Signals and Systems Project

Instructor: Prof. Hamid Aghajan

Sharif University of Technology

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

---

Authors:

Alireza Gargoori Motlagh — alireza.gargoorimotlagh@ee.sharif.edu
Mojtaba Lahijanian — mojtaba.lahijanian@ee.sharif.edu
Amirali Loghmani — amirali.loghmani@ee.sharif.edu
S. Moienadin Makkiyan — moien.makkiyan@sharif.edu

Spring 2023

Preface

Notes on the project:

- Due date: 1402/04/10
- The project must be done individually. Each individual will present his results in an online session on 1402/04/11.
- Please submit your project report as a `.pdf` file. Include all outputs and final results in the report. Make sure to list the practice text questions and provide a concise explanation of your problem-solving approach in each section.
- Ensure that all codes are provided in a separate `.m/.py/.ipynb` file. If a code cannot be tested accurately upon submission, the reported results will be considered invalid, and no points will be awarded in such cases.
- You have the flexibility to utilize either `MATLAB` or `Python` for your project. However, please be aware that `MATLAB` is recommended since certain aspects of the project rely on `MATLAB` toolboxes.
- Ensure that you save all files, including your report, codes, helper functions, and any additional outputs, if required, in a compressed file format such as `.zip` or `.rar`. This compressed file should then be uploaded to the Coursework CW submission platform.
- Your file names must be in the following format:

  `Project_#StudentID.zip/.rar/.pdf/.m/.py/.ipynb`

- The details of the grading system of this project will be provided in the coming days. Generally, the project is worth a total of 1 point, with an additional 1 point allocated for the bonus section. Part 5.1 carries 0.5 points, and another 0.5 points are assigned to part 5.2.
- In this project, it is essential to uphold the principles of academic integrity and refrain from any form of cheating or copying. Cheating undermines the learning process, diminishes personal growth, and compromises the trust placed in us as students/researchers/professionals. It is crucial to recognize that engaging in dishonest practices not only tarnishes our own reputation but also has serious consequences, both ethically and academically. We want to emphasize that if anyone is found to have cheated, their results will not be accepted in this project, and they will receive a zero mark.

Contents

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. [4]

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.

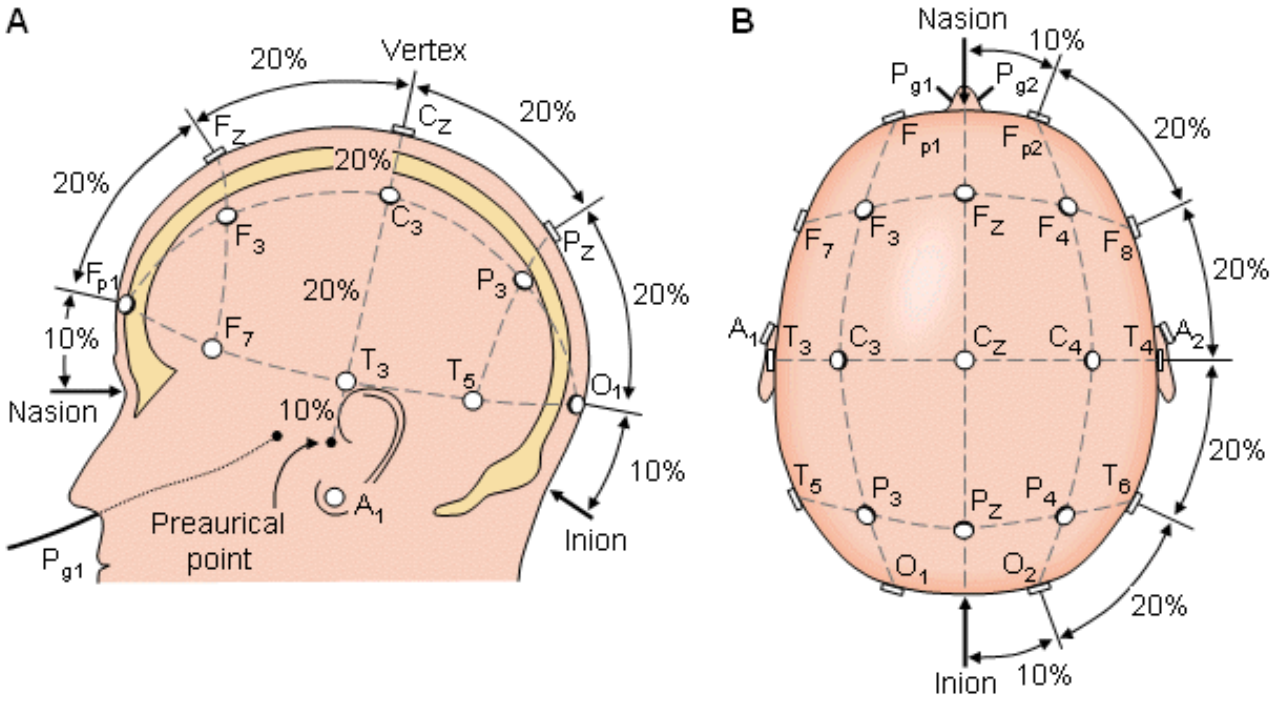

Figure 1: EEG 10-20 Electrode Placement System

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

Answer :

we have four lobe in brain :

Frontal lobe

Parietal lobe

Temporal lobe

Occipital lobe

so electrodes F,P,T,O stand for them and also electrode C is stands for region between Frontal and Parietal in the center of Brain and Fp stands for Pre-Frontal.

Odd numbers correspond to left side of brain and even numbers correspond to right side of brain.

In 10-20 standard we divide distance between Nasion and Inion to %10,%20,%20,%20,%20,%10 in 5 directions and also we divide distance between left and right Preaurical Point to %10,%20,%20,%20,%20 in 5 directions and name encountered points according to part they are in.

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]

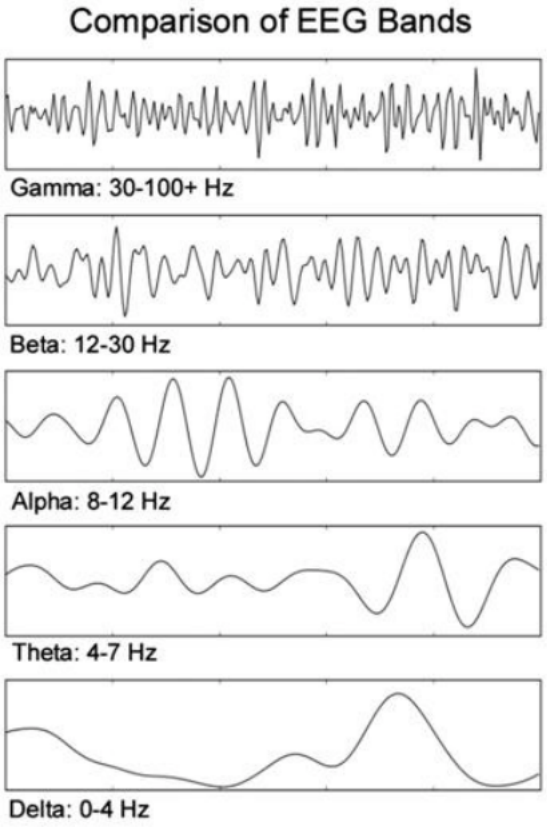

Figure 2: EEG Frequency Bands

Determine the activities each frequency band is associated with.

Answer :

Frequency Region : Example Activity
Gamma : Math Proccessing,Information Proccessing
Beta : Logical Thinking,Focused Attension,Decision-making
Alpha : Closing Eyes,Relax State of Mind
Thata : Creativity,Daydreaming
Delta : Deep Sleeping,Unconscious State,Meditative state

2.4 Sampling frequency

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

Answer :

The Nyquist criterion states that the sampling frequency should be at least twice the maximum frequency present in the signal to avoid aliasing. Considering the frequency bands of EEG signals, the highest frequency of interest is typically in the gamma range, which is around 30 to 100 Hz. So we should sample with Rate 200Hz.Ofcourse if we know that our signal just have content in lower frequency we can decrease sampling rate to twice of maximum frequency present in the signal.

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

[7] 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 [8]. The duration of odor presentation was set at 2s to enable regular breathing cycles for the participants.

3.2 Data Description

[7] 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.

In the `Dataset/Preprocess` folder you can find the raw data for 2 subjects with the corresponding additional information provided. In this section you are required to preprocess these data and save your final preprocessed cleaned data.
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:

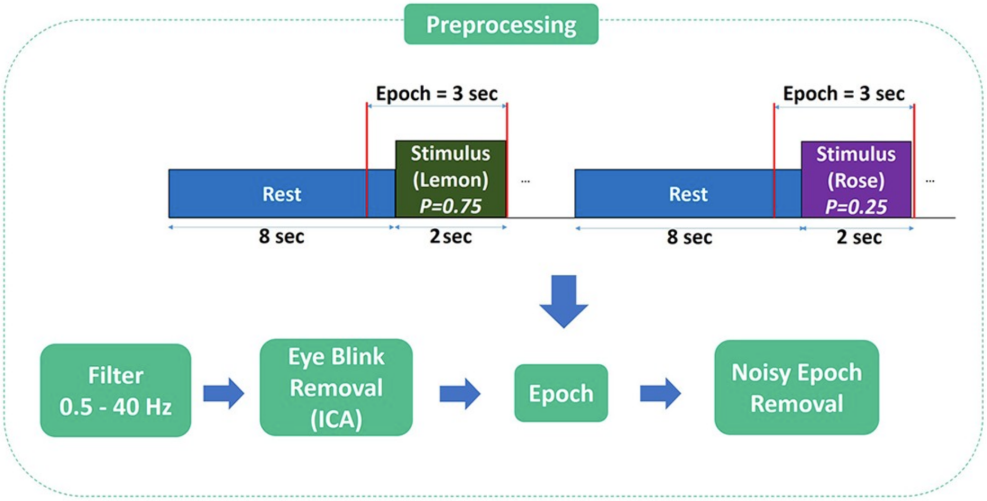

Figure 3: Task and Preprocessing Steps [5]

- **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 (However, keep this step in mind as this is a crucial step in EEG signal preprocessing!). Using FFT function or EEGLAB, plot the frequency spectrum of `Fz` channel data. (Just to note, your data will be saved at EEG struct in MATLAB workspace.)

  Observations :

  In this section first we needed to use function table2array() and transposing the result to loading subject1 and subject2 to eeglab.Then we removed 20th channel because we didn't need it(Figure 4).

```
close all,clear,clc;

load Subject1.mat
load Subject2.mat

new_subject1=table2array(subject1)';
new_subject2=table2array(subject2)';

new_subject1=new_subject1(1:19,:);
new_subject2=new_subject2(1:19,:);
```

Figure 4: Load data and remove channel code

After loading data to eeglab first we re-referenced it and applied bandpass filter to it so we get Figure 6 and Figure 8.

The frequency spectrum of Fz channel data is Figure 5 and Figure 7.

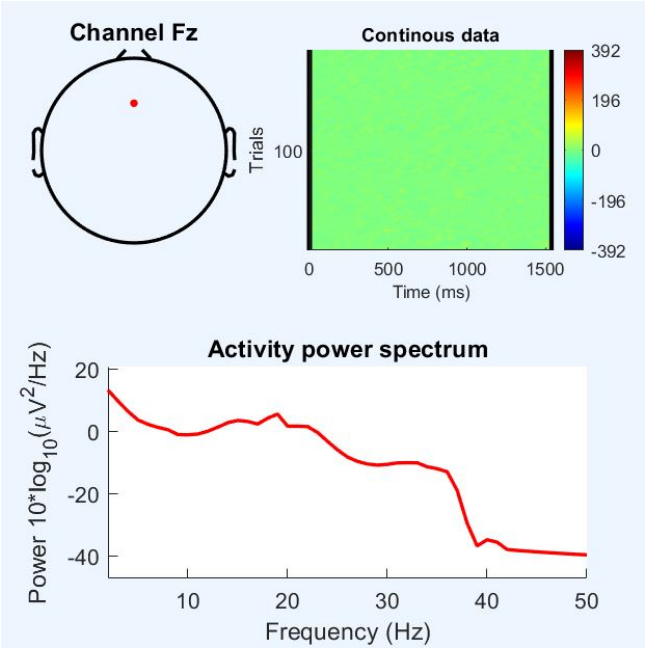

Figure 5: Frequency spectrum of Fz channel of subject1

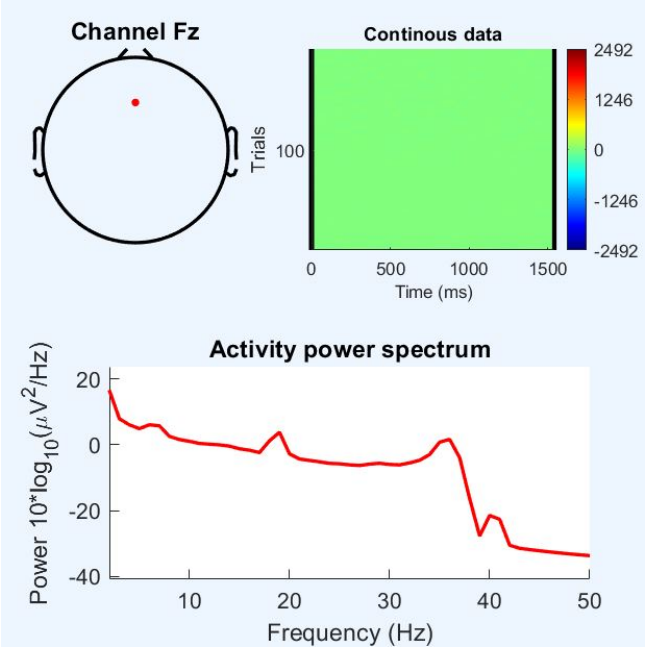

Figure 7: Frequency spectrum of Fz channel of subject2

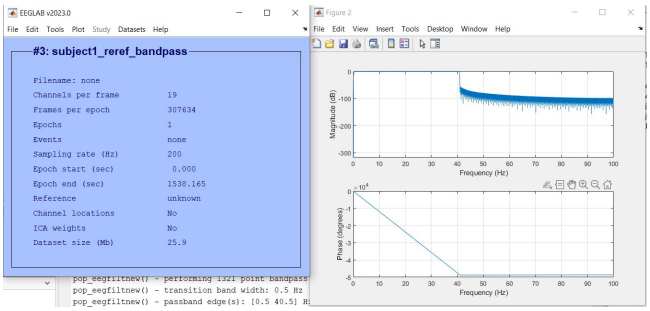

Figure 6: Band pass filter of subject1

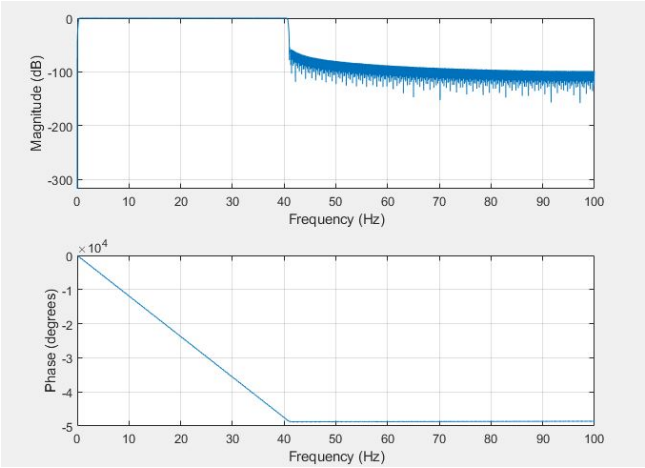

Figure 8: Bandpass filter of subject2

- **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. Then you will have the a figure like Figure 4 by running `tools` → `classify components using ICLabel-label components.` By clicking on

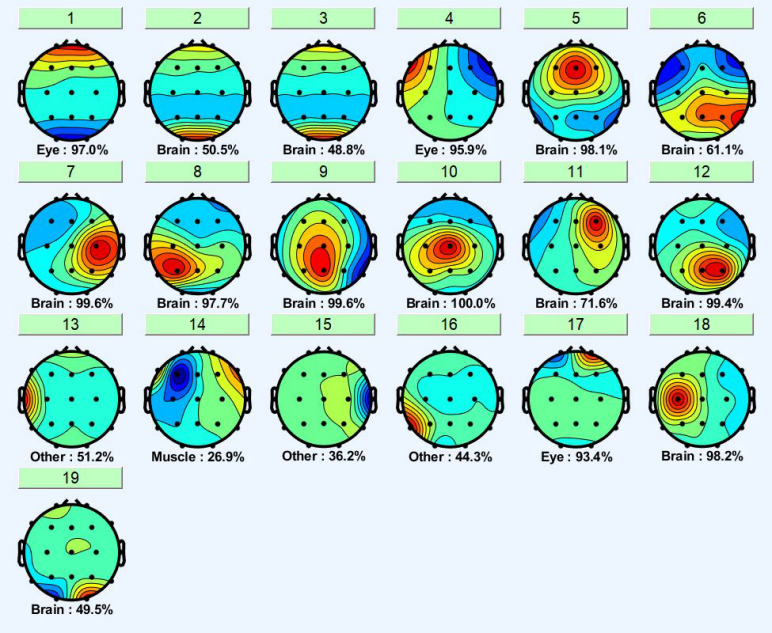

Figure 9: An example of ICA components

each component, you can some details about it as well. Present a figure from one of the brain components with its details.

Now remove all non-brain components. For this purpose, from `Tools-remove components from data` enter the number of components that must be removed.

Observations :

After Applying ICA we got Figure 10-13.

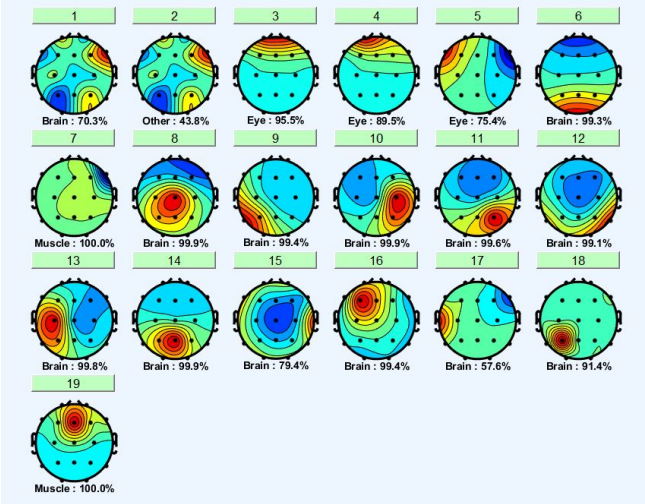

Figure 10: ICA1

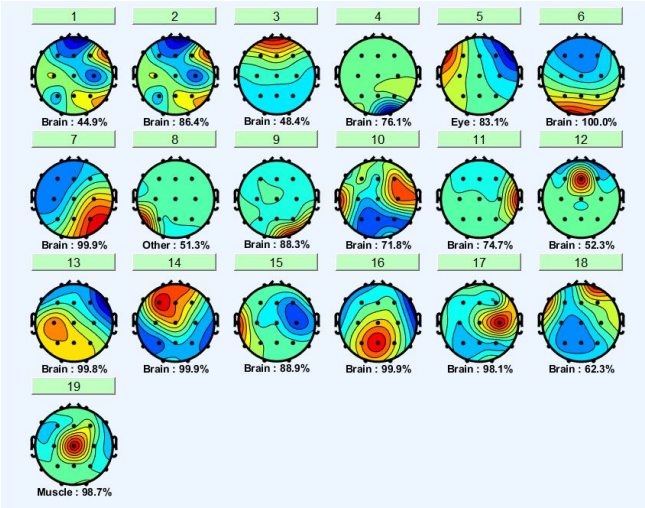

Figure 11: ICA2

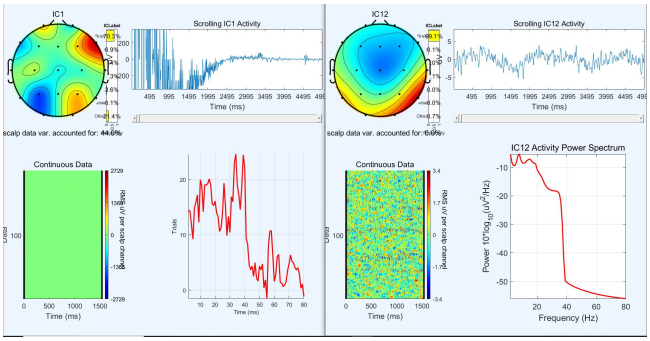

Figure 12: Brain and Non-Brain Component Example Of Subject1

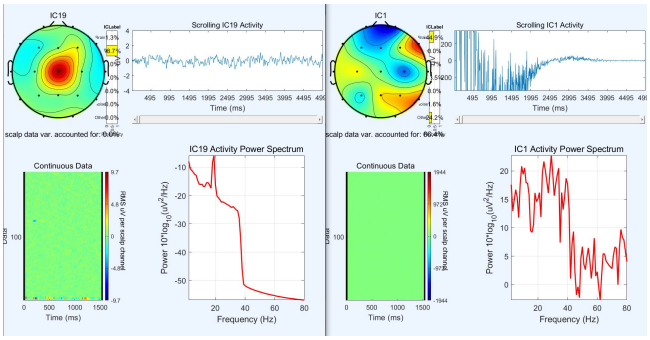

Figure 13: Brain and Non-Brain Component Example Of Subject2

Then we removed Non-brain component to analysis the data better.

- **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:

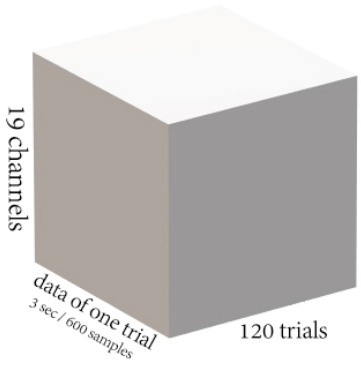

Figure 14: Epoch

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.

Observations :

In this section we load data from EEG.data to matlab and epoched signal and then we imported the epoched signal to eeglab again.Figure 15 is our code.

```
ns3 = []
remove_time = 14*200;
ns2 = EEG.data(:,remove_time:end );
for i=1:120
    a = ns2(:,i*600 + 4200:(i+1)*600-1 +  4200);
    ns3(: , : , i) = a;
end
```

Figure 15: Epoching code

- **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:

```
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.

In this section we should remove noisy trials so we decided to do it according to approach 2 because we had limitations with approach 1. Figure 16 is our code.

```
%%step 4
[channels, samples, trials] = size(ns3);
noisyTrials = [];
for ch = 1 : channels
    p = nan(trials, samples);
    for trial = 1:trials
        trialData = squeeze(ns3(ch, :, trial)); % Extract
        %data for the current trial
        power = fft(trialData).^2; % power spectrum for the current channel
        p(trial, :) = power;
    end
    % suggested commands
    variances = sum(nanstd(p, [], 2).^2, 2);
    noisyTrialsCh = find(abs(zscore(variances)) > 3.5);
    noisyTrials = union(noisyTrials, noisyTrialsCh);
end
cleanEpochData = ns3(:, :, setdiff(1:trials, noisyTrials));
save('cleand_data.mat', 'cleanEpochData');
```

Figure 16: remove noisy trial code

- **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.

we saved our final cleaned Data in name of finalsubject1.mat and finalsubject2.mat using the code of figure 17.

```
%%step 5
channelsToKeep = [1, 5, 10, 15];
numChannels = 19;
channelsIdx = zeros(1, numChannels);
for i = channelsToKeep
    channelsIdx(i) = 1;
end
selectedEpochData = ns3(logical(channelsIdx),:,:);
save('final.mat', 'selectedEpochData');
Subject1_final = selectedEpochData;
Normal = load('Normal.mat','normal');
odor = Normal.normal.odor;
noisy = Normal.normal.noisy;
myStruct = struct(...
    'Subject1_final', Subject1_final, ...
    'odor', odor, ...
    'noisy',noisy);
save('subject1_struct.mat', 'myStruct');
```

Figure 17: Save Data

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.

  Answer :

  Phase synchronization in the context of brain activity refers to the coordination or alignment of the phase angles of oscillatory neural signals between different brain regions. It signifies that the neural activity in those regions is temporally coupled or coordinated. From a functional point of view, phase synchronization is believed to play a crucial role in various cognitive processes and functional brain networks [4, 6, 9, 11, 13, 14]. Phase synchronization has several important implications:

  1. Communication and Integration: Phase synchronization facilitates efficient communication and integration of information across different brain regions, allowing for the exchange of information and the integration of distributed neural activity [14].

  2. Neural Network Dynamics: Phase synchronization patterns contribute to the formation and dissolution of transient functional networks, supporting flexible cognitive processing and adaptability [6].

  3. Cognitive Functions: Phase synchronization is implicated in various cognitive functions such as attention, perception, memory, and language processing. For example, phase synchronization in specific frequency bands is associated with attentional processes and the selection of relevant stimuli [4, 9].

  4. Disease and Disorders: Disruption of phase synchronization is observed in neurological and psychiatric disorders such as epilepsy, schizophrenia, and Alzheimer's disease. Abnormal phase synchronization patterns may reflect dysfunctional neural communication and contribute to the manifestation of symptoms in these conditions [11, 13]. Understanding phase synchronization provides insights into the coordination and communication between different brain regions during cognitive processes, revealing the functional connectivity of the brain. It contributes to our understanding of cognitive functions and the mechanisms underlying brain disorders.

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

Answer :

1. Hilbert Transform: The Hilbert transform is applied to each of the two signals of interest to obtain their analytic signals, which represent the original signal in a complex form. The analytic signal retains the original signal's amplitude and phase information.

2. Instantaneous Phase Calculation: From the analytic signals, the instantaneous phase of each signal is computed. The phase represents the angle of the complex signal and captures the oscillatory behavior.

3. Phase Difference Calculation: The phase difference between the two signals is calculated by subtracting the phase of one signal from the phase of the other. This phase difference captures the relative phase relationship between the two signals at each point in time.

4. Phase Locking: The phase differences obtained are then used to assess the degree of phase synchronization. Phase Locking Value (PLV) is typically calculated as the absolute value of the average of the complex exponential of the phase differences over a certain time interval or across multiple trials. It represents the tendency of the signals to have a consistent phase relationship.

Consider a pair of real signals $s_1(t)$ and $s_2(t)$, that have been band-pass filtered to a frequency range of interest. Analytic signals $z_i(t) = A_i(t)e^{j\varphi_i(t)}$ for $i = \{1, 2\}$ and $j = \sqrt{-1}$ are obtained from $s_i(t)$ using the Hilbert transform:

$$z_i(t) = s_i(t) + j\mathrm{HT}\left(s_i(t)\right)$$

where HT $(s_i(t))$ is the Hilbert transform of $s_i(t)$ defined as

$$\mathrm{HT}\left(s_i(t)\right) = \frac{1}{\pi}\mathrm{P.V} \cdot \int_{-\infty}^{\infty} \frac{s_i(t)}{t-\tau} d\tau$$

and P.V. denotes Cauchy principal value. Once the analytic signals are defined, the relative phase can be computed as

$$\Delta\varphi(t) = \arg\left(\frac{z_1(t)z_2^*(t)}{|z_1(t)|\,|z_2(t)|}\right)$$

The instantaneous PLV is then defined as (Lachaux et al.,1999; elka, 2007)

$$\mathrm{PLV}(t) \triangleq \left|\mathrm{E}\left[e^{j\Delta\varphi(t)}\right]\right|$$

where $E[\,[]$ denotes the expected value. The PLV takes values on $[0, 1]$ with 0 reflecting the case where there is no phase synchrony and 1 where the relative phase between the

two signals is identical in all trials. PLV can therefore be viewed as a measure of trial to trial variability in the relative phases of two signals. In this work we use the Hilbert transform but the continuous Morlet wavelet transform can also be used to compute complex signals, producing separate band-pass signals for each scaling of the wavelet. The Phase Locking Value (PLV) of a smaple is calculated as:

$$PLV_{sample} = \left| \frac{1}{N} \sum_{n=1}^{N} e^{i\Delta\Phi_n} \right|$$

where:

N is the total number of phase difference values,
$\Delta\Phi_n$ represents the phase difference between the two oscillatory signals at the nth time point or trial,
$e^{i\Delta\Phi_n}$ is the complex exponential of the phase difference.

- Implement a function which 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.)

```
function plv = PLV2(epoch, samrate, filterRange, channelA, channelB, odors, type)
    samples = size(epoch,2);
    trials =  size(epoch,3);
    filterData = filter(fir1(50, 2/samrate*filterRange),1, epoch, [], 2);
    z = zeros(2, size(epoch,2), size(epoch,3));
    z(1,:,:) = filterData(channelA, :, :)+1i*hilbert(filterData(channelA, :, :));
    z(2,:,:) = filterData(channelB, :, :)+1i*hilbert(filterData(channelB, :, :));
    plv_hat = zeros(1,trials);
    num = 0;
    for trial = 1:trials
        if odors(trial)==type
            phi = angle(z(1,:,trial).*conj(z(2,:,trial)));
            plv_hat(trial) = abs(sum(exp(1i*phi))/samples);
            num = num+1;
        end
    end
    plv=sum(plv_hat)/num;
%     'done'
end
```

Figure 18: Enter Caption

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 .

Observations :
Matrixes which have been specified in Figure are our PLV results.

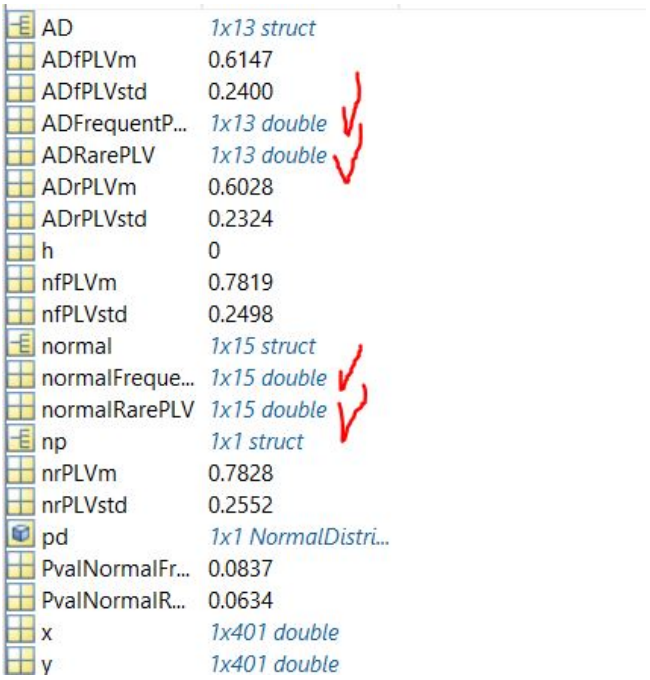

Figure 19: PLVS

4.2 Distributions

Draw the box plots 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. You need to specify the corresponding `p-values` to evaluate the statistical significance of your findings.

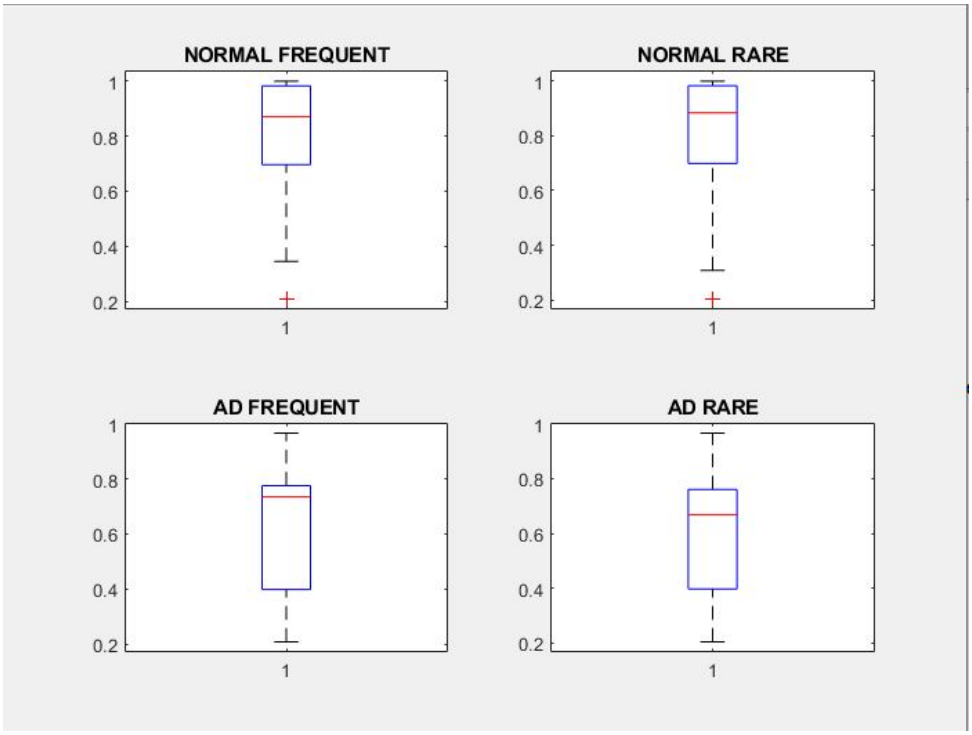

Figure 20: Boxplot of PLVS

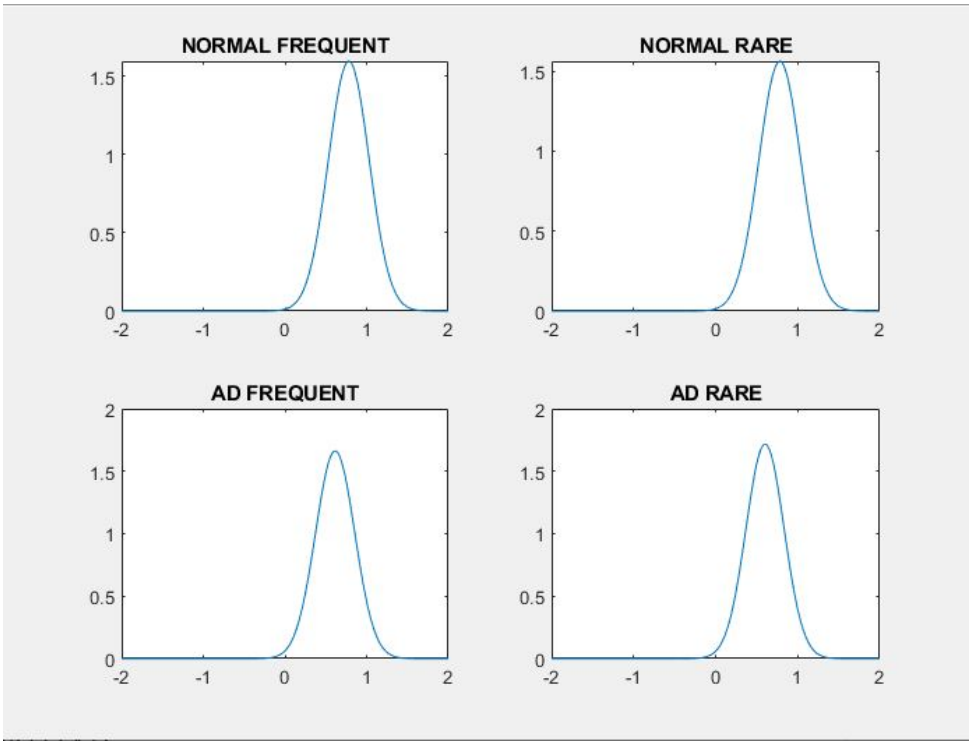

Figure 21: Fitting Guassian

p-value between normal-frequent and AD-frequent is 0.0837.
p-value between normal-rare and AD-rare is 0.0634.

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".

Answer :

According to our observations in both case p-value was more than 0.05 so these two odor can't be as biomarkers of AD people towards normal people.

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.

Observations :

In this section we should draw polar histogram of Phase difference of All subjects of two groups normal-frequent and AD-frequent.we calculated these values in section 4.1 so we just need to use function polarhistogram().Figure indicate difference between two groups.

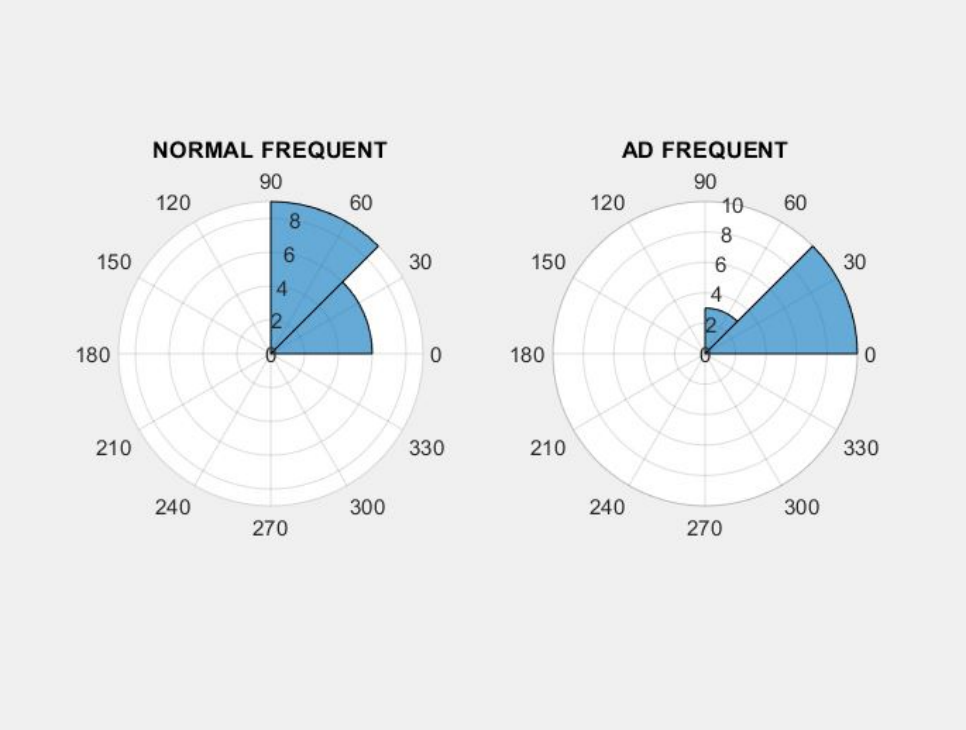

Figure 22: Polar Histogram

Then we got mean of all.Figure indicates our results.

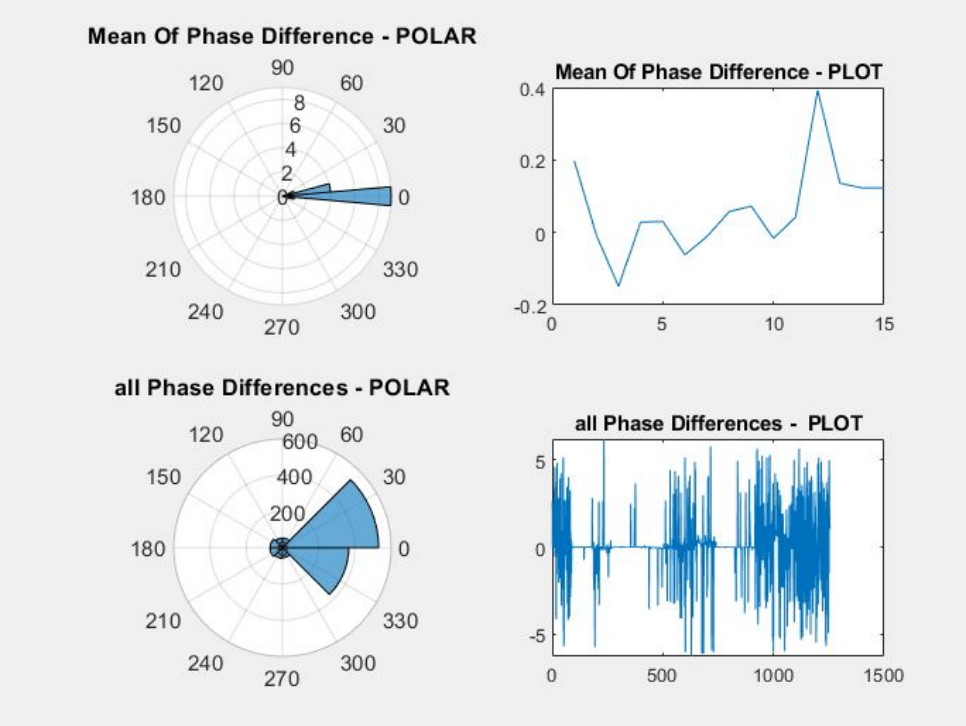

Figure 23: Enter Caption

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`).)

Observations :

we have 4 heatmaps of groups normal-frequent,normal-rare,ad-frequent and ad-rare.Each heatmap is a 4x4 matrix and each item of this matrix is PLV between 2 of 4 channels Fp,Fz,Cz,Pz.Our PLV2 Function give us mean PLV of all trials of a subject between 2 specific channels we get mean over all subjects and save it into one of item of this matrix.Figure indicate heatmaps.

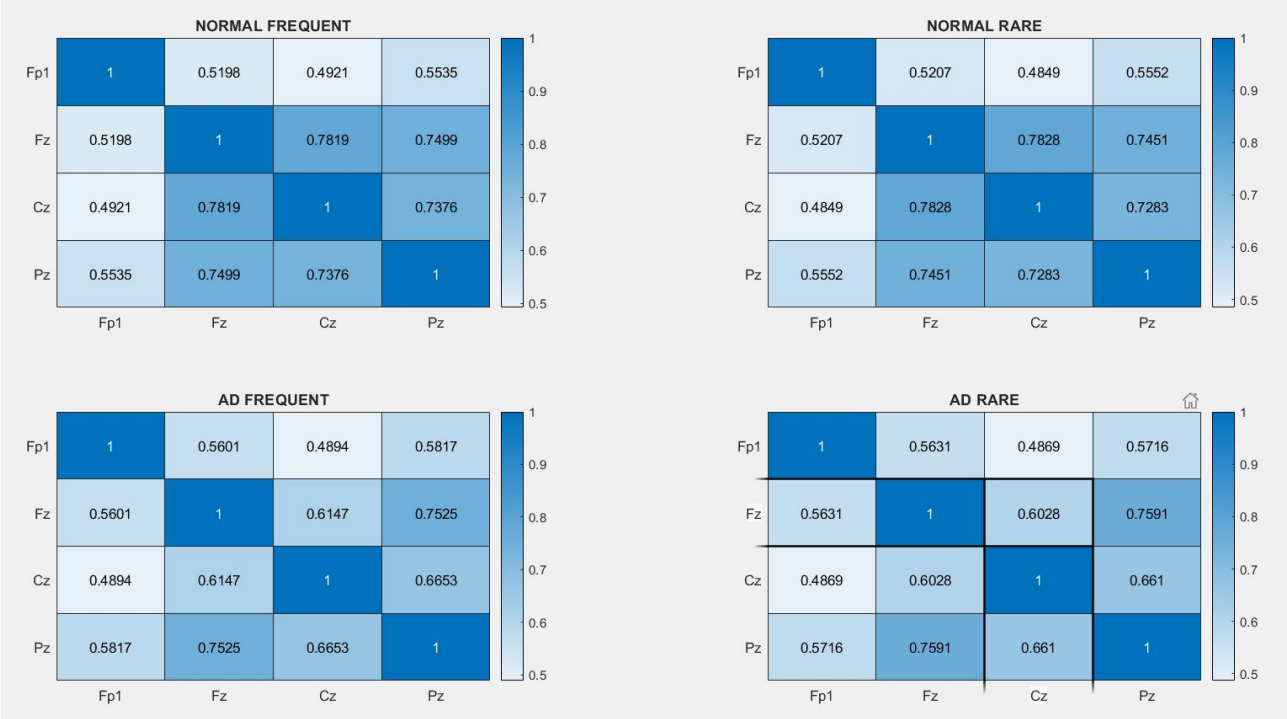

Figure 24: Heatmaps

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]

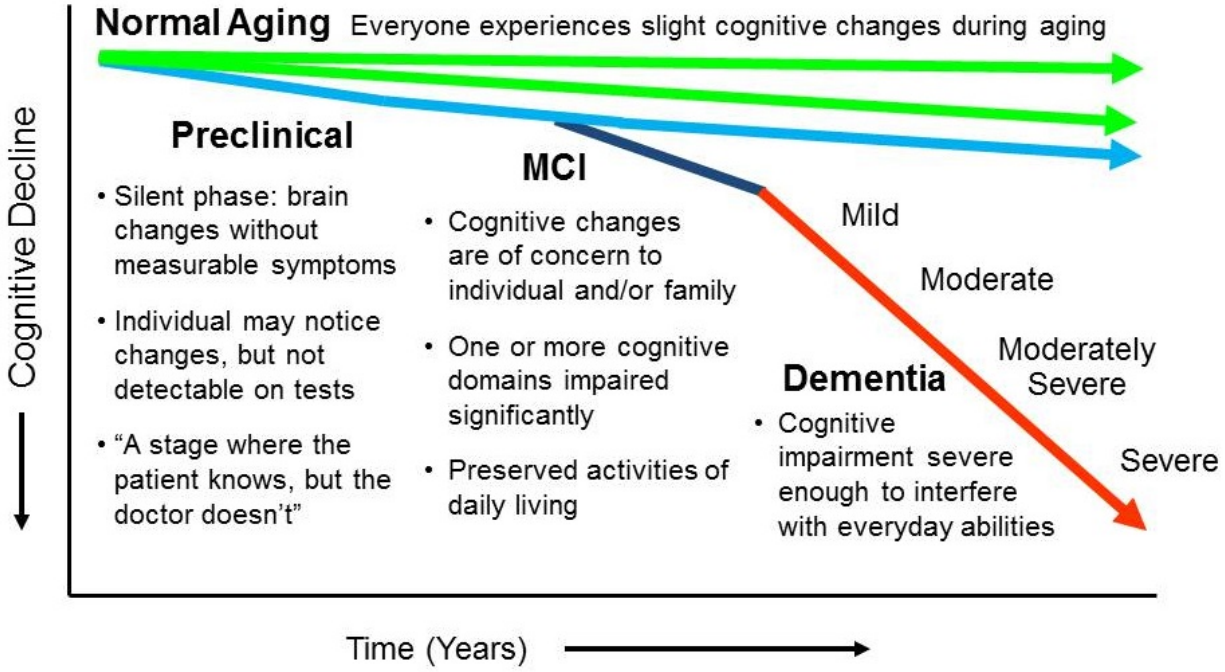

Figure 25: Normal Aging to Demantia Process

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.

Answer :

The relationship between MCI (Mild Cognitive Impairment) and AD (Alzheimer's Disease) is complex. MCI is considered to be a transitional stage between the normal cognitive changes of aging and the more severe cognitive decline associated with AD. However, it is important to note that not all individuals with MCI will progress to AD. MCI refers to a mild but noticeable decline in cognitive abilities, such as memory, attention, and thinking skills. Individuals with MCI may experience difficulties in their daily life and show cognitive impairments beyond what is expected for their age and education level. However, the impairments are not severe enough to meet the criteria for a diagnosis of dementia, including AD. While MCI can be a precursor

to AD, it does not always lead to AD. Some individuals with MCI may remain stable and not experience further cognitive decline, while others may even improve over time. However, individuals diagnosed with MCI are at an increased risk of developing AD compared to those without MCI. The causes of MCI are multi-factorial and can vary among individuals. Some potential causes and risk factors for MCI include: 1. Age: Advanced age is a significant risk factor for MCI. As individuals grow older, the likelihood of experiencing some cognitive decline increases. 2. Neurodegenerative changes: MCI can be associated with the early stages of neurodegenerative diseases, such as AD. The accumulation of abnormal proteins like beta-amyloid and tau in the brain can contribute to cognitive impairments. 3. Vascular factors: Conditions that affect blood circulation to the brain, including high blood pressure, diabetes, and atherosclerosis, may increase the risk of MCI. 4. Genetics: Certain gene variations, such as the APOE-e4 allele, have been associated with an increased risk of both MCI and AD. 5. Lifestyle factors: Unhealthy lifestyle choices, including sedentary behavior, smoking, excessive alcohol consumption, poor diet, and lack of mental and physical activity, may contribute to the development of MCI. 6. Medical conditions: Certain medical conditions, such as cardiovascular disease, stroke, depression, and sleep disorders, have been linked to an increased risk of MCI. 7. Environmental factors: Exposure to environmental toxins and pollutants may also play a role in the development of cognitive impairments. It's important to note that MCI can have different subtypes, including amnestic MCI (primarily affecting memory) and non-amnestic MCI (affecting other cognitive domains such as language, attention, or executive function). The underlying causes and progression of MCI can vary among individuals and may involve a combination of factors. While MCI increases the risk of developing AD, it is not a guarantee that every individual with MCI will progress to AD. Some individuals with MCI may remain stable or even improve over time, while others may develop other forms of dementia or cognitive disorders. Regular monitoring, proper medical care, lifestyle modifications, and early intervention can help manage MCI and potentially reduce the risk of progression to AD.

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`.

Answer :

we calculated PLVs like before.

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. [6]

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

In this section, you are required to thoroughly examine and analyze the results you have obtained throughout this project. You must provide a comprehensive discussion of your findings, highlighting their significance and relevance to the research question. You should also present any limitations or weaknesses in your study and suggest possible areas for future research. Overall, this section is critical to demonstrating the quality and validity of your research and should be approached with careful attention to detail and clarity of expression.

References

[1] Mild cognitive impairment (mci). https://www.mayoclinic.org/diseases-conditions/mild-cognitive-impairment/symptoms-causes/syc-20354578#:~:text=Overview,mental%20function%20has%20%22slipped.%22. Last Reviewed: Jan. 18, 2023.

[2] Neural oscillations – interpreting eeg frequency bands. https://imotions.com/blog/learning/best-practice/neural-oscillations/.

[3] Neurodegenerative diseases. https://www.niehs.nih.gov/research/supported/health/neurodegenerative/index.cfm. Last Reviewed: June 09, 2022.

[4] Marin C, Vilas D, Langdon C, Alobid I, López-Chacón M, Haehner A, Hummel T, and Mullol J. Olfactory dysfunction in neurodegenerative diseases. In *Curr Allergy Asthma Rep*, volume 18, 2018 Jun 15.

[5] Sedghizadeh MJ, Hojjati H, Ezzatdoost K, Aghajan H, Vahabi Z, and Tarighatnia H. Olfactory response as a marker for alzheimer's disease: Evidence from perceptual and frontal lobe oscillation coherence deficit. *PLOS One*, 15(12), December 15, 2020.

[6] T.T.K. Munia and S. Aviyente. Time-frequency based phase-amplitude coupling measure for neuronal oscillations. In *Scientific Reports 9, 12441*, 27 August 2019.

[7] Mohammad Javad Sedghizadeh, Hamid Aghajan, and Zahra Vahabi. Brain electrophysiological recording during olfactory stimulation in mild cognitive impairment and alzheimer disease patients: An eeg dataset. *Data in Brief*, 48:109289, 2023.

[8] Cécilia Tremblay and Johannes Frasnelli. Olfactory and Trigeminal Systems Interact in the Periphery. *Chemical Senses*, 43(8):611–616, 07 2018.