current dipoles.

10. Further clean the data by source (dipole) selection using `ICLabel()` plugin in EEGLAB.

However, there is no need to fully implement the Makoto's pipeline and a simplified version of this is as follows; follow the instructions below and provide the required results in each step:

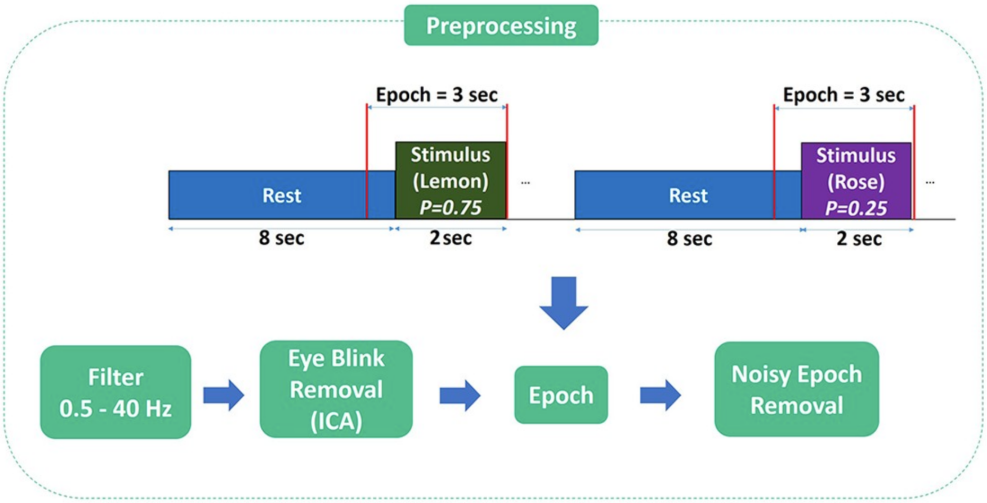
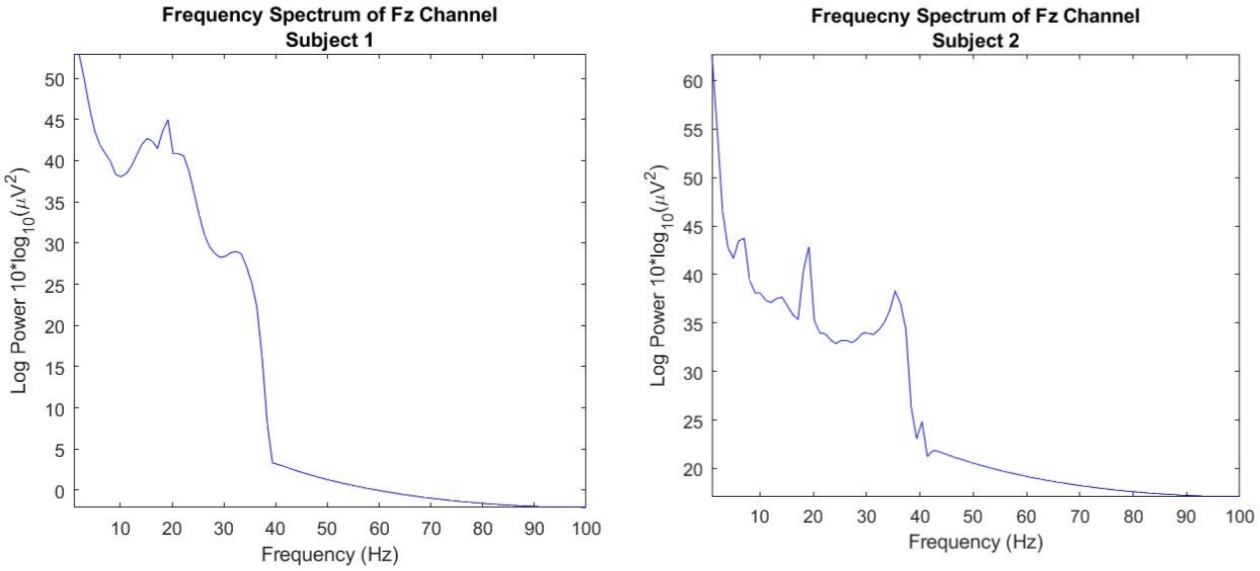


Figure 3: Task and Preprocessing Steps [9]

- **Step 1**: To preproccess using EEGLAB, first re-reference data to the mean of the channels. Then use a bandpass filter to filter 0.5 - 40.5 Hz frequencies. As we have filtered to 40.5 Hz, there is no need to apply a 49.9 - 50.1 Hz notch filter to remove the line noise. Using FFT function or EEGLAB, the frequency spectrum of `Fz` channel data is plotted for both subjects in Figure 4.

- **Step 2**: In this part you would remove the artifacts of the signal. Artifacts include blinking, eye movement, muscle movement, heart rate and etc. For this, load your data at EEGLAB. Now load `Standard-10-20-Cap19.loc` file from `edit-channel loacations` menu that contains locations of channels. Then run ICA (Independent Component Analysis) algorithm from `tools-decompose data` by ICA menu. Please note that this part would probably takes more time. By running `tools` → `classify components using ICLabel-label components`, Figure 5 is obtained for the **Subject 1**, and Figure 6 respectively for **Subject 2**. Also, a detailed overview of one of the IC components of **Subject 2** is provided in Figure 7.



(a) Fz Spectra of Subject 1 **(b)** Fz Spectra of Subject 2

Figure 4: Fz Spectra of the Subjects

- **Step 3**: Epoch the data of each subject. Epoch is a 3D matrix of the shape {`Num_Channels` × `Samples` × `Num_Trials`}. In fact, all data must be reshaped as the following figure suggests:

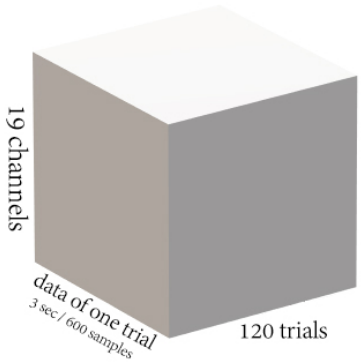


Figure 8: Epoch

For epoching the data, starting point of the experiment is required. This is provided in the `help` file for each subject. Please note that you must epoch the data by considering this time as the start. Also, the data after 120 trials should be neglected as well.

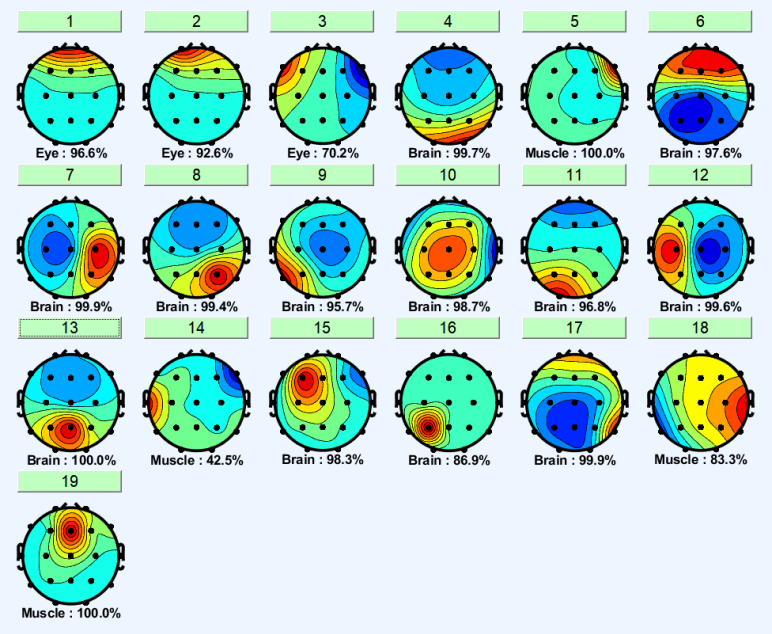


Figure 5: Brain Map of Subject 1

- **Step 4**: In this step, you need to remove noisy trials. There are two ways to achieve this:
  1. Observe data at EEGLAB and remove any trial that seems noisy. (PREFERRED!)
  2. Using power spectrum of each trial, remove trials that their standard deviation of their power spectrum is bigger than 3.5 .Create a 3D matrix by each trial's power spectrum for each channel using `pspectrum` in MATLAB. You can use the following commands to find noisy trials:

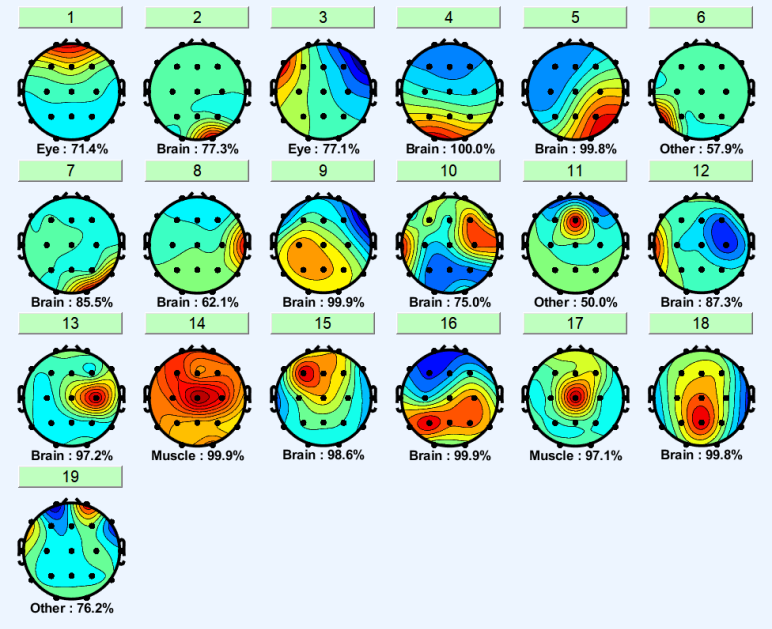


Figure 6: Brain Map of Subject 2

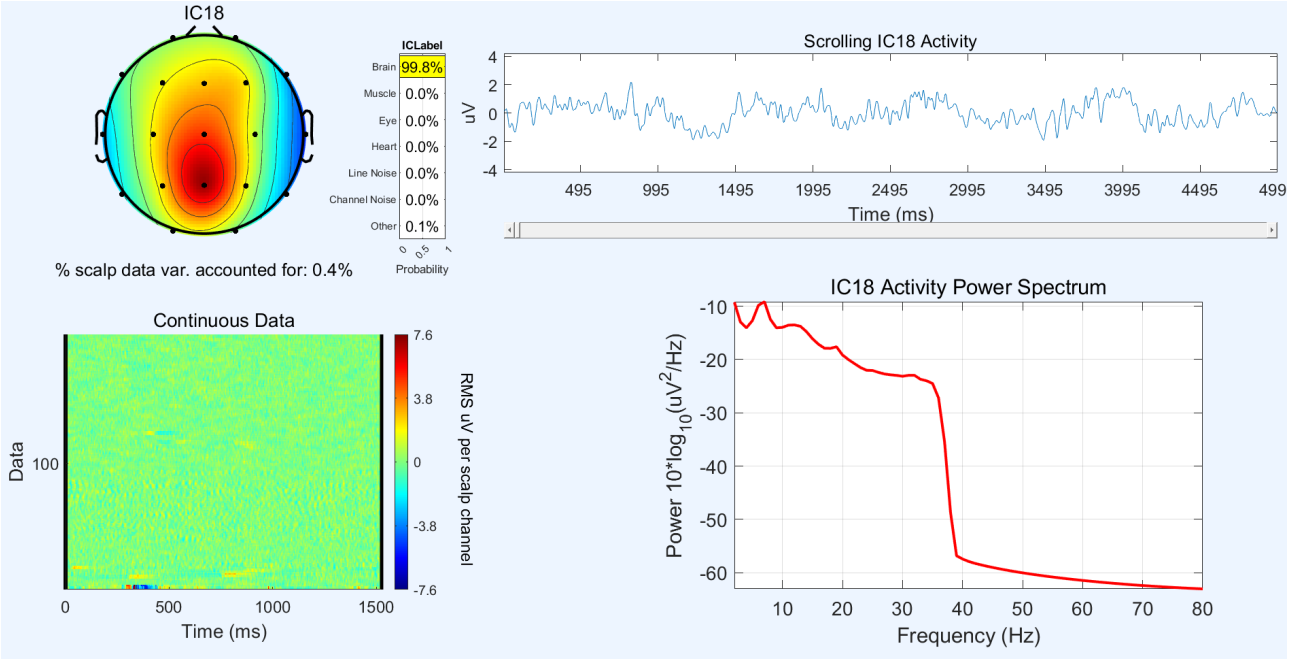


Figure 7: Detail of IC18 of Subject 2

```
vr = sum(nanstd(p,[],2).^2,2);
noisy_trials = find(abs(zscore(vr))>3.5);
```

In these commands, `p` is a matrix of frequency spectrums of all trials of a channel. `noisy_trials` contains the number of noisy trials of that channel. These commands must run for each channel individually and the resultant noisy trials must be accumulated over all channel. Then remove all `noisy_trials` from your epoch.

- **Step 5**: In the final step, only subsample the data corresponding to the `Fp1, Fz, Cz & Pz` channels. You can find the channels' orders in the `Channels.jpg`.

Do these 5 steps for each subject and save the final data through an `struct` with the same format as described in Table 1. Also, consider the order of `odor` being the same as the ones used for normal participants.

3.4 Phase Locking Value (PLV)

Phase Locking Value (PLV) is a metric used to quantify the degree of phase synchronization or phase consistency between two oscillatory signals. It assesses the relationship between the phases of two signals at a specific frequency range. PLV is commonly used in the analysis of neural signals, including electroencephalography (EEG) and magnetoencephalography (MEG), to investigate the synchronization of oscillatory activity between different brain regions or across different frequency bands within a single region.. It provides insights into the functional connectivity and coordination of neural activity.

PLV ranges from 0 to 1, where a value of 1 indicates perfect phase synchronization, while a value close to 0 represents a lack of synchronization. High PLV values suggest that the phases of the two signals are consistently aligned or coupled, indicating strong synchronization. This synchronization can reflect functional interactions between brain regions or coordinated activity within a network. In contrast, low PLV values indicate weaker or desynchronized activity, suggesting less functional coupling between the signals.

- What does phase synchronization indicate from a functional point of view? Discuss its importance with valid references.

  Phase synchronization, as quantified by the Phase Lock Value (PLV), offers valuable insights into the coordination and communication among brain regions by assessing the alignment of their neural oscillations [11]. It indicates the extent to which the phase angles of two signals exhibit consistency over time, thereby reflecting the functional connectivity and information exchange between these regions. This measure plays a crucial role in understanding cognitive processes such as attention [14], perception [6], memory [4], and decision-making [7], as it facilitates precise timing and efficient neural communication. By examining phase synchronization, researchers gain a deeper understanding of the dynamic functional connectivity of the brain and its implications for various brain disorders. Notably, studies on generalized synchronization, large-scale integration, neural oscillations in schizophrenia, and the role of infra-slow fluctuations in brain dynamics provide valid references that underscore the significance of phase synchronization and PLV analysis [8].

- Formulate the definition of PLV and briefly discuss the mathematical tools needed to calculate it.

$$PLV_{i,j}(t) = \frac{1}{N}\left|\sum_{n=1}^{N} e^{-i(\varphi_i(t,n)-\varphi_j(t,n)}\right|$$

  where N is the number of the trials, and $\varphi_i(t,n)$ is the instantaneous phase for signal i in trial n at time t.Therefore extracting the instantaneous phase $\varphi_i(t,n$ is necessary. Besides, for the phase to be physically meaningful, it is necessary that only one oscillator is present in each signal. This is achieved, e.g., by means of a narrow-band pass filtering or, equivalently, the convolution with a narrow band complex wavelet such as that of Morlet and also Hilbert transform.

- Implement a function that finds the PLV between two channels in a specific frequency range. This function is going to be needed in the section 4. (NOTE: You are allowed to define this function with any required input arguments.)

4 Results

In this section, you need to present the required results to assess the difference of Phase Locking Values (PLV) among two groups, namely AD and Normal in the slow gamma frequency range, which is 35 to 40 Hz.

To fairly compare your results in this part, you do not need to use your preprocessing data from section 3.3 and the preprocessed data of 15 healthy (normal) (age = 69.27±6.65, female = 53.33%) individuals and 13 AD patients (age = 75.31±9.90, female = 61.54%) are availabe through `Dataset/Normal.mat` and `Dataset/AD.mat`.

4.1 Values

Find the PLV for all participants of both groups on both frequent and rare odors between the `Fz` and `Cz` channels using the function you implemented in section 3.4 .

4.2 Distributions

Draw the box plots(Figure 9) of PLVs you found in the previous part among two groups and two odors. Also, fit a gaussian distribution on these PLVs and present you results(Figure 10). You need to specify the corresponding `p-values` to evaluate the statistical significance of your findings.

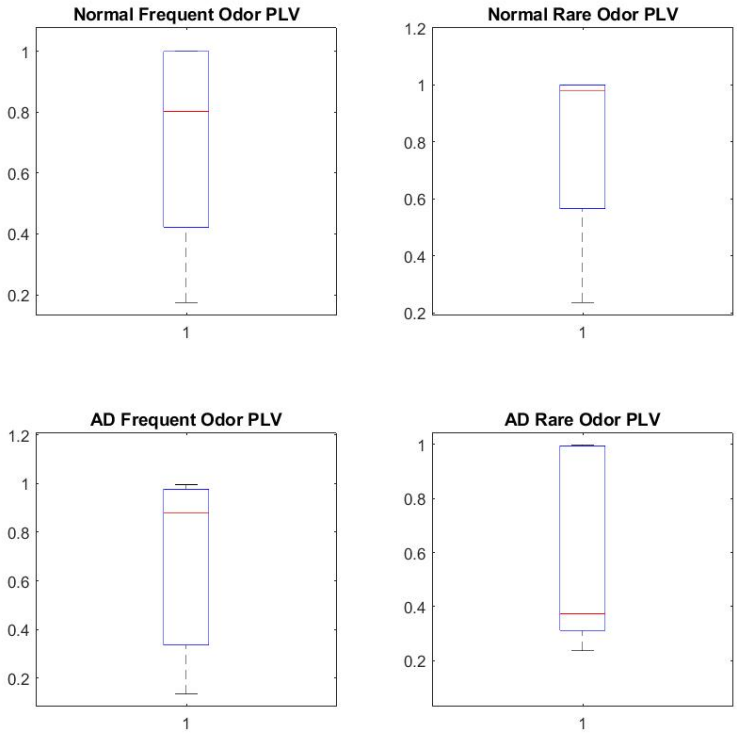


Figure 9: Box Plots of Normal and AD Groups' PLVs Responding to Frequent and Rare Odors

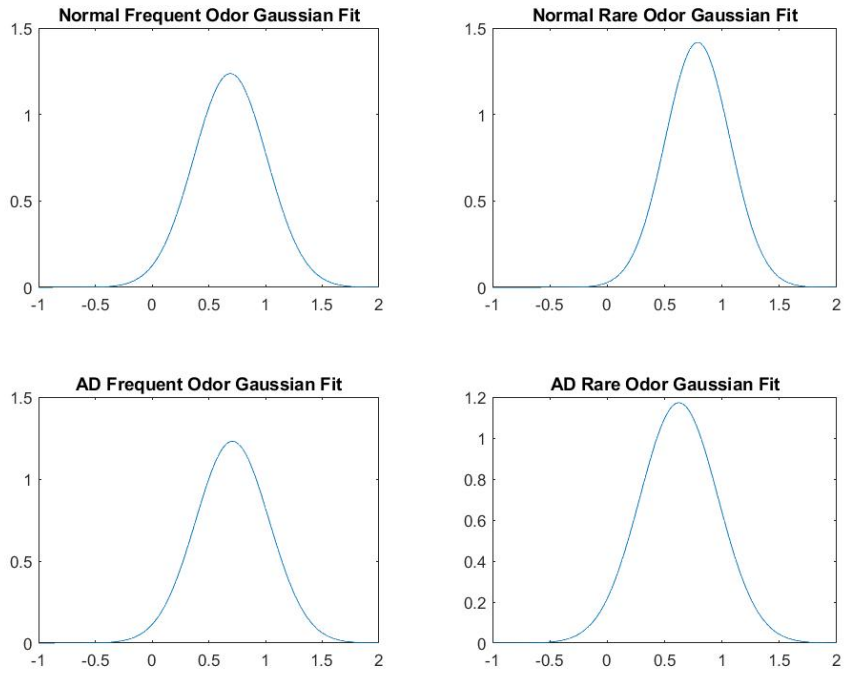


Figure 10: Fitted Gaussian Distribution on theNormal and AD Groups' PLVs Responding to Frequent and Rare Odors

Using the function `ttest2`,the corresponding `p-values` are founded as **0.3846** for **Normal**, and **0.5260** for **AD**.

4.3 Statistical Significance

Based on the `p-values` you founded in the previous part, discuss whether we could state that the "PLV is significantly different among AD and Normal subjects in the slow gamma frequency range".

By comparing the `p-values` obtained from previous parts, this conclusion could be drawn that Normal people have higher `p-values` compared to AD people. This is in fact in accordance with the definition of `p-value`. Higher the `p-value`, more similar the responses. The high `p-value` of AD group indicates that they respond much more equal to different odors than normal group, which would be a sign of early Alzeihmer and losing the ability to distinguish the odors.

4.4 Phase Difference

Draw a polar histogram of the phase difference between `Fz` and `Cz` channels during frequent odor trials for a random subject in each group and compare the results. Also, plot the mean value of this quantity among all the subjects of each group and discuss the results.

It's visible that AD group have wider range phase differences, compared to Normal group.

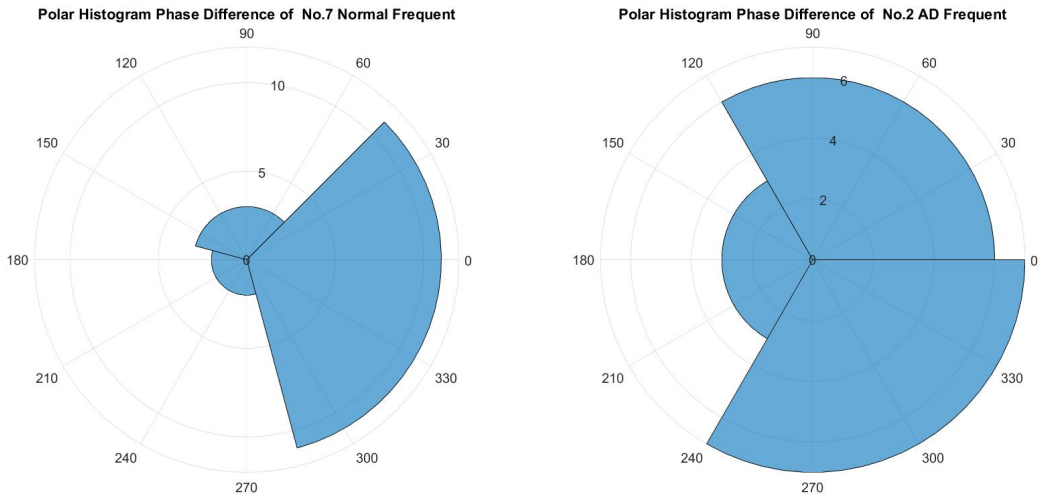


Figure 11: Polar Histogram of the Phase Difference between Fz and Cz Channels During Frequent Odor Trials for a Random Subject in Each Group

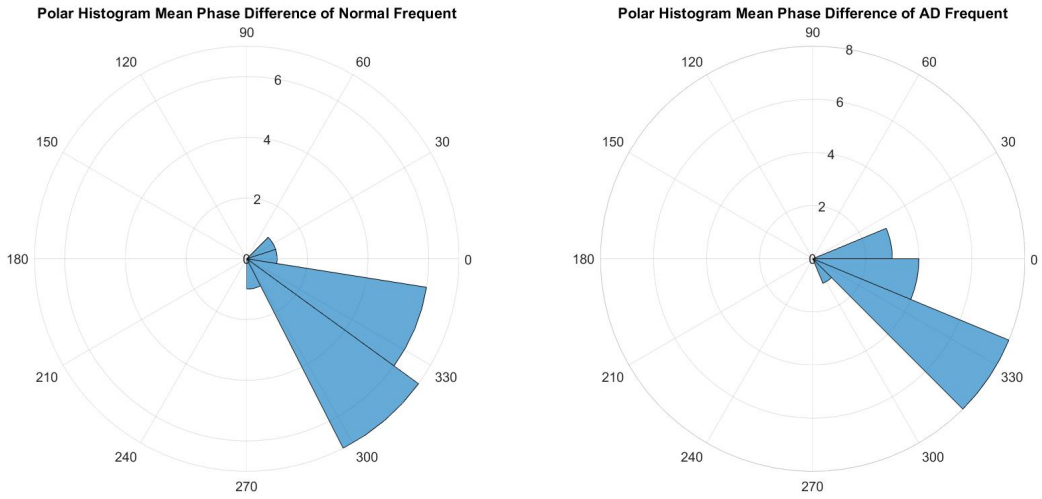


Figure 12: Polar Histogram of the Mean Phase Difference between Fz and Cz Channels During Frequent Odor Trials for Each Group

4.5 Heatmaps

Now you need to plot a heatmap which has the PLVs between each pair of the channels. Find whether PLV between other channel pairs are significantly different among two groups in the slow gamma frequency range and test your results. (NOTE: You need to provide `p-values` for your hypothesis if you found any significantly different channel pairs apart from (`Fz`,`Cz`).)

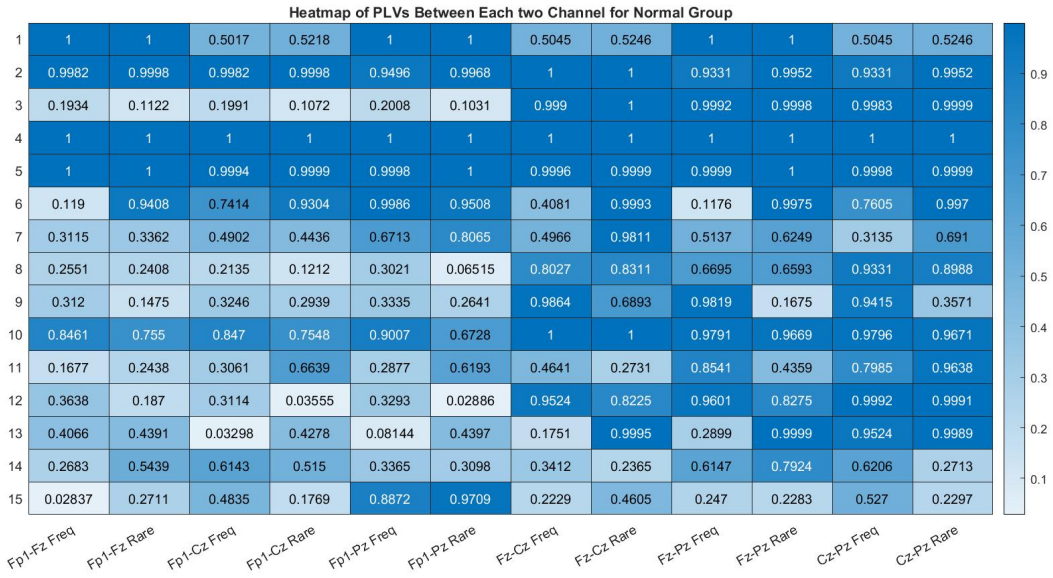


Figure 13: Heatmap of PLVs Between Each Two Channels for Normal Group

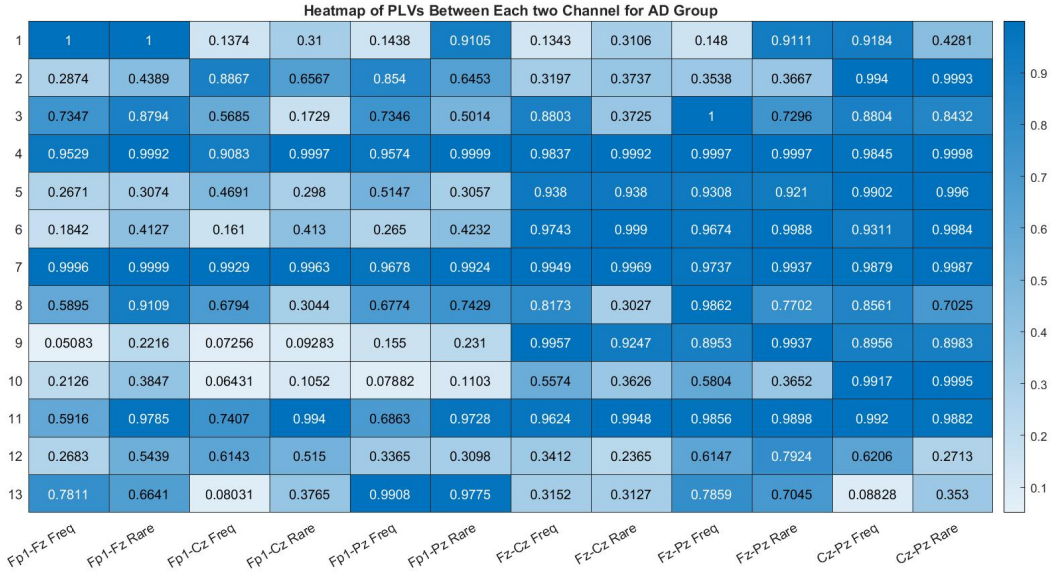


Figure 14: Heatmap of PLVs Between Each Two Channels for AD Group

5 *Bonus

5.1 Mild Cognitive Impairment (MCI)

Mild Cognitive Impairment (MCI) is the stage between the expected decline in memory and thinking that happens with age and the more serious decline of dementia. MCI may include problems with memory, language or judgment. People with MCI may be aware that their memory or mental function has slipped. [1]

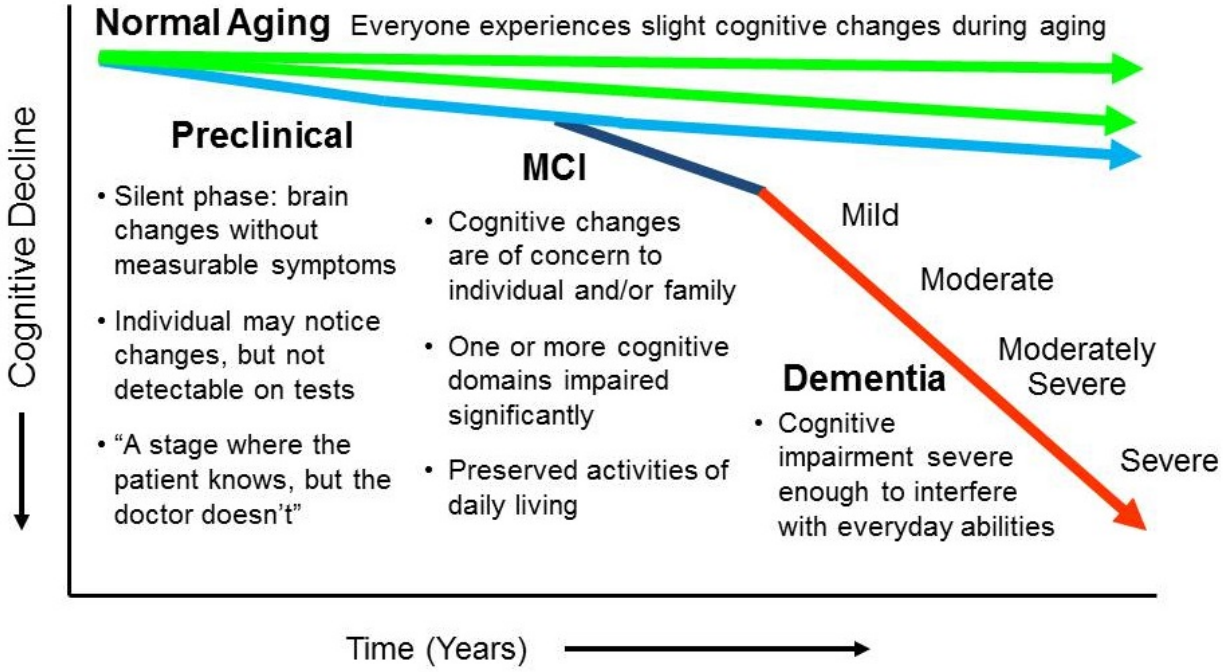


Figure 15: Normal Aging to Demantia Process

5.1.1 Additional Information

Describe the relationship between MCI and AD. Explain whether MCI would always result in AD and briefly investigate the causes of MCI.

5.1.2 MCI Data Processing

In the provided dataset, you can find `MCI.mat` file. This dataset contains preprocessed cleaned EEG recording of the same task described in sections 3.1 and 3.2 for 7 MCI patients.

Based on the significantly different coupled channels you found for differentiation between AD and Normal groups, find the Phase-Locking-Value (PLV) for the MCI subjects and provide the required results by comparing all the the 3 states (Normal, MCI, AD). Your findings must include the significance testing by providing the corresponding `p-values`.

5.2 Phase-Amplitude Coupling (PAC)

PLV was just one instance of the Phase-Amplitude Coupling (PAC) metrics. PAC is a form of cross-frequency coupling where the amplitude of a high frequency signal is modulated by the phase of low frequency oscillations. PAC is the most-studied type of cross-frequency coupling and is thought to be responsible for integration across populations of neurons. Low frequency brain activity controls the information exchange between brain regions by modulating the amplitude of the high frequency oscillations. [10]

5.2.1 Metrics

Conduct a search about other PAC measures and briefly provide an explanation about two of them.

5.2.2 Implementation

Implement one of the metrics mentioned earlier as a biomarker for distinguishing between AD and Normal groups. Present the relevant results through plots and provide a discussion regarding the efficacy of the selected metric.

6 Conclusion

As we have examined in this research, we can use olfactory sense and clues in order to detect Alzheimer Diseaese in early stages. We found that in certain band-width of brain's EEG signal, there is some dissimilarity between the response of the AD group and Normal group. As further studies, we can focus on other channels, and a much more significant difference compared to PLV criterion.

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