

Signals & Systems Course

Final Project

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

Author:
Shervin Mehrtash

Sharif University of Technology



Spring 2023

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	4
2.3	Frequency Bands of EEG	4
2.4	Sampling frequency	5
3	EEG Signal Processing	6
3.1	Task Definition	6
3.2	Data Description	6
3.3	Pre-Processing	7
3.4	Phase Locking Value (PLV)	15
4	MATLAB Code	16
5	Results	27
5.1	Values	27
5.2	Distributions	28
5.3	Statistical Significance	30
5.4	Phase Difference	31
5.5	Heatmaps	32
6	Analyzing MCI Cases	34
6.1	Mild Cognitive Impairment (MCI)	34
6.1.1	Additional Information	34
6.1.2	MCI Data Processing	35
6.2	Phase-Amplitude Coupling (PAC)	37
6.2.1	Metrics	37
6.2.2	Implementation	37
7	Conclusion	39

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.

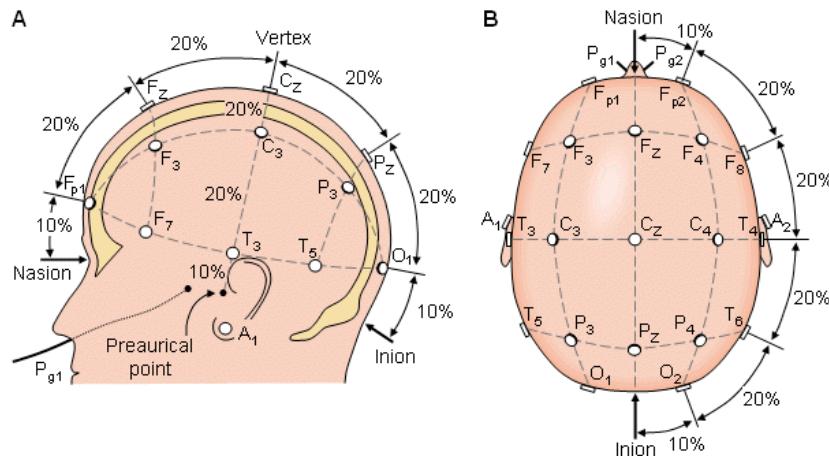


Figure 1: EEG 10-20 Electrode Placement System

The EEG headset is used to record the data of different sections of the brain. Each electrode placement site has a letter to identify the lobe, or area of the brain. The explanation of the electrodes in this particular configuration (10-20) is as follows \Rightarrow

1. F_p = Pre-Frontal
2. **F** = Frontal
3. **T** = Temporal
4. **P** = Parietal
5. **O** = Occipital
6. **C** = Central

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]

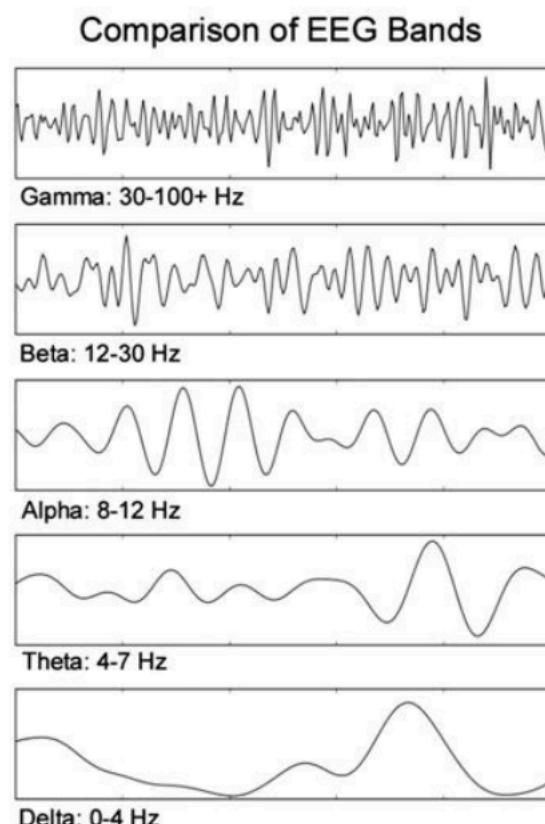


Figure 2: EEG Frequency Bands

As explained earlier, in adults, typical frequency bands and their approximate spectral boundaries are delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma (30–100 Hz) \Rightarrow

Delta: frontally in adults, posteriorly in children; high-amplitude waves; observable in adults' slow-sleep and some continuous-attention tasks

Theta: Found in locations not related to task at hand. Associated with inhibition of elicited responses (has been found to spike in situations where a person is actively trying to repress a response or action)

Alpha: posterior regions of head, both sides, higher in amplitude on dominant side. Cases: relaxed - Reflecting / Closing the eyes / Also associated with inhibition control, seemingly with the purpose of timing inhibitory activity in different locations across the brain.

Beta: both sides, symmetrical distribution, most evident frontally; low-amplitude waves. range span: active calm \rightarrow intense \rightarrow stressed \rightarrow mild obsessive.

Gamma: Somatosensory cortex / Displays during cross-modal sensory processing (perception that combines two different senses, such as sound and sight); Also is shown during short-term memory matching of recognized objects, sounds, or tactile sensations

2.4 Sampling frequency

The frequency range of the spectrum is from 0 to the half of the sampling rate (which is known as the Nyquist frequency). For example, if the EEG signal has a sampling rate of 200 Hz (As we'll use this rate later on other sections of the project), then the highest frequency that can be detected from the signal is 100 Hz.

According to this limitation, and to give an example of proper sampling rate to detect the EEG signals, we need to set the sampling rate on 24 Hz to detect all Alpha oscillations and the waves with less frequencies like Theta and Delta.

In order to observe and detect all EEG signals ranging from Delta to Gamma waves, we need to set the sampling rate on 200 Hz (2×100 which is the higher bound of Gamma oscillation).

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

[6] 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 [7]. The duration of odor presentation was set at 2s to enable regular breathing cycles for the participants.

3.2 Data Description

[6] 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 $4 \times 600 \times \text{Num_trials}$. 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 $\text{Num_trial} \times 1$. 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 $1 \times \text{Num_noisy}$. This array indicates noisy trials identified based on comparing the instantaneous and average trial amplitudes. These noisy trials 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 reference-independent 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 this project, we used a simplified version of this pipeline, speeding up the process and reaching all the goals defined earlier. Also, there are 2 Data files for 2 subjects.

- **Step 1:** In the first step, we used EEGLAB of MATLAB to re-reference data to the mean of the channels. This will remove any possible unwanted effect on all the channels and data. Then using a bandpass filter, we filtered the 0.5 - 40.5 Hz frequencies. The following figure shows the Phase and Amplitude of clipped frequency band for subject 1:

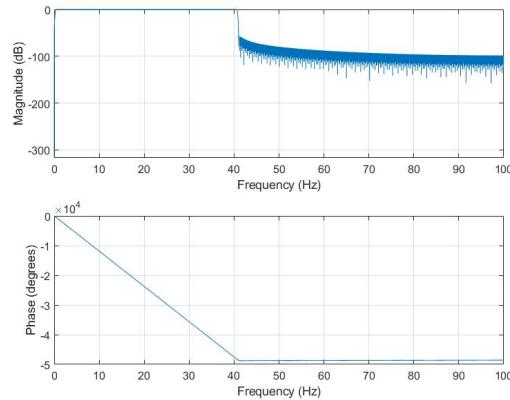


Figure 3: The Band-pass filter applied on the EEG signals of subject 1

The Phase and Amplitude of clipped frequency band for subject 2 would be as follows:

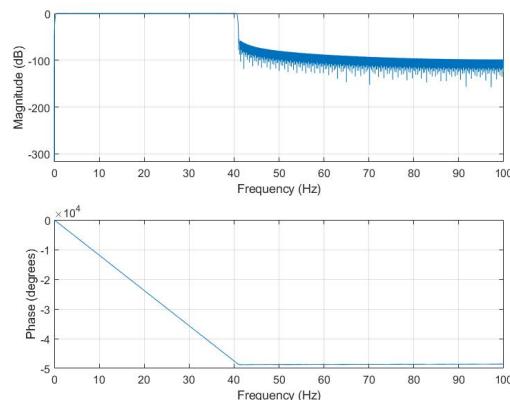


Figure 4: The Band-pass filter applied on the EEG signals of subject 1

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 EEGLAB environment, we plot the frequency spectrum of Fz Channel Data for both subjects:

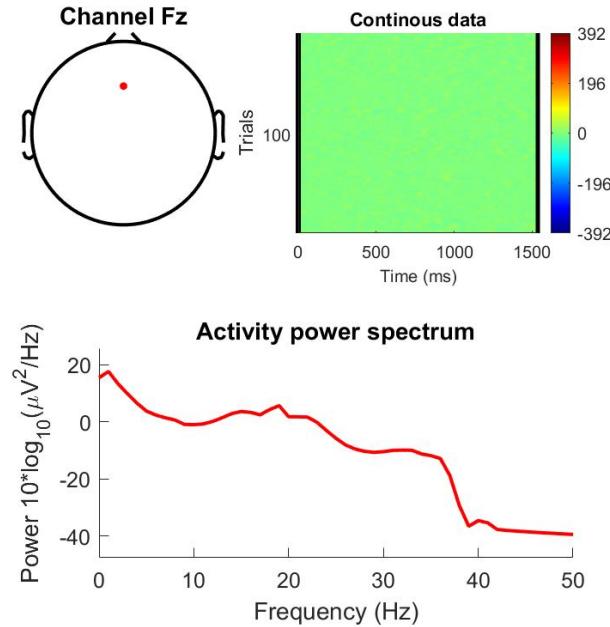


Figure 5: Frequency spectrum of channel Fz for subject 1

The frequency spectrum for subject 2 would be as follows:

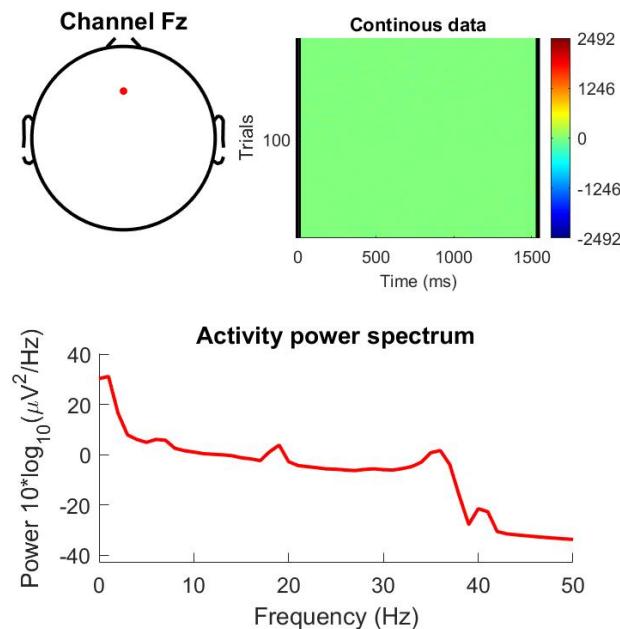


Figure 6: Frequency spectrum of channel Fz for subject 1

- 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 purpose, we load the data at EEGLAB and assign the locations of channels based on 10-20 standard which is mentioned earlier in this report. Then we ran ICA (Independent Component Analysis) algorithm to separate a multivariate signal into additive sub-components . After running this algorithm, we can observe all components, including brain, eye, muscle, etc. which would be as follows:

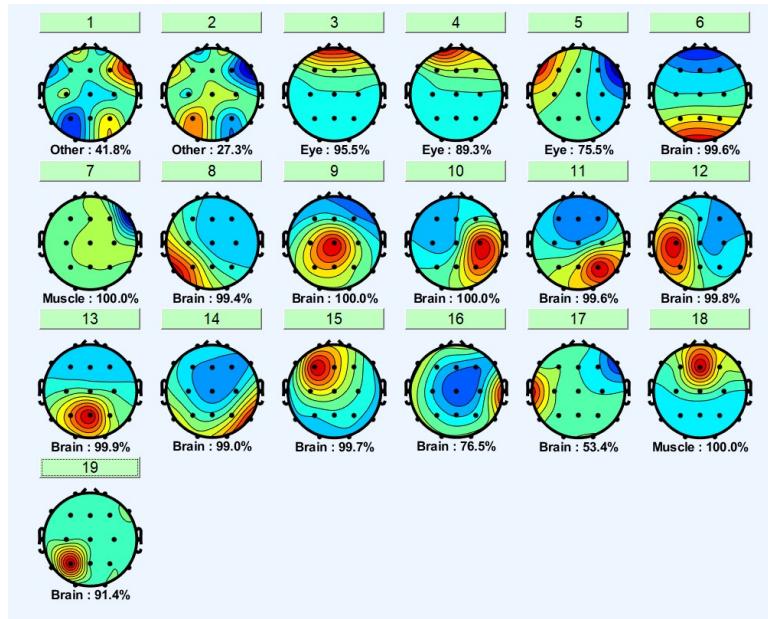


Figure 7: ICA components for subject 1

the similar figure for the subject 2 would be as follows:

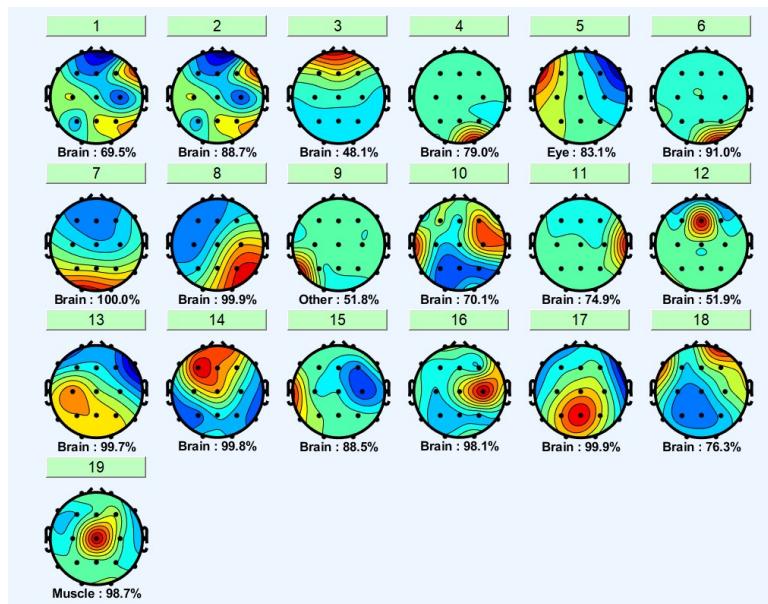


Figure 8: ICA components for subject 2

In order to see the details of one brain component, we can click on it in the EEGLAB environment. The result for both subjects would be as follows:

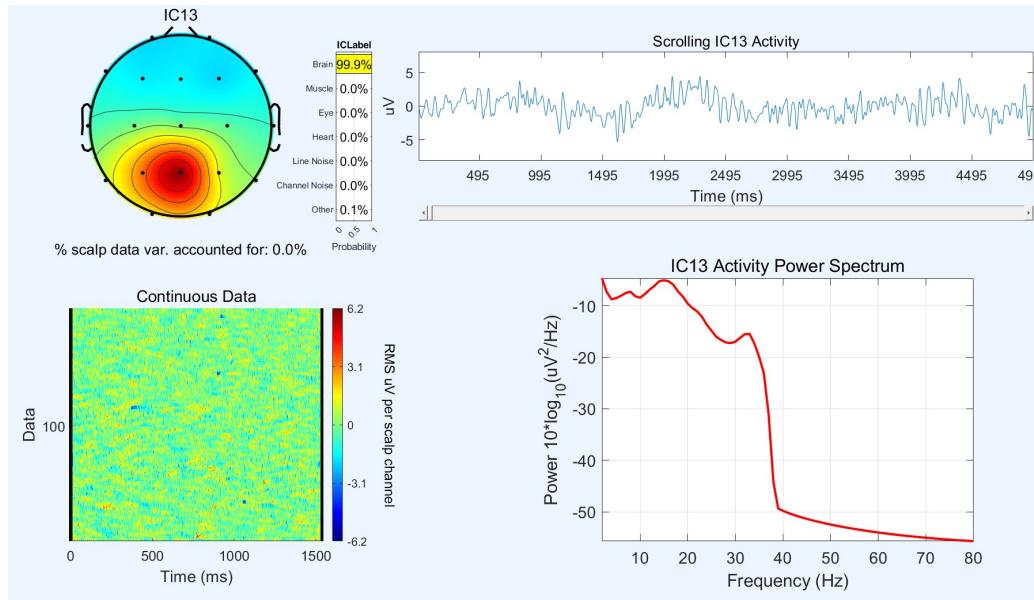


Figure 9: Specific Data of one brain component - Subject 1

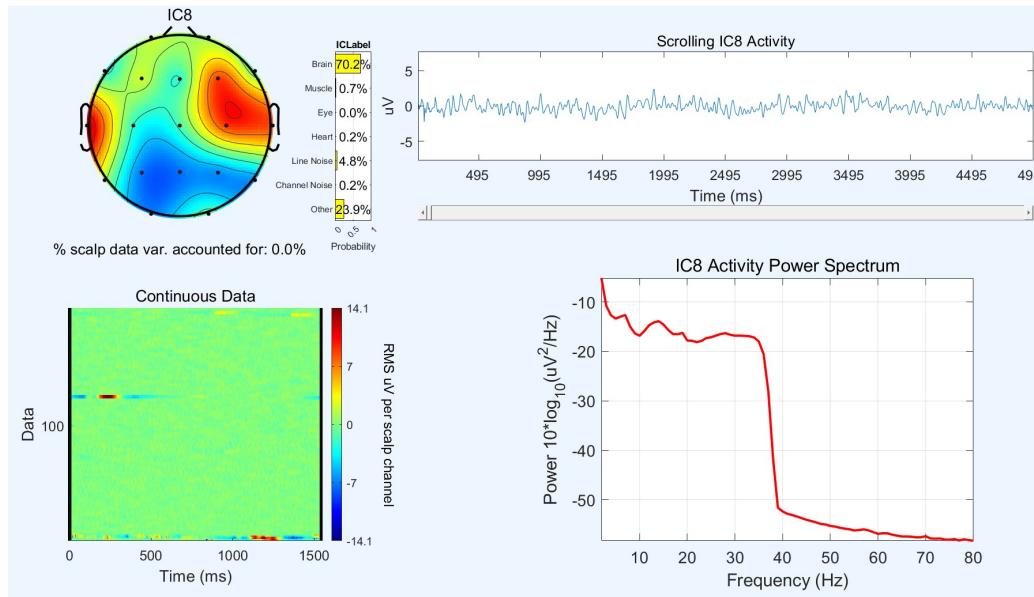


Figure 10: Specific Data of one brain component - Subject 2

To remove the effect of other organs like heart, muscles, eyes, and unwanted side-effects such as noise line, we can remove the respective components. By doing this, we'll have better ICA components purely containing brain components:

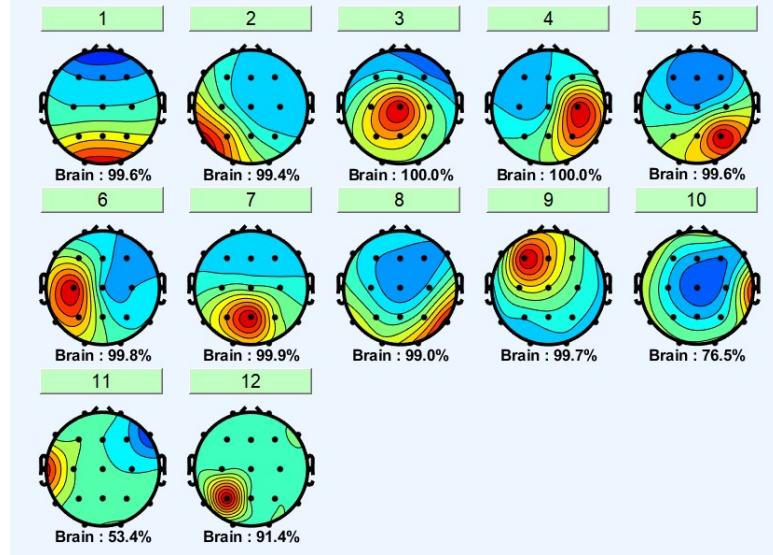


Figure 11: ICA components after filtering brain components - Subject 1

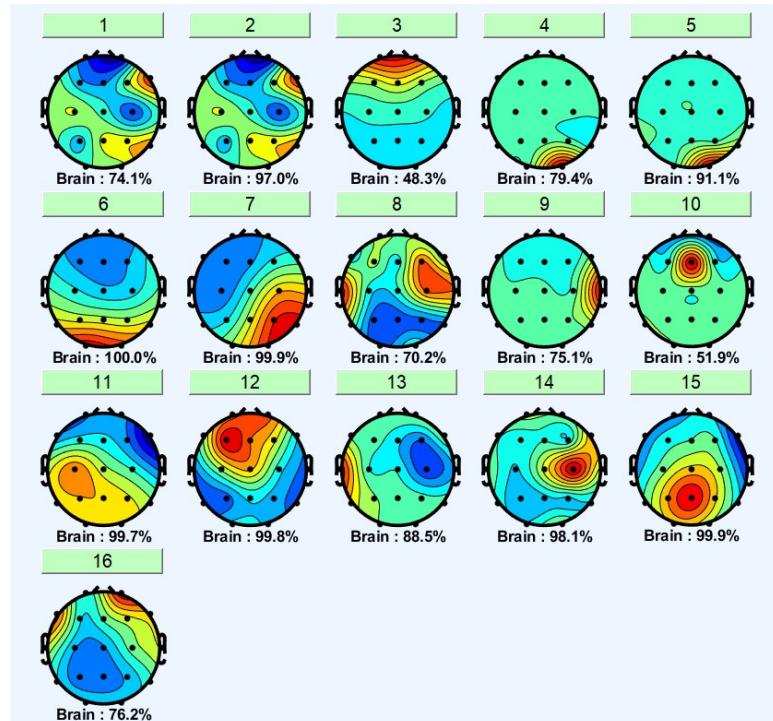


Figure 12: ICA components after filtering brain components - Subject 2

- **Step 3:** The goal of this step is to reshape the data in a way to simplify the further process, called **Epoch**. In fact, all data must be reshaped as the following figure suggests:

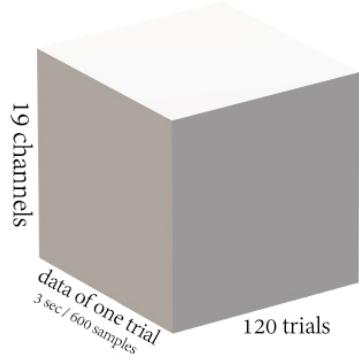


Figure 13: Epoch

This step is done using the MATLAB environment. It's important to know that we've ignored the first 14 seconds of the experiment, as it's not reliable. We also keep only 120 trials and ignore the rest. The created epoch would be a 3D matrix, with the dimensions of 19 (Representing number of channels/electrodes), 600 (number of samples in each trial, as we use 3 last seconds/600 samples), and 120 (number of trials we are interested to analyze).

The MATLAB code for this step would be as follows:

```
%> Epoching the Data -->

Data = EEG.data; % Loading the Data from EEG Workspace
Start = 14*200; % Starting sample - from 14 sec after start of
                  the event
End = 1214*200; % Ending Sample - Neglecting the data after 120
                  trials
Clean_Data = Data(:, Start:End);

%> Loop to fill the 3D epoch Matrix -->

Epoch = zeros(19,600,120);

for i = 1:19
    for j = 1:120
        Epoch(i, :, j) = Clean_Data(i, (j-1)*2000 + 601 : (j
            -1)*2000 + 1200);
    end
end
```

```
%% Deleting the unnecessary channels and keeping the subsamples
-->

Cleaned_Epoch = EEG.data;
Subsampled_Epoch = Cleaned_Epoch([1, 5, 10, 15], : , : ); % The
Final Epoch

% Converting the Subsampled Epoch array to struct -->
Epoch_Struct = struct('Epoch_Subsampled', Subsampled_Epoch);
```

The same process is done for subject 2, with little changes in the code in the line in which the data-set is chosen.

- **Step 4:** In the pre-final step, we load the epoch(with the reshaped data) into the EEGLAB environment, and remove noisy trials. There are many ways to do this, including using built-in functions of MATLAB, or any program-based approach. It's recommended to do this step by observation. Based on experience, it's more optimized to detect noisy trials with eye. To do this, we plot the channel data and scroll through all trials, and reject the ones which are considered to be noisy.

Some examples of the noisy trials would be as follows:

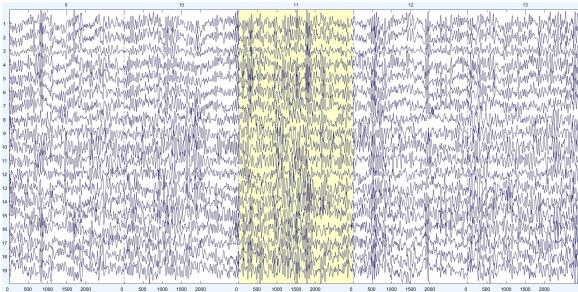


Figure 14: Example of a Noisy trial

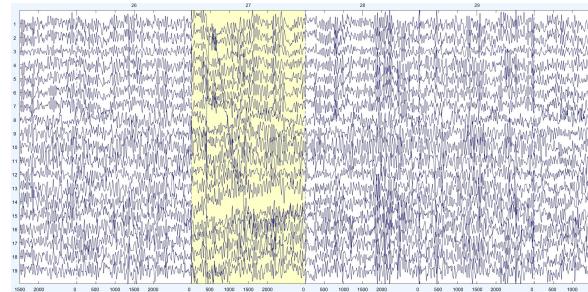


Figure 15: Example of a Noisy trial

- **Step 5:** In the final step, we sub-sample our data, epoch to simplify further processes. In this step, we only keep 4 channels among 19 channels which are more important and technically hold more precious data of the patient's brain. These 4 channels are F_{p1} , F_z , C_z , and P_z .

In processing the EEG signals, we'll use the data elicited from these 4 electrodes. This step is done using MATLAB code, which you can see the code in the step 3.

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.

Phase synchronization is a method to infer functional connectivity with multichannel neural signals, e.g., electroencephalography (EEG). The synchronization values are used to form a brain network at each stage of the experiment and network parameter values from various brain regions are compared to study the variation in connectivity between brain regions along successive stages of the experiment. (Source: <https://pubmed.ncbi.nlm.nih.gov/22665500/>)

In the next sections, we'll need to find the PLV for two signals. We define a function in MATLAB to receive two signals and find the PLV for the given inputs. The MATLAB code for this function would be as follows:

```
function PLV = PLV_Finder(data, channel1, channel2)
    % Extract the time series data for the two channels
    signal1 = data(channel1, :);
    signal2 = data(channel2, :);
    % Compute the Fourier transform of the signals
    fftSignal1 = fft(signal1);
    fftSignal2 = fft(signal2);
    % Define the frequency axis for FFT
    freqAxis = (0:length(signal1)-1)*(200/length(signal1));
    % Find indices corresponding to the desired frequency range
    freqIndices = find(freqAxis >= 35 & freqAxis <= 40);
    % Extract the phase angles for each frequency bin within the
    % range
    phaseSignal1 = angle(fftSignal1(freqIndices));
    phaseSignal2 = angle(fftSignal2(freqIndices));
    % Compute PLV as mean of phase differences across frequencies
    PLV = abs(mean(exp(1i * (phaseSignal1 - phaseSignal2))));
end
```

4 MATLAB Code

In the following sections, we will run different processes on the data-sets we have. In order to find the suitable result, we will need to find the Phase-Locking Value for different and various selections of signals, and also use different statistical methods to examine the elicited result.

The mentioned processed are done using the MATLAB code, which is provided in this section of the report. The source of MATLAB code in the next sections would be this additional section of the report.

The MATLAB code for processing data would be as follows:

```

1  %% Initial Commands
2  clear; clc;
3
4  %% Loading the required Datasets
5  load('Codes\AD.mat');
6  load('Codes\normal.mat');
7  load('Codes\MCI.mat');
8
9  %% Eliciting the Epoch for each patient
10 Normal_Data = zeros(15,2); % First column for Frequent and Second
    for Rare
11 AD_Data = zeros(13,2); % First column for Frequent and Second for
    Rare
12 MCI_Data = zeros(7,2); % First column for Frequent and Second for
    Rare
13
14 % Loop for narmal dataset
15 for n = 1:15
16     Epoch = normal(n).epoch;
17     Odor = normal(n).odor;
18     Normal_Data(n, :) = PLV_Calculator(Epoch, Odor);
19 end
20
21 % Loop for AD dataset
22 for n = 1:13
23     Epoch = AD(n).epoch;
24     Odor = AD(n).odor;
25     AD_Data(n, :) = PLV_Calculator(Epoch, Odor);
26 end
27
28 % Loop for MCI dataset
29 for n = 1:7
30     Epoch = MCI(n).epoch;
31     Odor = MCI(n).odor;
32     MCI_Data(n, :) = PLV_Calculator(Epoch, Odor);
33 end

```

```
34
35 % Finding the Boxplots for each group and each Odor
36 figure
37 subplot(2,2,1)
38 boxplot(Normal_Data(:,1));
39 title('PLV Data Summary for Normal patients exposed to Frequent
        Odor','Interpreter','latex');
40 subplot(2,2,2)
41 boxplot(Normal_Data(:,2));
42 title('PLV Data Summary for Normal patients exposed to Rare Odor','
        Interpreter','latex');
43 subplot(2,2,3)
44 boxplot(AD_Data(:,1));
45 title('PLV Data Summary for AD patients exposed to Frequent Odor','
        Interpreter','latex');
46 subplot(2,2,4)
47 boxplot(AD_Data(:,2));
48 title('PLV Data Summary for AD patients exposed to Rare Odor','
        Interpreter','latex');

49
50 %% Plotting the Distribution of PLVs for 4 different groups
51 Fit_Dist1 = fitdist(Normal_Data(:,1),"Normal");
52 Fit_Dist2 = fitdist(Normal_Data(:,2),"Normal");
53 Fit_Dist3 = fitdist(AD_Data(:,1),"Normal");
54 Fit_Dist4 = fitdist(AD_Data(:,2),"Normal");
55 X = -0.5:0.01:2;
56 PDF1 = pdf(Fit_Dist1,X); PDF2 = pdf(Fit_Dist2,X); PDF3 = pdf(
    Fit_Dist3,X); PDF4 = pdf(Fit_Dist4,X);
57 figure
58 subplot(2,2,1)
59 plot(X,PDF1);
60 title('Normal Distribution fit to the PLV (Normal patient -
        Frequent Odor)','Interpreter','latex');
61 subplot(2,2,2)
62 plot(X,PDF2);
63 title('Normal Distribution fit to the PLV (Normal patient - Rare
        Odor)','Interpreter','latex');
64 subplot(2,2,3)
65 plot(X,PDF3);
66 title('Normal Distribution fit to the PLV (AD patient - Frequent
        Odor)','Interpreter','latex');
67 subplot(2,2,4)
68 plot(X,PDF4);
69 title('Normal Distribution fit to the PLV (AD patient - Rare Odor)'
        , 'Interpreter','latex');
```

```
70
71 %% Finding the P-Values --->
72 [h1,p1] = ttest2(Normal_Data(:,1),AD_Data(:,1));
73 [h2,p2] = ttest2(Normal_Data(:,2),AD_Data(:,2));
74
75 %% Finding Phase Difference --->
76 % Choosing a Random Guy (Number 12 in normal and 6 in AD patients)
77 Epoch_Random_Normal = normal(2).epoch;
78 Odor_Random_Normal = normal(2).odor;
79 Epoch_Random_AD = AD(1).epoch;
80 Odor_Random_AD = AD(1).odor;
81
82 % Finding the number of frequent odors for each group
83 FreqNum_Normal = size(Odor_Random_Normal,1) - sum(
84     Odor_Random_Normal);
85 FreqNum_AD = size(Odor_Random_AD,1) - sum(Odor_Random_AD);
86
87 % Defining the arrays to store the value of Phase Difference for
88 % each group
89 PhaseDiff_Normal = zeros(FreqNum_Normal,1);
90 PhaseDiff_AD = zeros(FreqNum_AD,1);
91
92 Counter1 = 0; Counter2 = 0;
93
94 % Loop to find and store the phase difference of normal random guy
95 for i = 1 : size(Odor_Random_Normal,1)
96     if Odor_Random_Normal(i,1) == 0
97         Counter1 = Counter1 + 1;
98         x1 = Epoch_Random_Normal(2,:,:i);
99         x2 = Epoch_Random_Normal(3,:,:i);
100        Result = PDFinder(x1,x2);
101        PhaseDiff_Normal(Counter1,1) = Result;
102    end
103 end
104
105 % Loop to find and store the phase difference of AD random guy
106 for i = 1 : size(Odor_Random_AD,1)
107     if Odor_Random_AD(i,1) == 0
108         Counter2 = Counter2 + 1;
109         x1 = Epoch_Random_AD(2,:,:i);
110         x2 = Epoch_Random_AD(3,:,:i);
111         Result = PDFinder(x1,x2);
112         PhaseDiff_AD(Counter2,1) = Result;
113     end
114 end
```

```
113
114 % Plotting the polar histogram
115 figure
116 subplot(1,2,1)
117 polarhistogram(PhaseDiff_Normal);
118 title('Polar Histogram for Phase Difference of a Randomly selected
    Normal patient','Interpreter','latex');
119 subplot(1,2,2)
120 polarhistogram(PhaseDiff_AD);
121 title('Polar Histogram for Phase Difference of a Randomly selected
    A.D. patient','Interpreter','latex');
122
123 %% Finding the Mean value of Phase Difference for each group --->
124 % Defining the arrays to store the mean value of Phase Difference
125 Mean_PhaseDiff_Normal = zeros(15,1);
126 Mean_PhaseDiff_AD = zeros(13,1);
127 for n = 1 : 15
128     Mean_PhaseDiff_Normal(n,1) = PDPP(normal(n).epoch, normal(n).
        odor);
129 end
130
131 for n = 1 : 13
132     Mean_PhaseDiff_AD(n,1) = PDPP(AD(n).epoch, AD(n).odor);
133 end
134
135 Mean_Normal = sum(Mean_PhaseDiff_Normal) / size(
    Mean_PhaseDiff_Normal,1);
136 Mean_AD = sum(Mean_PhaseDiff_AD) / size(Mean_PhaseDiff_AD,1);
137
138 % Plotting the polar histogram
139 figure
140 subplot(1,2,1)
141 polarhistogram(Mean_PhaseDiff_Normal);
142 title('Polar Histogram for Mean of Phase Difference in Normal
    dataset','Interpreter','latex');
143 subplot(1,2,2)
144 polarhistogram(Mean_PhaseDiff_AD);
145 title('Polar Histogram for Mean of Phase Difference in AD dataset',
    'Interpreter','latex');
146
147 %% Finding the PLV between pair of channels
148
149 % For this section, I used the code that finds the PLV for a given
    pair
150 % of channels, And Manually calculate the PLV and store them in the
```

```
        below
151 % arrays ---->
152
153 % Code Used to find the proper values of PLV -->
154
155 % S = sum(Normal_Data(:,1)); % Or (:,2) for Rare Odor exposure
156 % S = S/15; % Or S/13 For AD group
157
158 % Normal Group Data -->
159 Normal_PLV = [
160     0.5897 0.5920;
161     0.5550 0.5616;
162     0.6175 0.6219;
163     0.8064 0.8071;
164     0.8169 0.8189;
165     0.7969 0.7973
166 ];
167
168 % AD Group Data -->
169 AD_PLV = [
170     0.6029 0.6026;
171     0.5467 0.5488;
172     0.6253 0.6264;
173     0.6458 0.6362;
174     0.7978 0.8008;
175     0.7254 0.7235
176 ];
177
178 % Cleared Data for the Heatmap -->
179 Final_PLV = [
180     0.5897 0.6029;
181     0.5550 0.5467;
182     0.6175 0.6253;
183     0.8064 0.6458;
184     0.8169 0.7978;
185     0.7969 0.7254;
186     0.5920 0.6026;
187     0.5616 0.5488;
188     0.6219 0.6264;
189     0.8071 0.6362;
190     0.8189 0.8008;
191     0.7973 0.7235
192 ];
193
194 % Plotting the heatmap of the elicited data
```

```

195 XAxis = {'Normal Group','AD Group'};
196 YAxis = {'Fp1/Fz - Frequent','Fp1/Cz - Frequent','Fp1/Pz - Frequent'
197   , 'Fz/Cz - Frequent','Fz/Pz - Frequent','Cz/Pz - Frequent','Fp1/
198   Fz - Rare','Fp1/Cz - Rare','Fp1/Pz - Rare','Fz/Cz - Rare','Fz/Pz
199   - Rare','Cz/Pz - Rare'};
200
201 % Finding the P-Values for Channel
202 % This section uses the function of other previous parts, so the
203 % code is
204 % commented to avoid any violence in other sections of the code -->
205 % [h3,p3] = ttest2(Normal_Data(:,1),AD_Data(:,1));
206 % [h4,p4] = ttest2(Normal_Data(:,2),AD_Data(:,2));
207
208 h3 = 0; h4 = 0; % Elicited Values for h of channels Cz and Pz
209 p3 = 0.3647; p4 = 0.3733; % Elicited Values for p-value of channels
210 % Cz and Pz
211 %% ----- BONUS SECTION 5.1 -----
212 % As mentioned earlier, the PLV values of Two different pair of
213 % channels
214 % are found manually, to avoid any violence in the code :)
215 % Code Used to find the proper values of PLV for MCI -->
216 % S = sum(MCI_Data(:,1));
217 % S = S/7;
218
219 % Cleared Data for the Heatmap of pair of channels (2,3 and 3,4)
220 %-->
221 Final_PLV_3State = [
222   0.8064 0.7087 0.6458;
223   0.8071 0.6995 0.6362;
224   0.7969 0.7124 0.7254;
225   0.7973 0.7105 0.7235
226 ];
227
228 % Plotting the heatmap of the elicited data
229 XAxis = {'Normal Group','MCI Group','AD Group'};
230 YAxis = {'Fz/Cz - Frequent','Fz/Cz - Rare','Cz/Pz - Frequent','Cz/
231   Pz - Rare'};
232
233 figure
234 heatmap(XAxis, YAxis, Final_PLV_3State);

```

```

232
233 % Elicited values for p-value
234 % Similarly, we used the code of the previous sections to avoid any
235 % violation
236 pVal1 = 0.3221; % Normal/MCI - Frequent - Fz/Cz
237 pVal2 = 0.5154; % MCI/AD - Frequent - Fz/Cz
238 pVal3 = 0.3015; % Normal/MCI - Rare - Fz/Cz
239 pVal4 = 0.5347; % MCI/AD - Rare - Fz/Cz
240 pVal5 = 0.3614; % Normal/MCI - Frequent - Cz/Pz
241 pVal6 = 0.8908; % MCI/AD - Frequent - Cz/Pz
242 pVal7 = 0.3656; % Normal/MCI - Rare - Cz/Pz
243 pVal8 = 0.8935; % MCI/AD - Rare - Cz/Pz
244
245
246 %% ----- BONUS SECTION 5.2 -----
247 % Finding the MVL for signals from channels Fz and Cz -->
248 % Defining vectors to store the MVLs
249 MVL_Normal = zeros(15,1);
250 MVL_MCI = zeros(7,1);
251 MVL_AD = zeros(13,1);
252
253 % Loop for normal dataset
254 for n = 1:15
255     Epoch = normal(n).epoch;
256     Odor = normal(n).odor;
257     MVL_Normal(n,1) = MVL_Calculator(Epoch, Odor);
258 end
259
260 % Loop for MCI dataset
261 for n = 1:7
262     Epoch = MCI(n).epoch;
263     Odor = MCI(n).odor;
264     MVL_MCI(n, 1) = MVL_Calculator(Epoch, Odor);
265 end
266
267 % Loop for AD dataset
268 for n = 1:13
269     Epoch = AD(n).epoch;
270     Odor = AD(n).odor;
271     MVL_AD(n, 1) = MVL_Calculator(Epoch, Odor);
272 end
273 Sum1 = sum(MVL_Normal/size(MVL_Normal,1));
274 Sum2 = sum(MVL_MCI/size(MVL_MCI,1));
275 Sum3 = sum(MVL_AD/size(MVL_AD,1));
276 %

```

```
277 %
278
279
280
281 %% Function used to find the Mean value for Phase Difference --->
282
283 function PD = PDPP(Epoch_Random_Normal, Odor_Random_Normal)
284 % Finding the number of frequent odors
285 FreqNum_Normal = size(Odor_Random_Normal,1) - sum(
286     Odor_Random_Normal);
287
288 % Defining the arrays to store the value of Phase Difference
289 PhaseDiff_Normal = zeros(FreqNum_Normal,1);
290
291 Counter1 = 0;
292
293 % Loop to find and store the phase difference of normal random guy
294 for i = 1 : size(Odor_Random_Normal,1)
295     if Odor_Random_Normal(i,1) == 0
296         Counter1 = Counter1 + 1;
297         x1 = Epoch_Random_Normal(2,: ,i);
298         x2 = Epoch_Random_Normal(3,: ,i);
299         Result = PDFinder(x1,x2);
300         PhaseDiff_Normal(Counter1,1) = Result;
301     end
302 end
303
304 PD = sum(PhaseDiff_Normal) / size(PhaseDiff_Normal,1);
305
306
307 %% Function used to find the Phase Difference --->
308 function PhaseDiff = PDFinder(x1,x2)
309     dot_product = dot(x1, x2);
310     norm_product = (norm(x1) * norm(x2));
311     PhaseDiff = acos(dot_product / norm_product);
312 end
313
314
315 %% Function used to find the PLV value --->
316 function PLV = PLV_Finder(data, channel1, channel2)
```

```
317
318 % Extract the time series data for the two channels
319 signal1 = data(channel1, :);
320 signal2 = data(channel2, :);
321
322 % Compute the Fourier transform of the signals
323 fftSignal1 = fft(signal1);
324 fftSignal2 = fft(signal2);
325
326 % Define the frequency axis for FFT
327 freqAxis = (0:length(signal1)-1)*(200/length(signal1));
328
329 % Find indices corresponding to the desired frequency range
330 freqIndices = find(freqAxis >= 35 & freqAxis <= 40);
331
332 % Extract the phase angles for each frequency bin within the
333 % range
334 phaseSignal1 = angle(fftSignal1(freqIndices));
335 phaseSignal2 = angle(fftSignal2(freqIndices));
336
337 % Compute PLV as mean of phase differences across frequencies
338 PLV = abs(mean(exp(1i * (phaseSignal1 - phaseSignal2))));
```

339

340

341

342

```
%% Function to process and manage the storing of PLVs --->
344 function PLVPP = PLV_Calculator(Epoch, Odor)
345     Num_of_Frequent = size(Odor,1) - sum(Odor);
```

346

```
% Loop to find the PLV for each trial -->
```

348

```
% Defining an array to store the PLV values for each patient
350 PLV_Array = zeros(1,size(Epoch,3));
```

351

```
for i = 1 : size(Epoch,3)
    PLV_Array(1,i) = PLV_Finder(Epoch(:,:,i),2,3);
end
```

355

```
% Defining vars to store the sum of different exposures
357 Sum_Frequent = 0;
358 Sum_Rare = 0;
```

359

```
% Dividing Frequent and Rare exposures of each trial
```

```

361     for i = 1:size(Odor,1)
362         if Odor(i,1) == 0
363             Sum_Frequent = Sum_Frequent + PLV_Array(1,i);
364         end
365         if Odor(i,1) == 1
366             Sum_Rare = Sum_Rare + PLV_Array(1,i);
367         end
368     end
369
370     % Finding the Average PLV for Frequent and Rare exposures
371     PLV_Frequent = Sum_Frequent / Num_of_Frequent;
372     PLV_Rare = Sum_Rare / (size(Odor,1) - Num_of_Frequent);
373     PLVPP = [PLV_Frequent, PLV_Rare];
374 end
375
376
377
378
379 %% Function to Find the MVL of two signals --->
380 function MVL = MVLFinder(data, channel1, channel2)
381 % Extract the time series data for the two channels
382 signal1 = data(channel1, :);
383 signal2 = data(channel2, :);
384
385 % Compute the analytic signals of the two signals
386 analytic_signal1 = hilbert(signal1);
387 analytic_signal2 = hilbert(signal2);
388
389 % Compute the pairwise multiplication of the analytic signals of
390 % the two signals
391 pairwise_multiplication = analytic_signal1 .* conj(analytic_signal2);
392
393 % Compute the mean vector resulting from the pairwise
394 % multiplication of the analytic signals of the two signals
395 mean_vector = mean(pairwise_multiplication);
396
397 % Compute the length of the mean vector resulting from the pairwise
398 % multiplication of the analytic signals of the two signals
399 MVL = abs(mean_vector);
400
401 %% Function to process and manage the storing of MVLs --->
402 function MVLPP = MVL_Calculator(Epoch, Odor)

```

```
402 % Loop to find the PLV for each trial -->
403 % Defining an array to store the PLV values for each patient
404 MVL_Array = zeros(1,size(Epoch,3));
405
406 for i = 1 : size(Epoch,3)
407     MVL_Array(1,i) = MVLFinder(Epoch(:,:,i),2,3);
408 end
409
410 % Defining vars to store the sum
411 Sum = 0;
412
413 % Finding the sum
414 for i = 1:size(0dor,1)
415     Sum = Sum + MVL_Array(1,i);
416 end
417
418 % Finding the Average MVL for the person
419 MVLPP = Sum / size(0dor,1);
420 end
```

5 Results

In this section, we examine 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 the results in this part, 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 used.

5.1 Values

In this sub-section, we find the PLV for all participants of both groups on both frequent and rare odors between the Fz and Cz channels using the function in section [3.4](#).

You can see the MATLAB code of this section in MATLAB section, from **line 9 to 34**.

The function which is used to find the numeric value of PLV is available in MATLAB section from **line 283 to 308**.

There is another function which handles the storing of the data, which is available in MATLAB section from **line 309 to 340**.

The final PLV of all participants of both normal and AD group, exposed to 2 different odors (Frequent and Rare) would be as follows:

Num. of Case	Frequent Odor PLV	Rare Odor PLV
1	0.5700	0.5017
2	0.9962	1.0000
3	0.9421	0.9710
4	1.0000	1.0000
5	0.9985	0.9998
6	0.9271	0.9550
7	0.9103	0.9395
8	0.7586	0.7959
9	0.9304	0.9288
10	1.0000	0.9994
11	0.9072	0.8975
12	0.7002	0.7153
13	0.7980	0.7449
14	0.2886	0.2945
15	0.3687	0.3627

Table 2: PLV for Normal Group elicited differently for Frequent and Rare Odor

Num. of Case	Frequent Odor PLV	Rare Odor PLV
1	0.7096	0.7398
2	0.3122	0.2727
3	0.5503	0.4903
4	0.8393	0.8628
5	0.7983	0.7753
6	0.8668	0.8100
7	0.9754	0.9654
8	0.7189	0.7373
9	0.7736	0.8212
10	0.6066	0.5915
11	0.6353	0.5961
12	0.2886	0.2945
13	0.3204	0.3138

Table 3: PLV for Alzheimer's Disease Group elicited differently for Frequent and Rare Odor

5.2 Distributions

In this section, we draw the box plots of PLVs you found in the previous part among two groups and two odors, which will result in 4 different box plots. Also, we fit a Gaussian distribution on these PLVs to observe the distribution.

The box plots would be as follows:

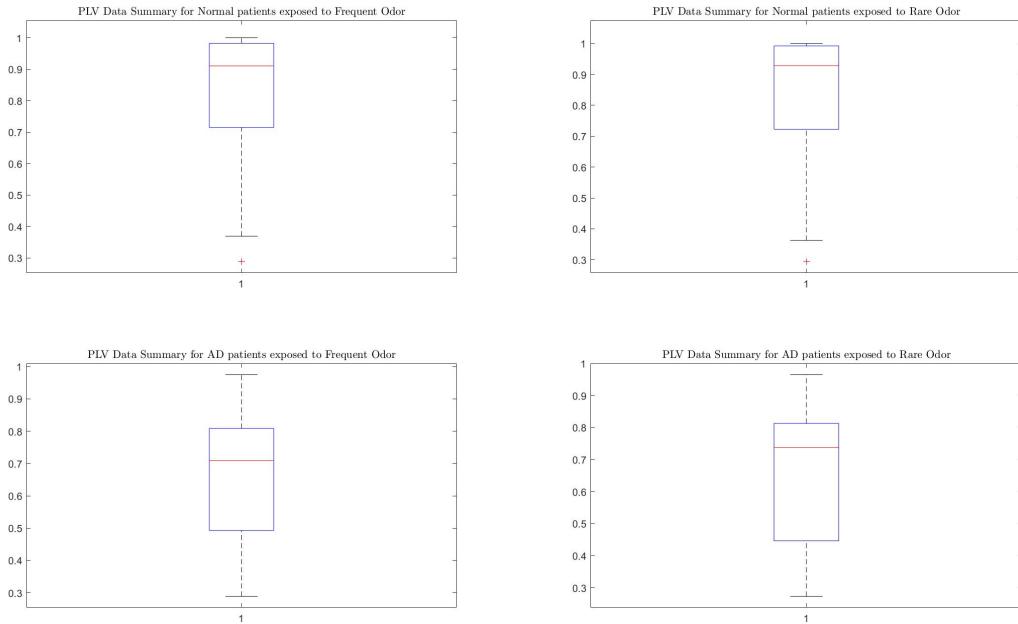


Figure 16: Box Plots for both normal and AD group, Exposed to Frequent and Rare Odors

Analyzing the box plots we've found in this section, we can clearly say that the group of normal participants has a larger PLV, while the group of AD participants has smaller PLV. This difference makes sense, as we expect the AD group to have a less synchronized brain compared to the normal participants.

Also, there is a difference in the mean of PLV for AD group, when exposed to Frequent odor vs. Rare odor. The mean of PLV is larger when exposed to the Rare odor, which can be the result of some stimulation to the brain with new, rare odor.

We can find the p-value to examine the results better and more accurate. Finding the p-value is a measure which helps us to decide whether the elicited results for normal and AD groups are close enough to each other.

Using the MATLAB code in MATLAB section, from **line 71 to 74**, we find the p-value for both frequent and rare odor.

The result would be as follows:

	Normal vs. AD (Frequent)	Normal vs. AD (Rare)
p-value	0.0738	0.0670

Table 4: p-value of Normal vs. AD group; channels **Fz/Cz**

Also by fitting the Gaussian distribution on the data, we'll have the following results:

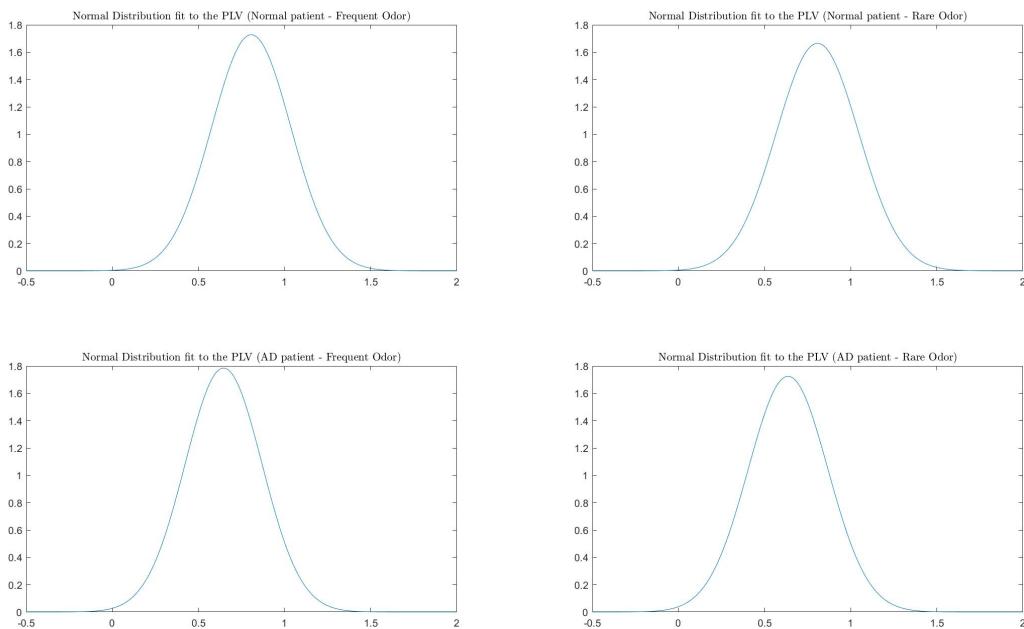


Figure 17: Normal Gaussian Distribution fit to the data of 2 groups and 2 odors

As it's clear in the above figure, the mean of the PDF for Normal individuals is a bit greater compared to the AD group, which indicates larger PLV for normal participants.

5.3 Statistical Significance

We can compare the response of the brain for normal and AD group using the p-value. By definition, we know that the p-value is a statistical measurement used to validate a hypothesis against observed data. It is defined as the probability of getting a result that is either the same or more extreme than the actual observations.

Regarding to the elicited results, p-value in the exposure of Rare odor is a little bit smaller, which can be a sign that the response of these two groups to a Rare odor is more different than the case of exposure to frequent odor.

The elicited p-value and the PLVs of the previous section leads us to the point that the brain functionality of Normal people to a new, rare odor should be better than the AD group.

5.4 Phase Difference

In this section, we pick a random case from both normal and AD group, and find the phase-difference. Theoretically, we assume that the phase difference of the signals come from electrodes for normal person should be less than the same value for an AD participant.

You can find the MATLAB code of this section in the MATLAB section, from **line 75 to 122**.

The output figure showing the phase difference of the randomly selected case from both normal and AD group (comparing the data of channels Fz and Cz) would be as follows:

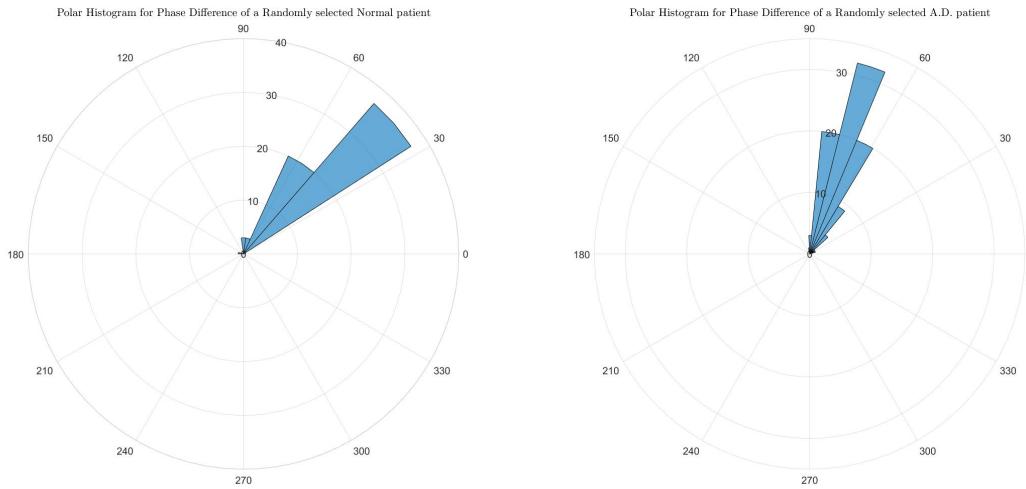


Figure 18: The phase difference between the data of channels Fz and Cz, for random selections of normal and AD group

The figure clearly states that the phase difference for a normal person seems to be less than a person with Alzheimer's Disease. It means that the different section of a normal person's brain is more connected and matched, compared to a person from AD group.

In order to have a more reliable results, we find the mean of phase difference for both groups, keeping this point in mind that We are ignoring the trials (Frequent vs. Rare).

The MATLAB code for this section is accessible in the MATLAB section, from **line 123 to 146**.

The output figure showing the phase difference between normal and AD group (comparing the data of channels Fz and Cz) would be as follows:

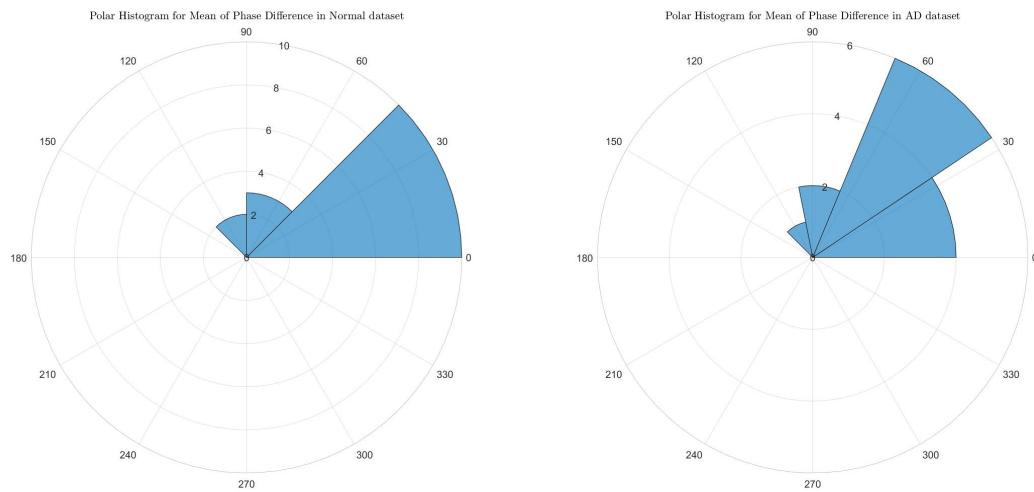


Figure 19: The phase difference between the data of channels Fz and Cz, for random selections of normal and AD group

5.5 Heatmaps

Heatmap is a great tool to show the difference of a specific value and helps the examiner to observe the difference visually.

The MATLAB code for this is accessible in the MATLAB section, from **line 147 to 210**.

As explained in the code body, I used the previous function and found the PLVs manually without defining another function, as it could violate the whole code and use more space.

In the pre-process step, the epoch has 4 channels. So we will have 6 different pair of channels which we are interested to find the PLV between them, while dividing the trials into two parts(The frequent and rare odors).

The output figure for the heatmap would be as follows:

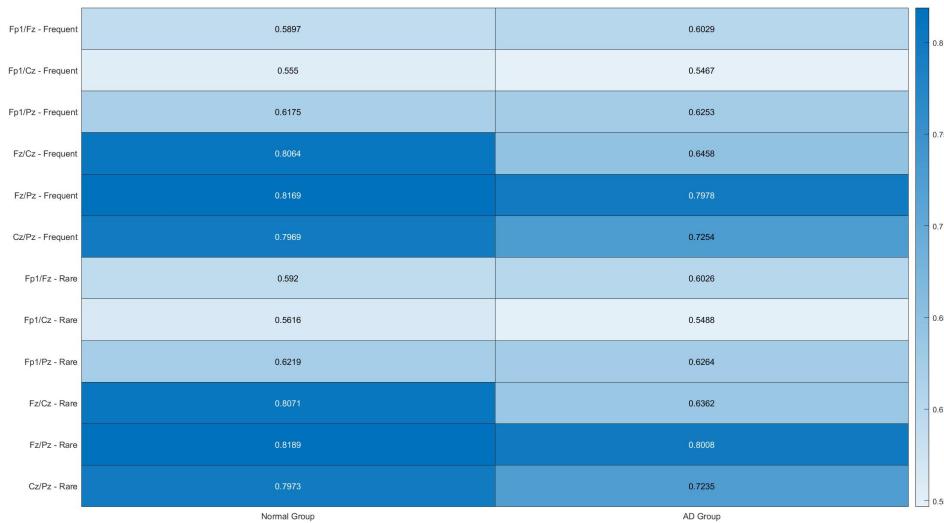


Figure 20: The Heatmap for all pair of channels, comparing two parameters: normal vs. AD and Frequent vs. Rare

As mentioned in the code, and similar to the previous sections, I manually found the PLV values in order to avoid any violation in the code and overuse of functions and loops.

As you can see in the heatmap, most of the paired channels have almost the same PLV, while there are two channels that obviously have quite different PLVs, the channels **Fz/Cz** and **Cz/Pz**.

We've already found the p-value for the channels **Fz/Cz** and discussed the results. In this section, we find the p-value similarly for the channels **Cz/Pz**.

	Normal vs. AD (Frequent)	Normal vs. AD (Rare)
p-value	0.3647	0.3733

Table 5: p-value of Normal vs. AD group; channels **Cz/Pz**

6 Analyzing MCI Cases

6.1 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]

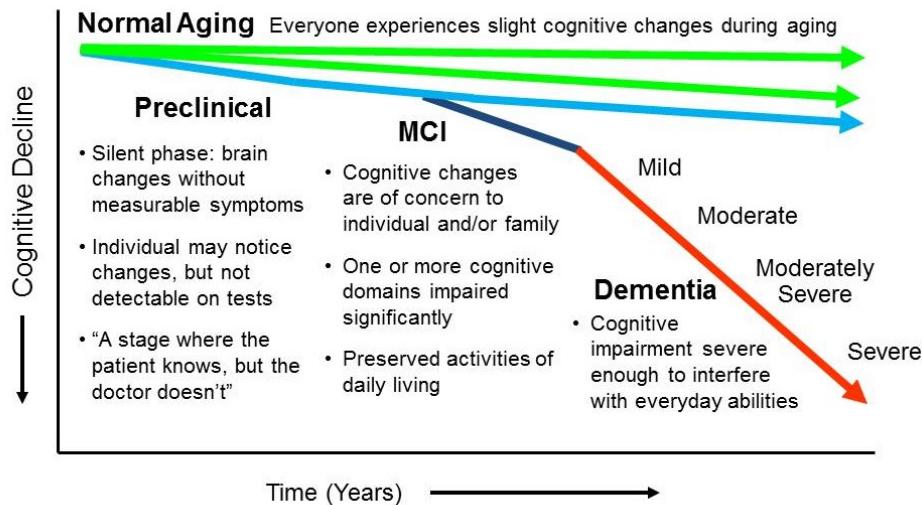


Figure 21: Normal Aging to Demantia Process

6.1.1 Additional Information

Mild Cognitive Impairment (MCI) is a general term most commonly defined as a subtle but measurable memory disorder. MCI is characterized by ongoing memory problems but not by confusion, attention problems, or language difficulties. Current evidence indicates that MCI often arises from a lesser degree of the same types of brain changes seen in Alzheimer's disease or other forms of dementia. Some of these changes have been identified in autopsy studies of people with MCI. These changes include abnormal clumps of beta-amyloid protein (plaques) and microscopic protein clumps of tau characteristic of Alzheimer's disease (tangles) and Lewy bodies, which are microscopic clumps of another protein.

However, **MCI does not always result in AD**. Some people with MCI remain stable and never get worse, some improve, and others eventually decline to dementia due to Alzheimer's disease or another type of dementia. The cause of MCI is unknown but it does appear to have **similar risk factors to Alzheimer's** such as age, education level, and certain brain/body health factors like stroke, diabetes, cholesterol, heart health, and blood pressure.

6.1.2 MCI Data Processing

According to the progress of processing Normal and AD data in the previous section, we observed that there is a significant difference in the PLV when we find the value for two specific channel pairs; **Fz/Cz** and **Cz/Pz**.

The Difference encourages us to investigate more, and analyze the PLV for the same channel pairs in MCI patients.

Same process is done to find the PLV for MCI data-set. You can check the process in the MATLAB section, from **line 211 to 244**.

In this section, we first find the PLV just like what we did in the previous sections. Then by creating the desired matrix, we can plot the heatmap for all 3 states (Normal - MCI - AD). This heatmap would be as follows:



Figure 22: HeatMap showing the PLV for Normal, MCI, and AD groups, in both suspected channel pairs and odors

The provided heatmap includes all 3 states, also divided into 4 parts, so that we can compare the results for different odors (Frequent and Rare) and suspected channels (**Fz/Cz** and **Cz/Pz**).

As you can see, there is a decreasing behavior in the PLV from Normal Group to AD Group, which totally makes sense. We know that as people age, the connection and synchronization of different brain sections may decrease.

The significant difference between these channel pairs is a good reason to look for finding the p-values and expand our analysis.

In the next table, you can see the p-value calculated for each pair of cells of the heatmap:

Description	p-value
Normal Vs. MCI - Fz/Cz - Frequent	0.3221
MCI Vs. AD - Fz/Cz - Frequent	0.5154
Normal Vs. MCI - Fz/Cz - Rare	0.3015
MCI Vs. AD - Fz/Cz - Rare	0.5347
Normal Vs. MCI - Cz/Pz - Frequent	0.3614
MCI Vs. AD - Cz/Pz - Frequent	0.8908
Normal Vs. MCI - Cz/Pz - Rare	0.3656
MCI Vs. AD - Cz/Pz - Rare	0.8935

Table 6: p-values for the heatmap comparing all 3 states

This table contains lot of data which can help us decide whether we can reject the hypothesis of assuming the equality between PLV values of two different group.

According to the statistics, we can analyze the elicited p-values based on the most common threshold of p-value which is considered to be 0.05. As it's clear, none of the p-values have reached the threshold of rejecting the H_0 , but there is a difference in the p-values, so at least we can compare them.

Based on the above table, the p-values for all comparisons between MCI and AD are greater than those for comparison between Normal and MCI. This fact could be used to say that two individuals with normal/MCI brain state have quite more different symptoms and reactions compared to the individuals of MCI and AD group.

Furthermore, we can compare the p-value for Frequent and Rare odor exposures. Although the difference is negligible, but in most cases, the exposure with rare odor has resulted in a greater p-value, and equivalently, in a closer PLVs. This finding could suggest the idea that the brain's reaction to new, rare stimuli is often better.

6.2 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. [5]

6.2.1 Metrics

Phase-Amplitude Coupling (PAC) metrics is a measure of the relationship between the phase of low-frequency oscillations (LFO) and the amplitude of high-frequency oscillations (HFO). It plays an important functional role in neural information processing and cognition.

Other PAC measures include:

1. **Modulation Index (MI):** MI is a measure of the strength of PAC. It is defined as the difference between the mean amplitude of HFOs at different phase angles relative to LFOs divided by their sum.
2. **Mean Vector Length (MVL):** MVL is a measure of the strength of PAC. It is defined as the length of the mean vector resulting from the pairwise multiplication of the analytic signals of two signals.

6.2.2 Implementation

As mentioned earlier, the MVL (Mean Vector Length) is a measure of the strength of PAC. Although PLV seems to be a better measure as we can analyze a single value and compare more easily, but MVL is useful too.

The MATLAB function for this biomarker (finding the MVL using this function) is as follows:

```

1  %% Function to Find the MVL of two signals --->
2  function MVL = MVLFinder(data, channel1, channel2)
3  % Extract the time series data for the two channels
4  signal1 = data(channel1, :);
5  signal2 = data(channel2, :);
6
7  % Compute the analytic signals of the two signals
8  analytic_signal1 = hilbert(signal1);
9  analytic_signal2 = hilbert(signal2);
10
11 % Compute the pairwise multiplication of the analytic signals of
12 % the two signals
12 pairwise_multiplication = analytic_signal1 .* conj(analytic_signal2
13 );
```

```
14 % Compute the mean vector resulting from the pairwise  
15 % multiplication of the analytic signals of the two signals  
16 mean_vector = mean(pairwise_multiplication);  
17 % Compute the length of the mean vector resulting from the pairwise  
18 % multiplication of the analytic signals of the two signals  
19 MVL = abs(mean_vector);  
20 end
```

As stated in the above code, we apply a pairwise operation on both input signals after finding the analytic signals.

The Hilbert transform is a mathematical operation that takes a real-valued function of time and produces another function of time that is called the analytic signal. The analytic signal is a complex-valued function that contains all the information about the original signal, including its amplitude, frequency content, and phase.

The same process is done to store the results of MVL found for all three groups(Normal, MCI, and AD). You can find the process in MATLAB section, from **line 400 to 420**.

Note: The process of finding MVL values for all 3 groups were done, while the difference in odor exposure was ignored for this section and only a single value for MVL is assigned to every individual of these groups. However, the elicited results were not satisfying enough to suggest any further process on the data.

7 Conclusion

The main goal in this project was to consider the olfactory dysfunction as a biomarker for differential diagnosis of normal individuals from those with Alzheimer's Disease (AD) or Mild Cognitive Impairment (MCI). In order to find any relation between these two subjects, we can observe the EEG signals elicited from the participants' brain. We designed an experiment, including more than 100 trials for each individual, exposing them to two different odors known as Frequent odor (Lemon flavor) and Rare odor (Rose flavor).

The response of the brain (neurons) for these two different approaches and also for the two groups was different enough to lead us to reliable results. We used different measures, methods, and visual tools (plotting) to compare the results.

PLV was one of the most important measures we found in the process section. This measure indicates how synchronized the different parts of brain are. We clearly observed that the PLV for a normal person is higher compared to the individual diagnosed with AD or even MCI, although the MCI cases had a little bit greater PLV on average.

The elicited results for PLV of all groups were shown in different ways, including box plots, heatmap, etc.

We also find the phase difference between the signals from different pair of channel. The phase difference is another reliable measure which can indicate the functionality of brain parts. As we expected, the difference in the phase of signals elicited from normal individuals were less than the respective value in those with AD/MCI.

The results of this examination were presented visually using polar histogram.

We know that the MCI is theoretically categorized as a middle-stage disease between a normal person and AD diagnosed person in the process of aging. Heatmap was used in the pre-final section to visualize the PLV values of MCI group compared to other groups. As expected, the decreasing behavior was seen in the PLV from normal group to AD group.

The main limitations in this study was the small number of cases for each group, which may increase the effect of any artifact, or outlier. We also were limited to examine the data of some selected channels of the EEG data (Fp1, Fz, Cz, and Pz).

It's important to note that in some sections, we totally ignored the unwanted outcomes and focused on some specific results, as we only analyze the data of two pair of channels in the MCI group analysis section.

Any further study in this area would be more reliable by considering all available data and analyzing the whole set of channels.

References

- [1] Mild cognitive impairment (mci). <https://www.mayoclinic.org/diseases-conditions/mild-cognitive-impairment/symptoms-causes/syc-20354578#:~:text=Overview,mental%20function%20has%20slipped.%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] 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.
- [6] 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.
- [7] Cécilia Tremblay and Johannes Frasnelli. Olfactory and Trigeminal Systems Interact in the Periphery. *Chemical Senses*, 43(8):611–616, 07 2018.