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ORIGINAL ARTICLE

# Neurophysiological Insights into Network Decoding of Working Memory: An Analysis of Human Brain Electrophysiological Signals

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## Abstract

**Purpose:** The human brain is comprised of distinct regions, each contributing uniquely to behavioral control. The execution of even basic tasks necessitates synchronized activities among multiple brain regions. Fundamental cognitive functions hinge on the capacity to retain and flexibly manipulate information, a key role ascribed to Working Memory (WM). This study seeks to enhance our understanding of the neural mechanisms underlying WM and elucidate the coordinated neural activities spanning various brain regions.

**Materials and Methods:** To achieve this objective, the invasively recorded electrophysiological activities from the Medial Temporal (MT) cortex of humans using a high number of electrodes were analyzed. The subjects did a verbal working memory task including three phases: encoding, maintenance, and retrieval.

Phase synchronization between electrode signals in common frequency rhythms determined by Phase Locking Value (PLV) was used to create brain network graphs.

**Results:** This study validates prior findings on neural synchronization in the hippocampus, entorhinal cortex, and amygdala during WM within the theta, alpha, and beta bands. Analysis of Phase Locking Value (PLV) dynamics during encoding and maintenance, reveals strong modulation in the theta, alpha, and beta rhythm. Notably, the PLV of theta oscillation between channels within the posterior hippocampal region was significantly reduced during maintenance. Conversely, PLV of theta-alpha rhythms between the Anterior Hippocampal region (AHL) and amygdala/entorhinal cortex was significantly increased by WM.

**Conclusion:** This study, for the first time, demonstrates the networks involved in WM within MT areas in the human brain. These findings underscore the frequency-specific intricacies in WM modulation, providing valuable insights into neural coordination during specific processing stages.

**Keywords:** Brain Connectivity; Working Memory; Maintenance; Phase Locking Value; Intracranial Electroencephalography.

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# 1. Introduction

The observation of disrupted brain oscillations and synchronization in various mental disorders highlights their crucial role in normal brain function. These alterations in neural synchrony not only enhance our comprehension of underlying neurological mechanisms but also offer potential as a diagnostic approach. Detecting these disruptions early on can significantly contribute to the development of effective treatments; working memory (WM), a fundamental cognitive function, is notably impacted by these disorders. Understanding the neural mechanisms of WM is crucial for the treatment of conditions such as schizophrenia, bipolar disorder, autism disorder, attention deficit, and hyperactivity disorder [1].

## 1.1. Conventional WM Analysis

Traditional neuroscientific investigations into WM have primarily concentrated on pinpointing the brain regions responsible for storing information during maintenance periods. The predominant perspective suggests that the prefrontal, parietal, and sensory cortices play crucial roles in representing the contents of working memory. Certain models advocate for a hierarchical organization of memory representations within the cerebral cortex. Inter-regional neural synchronization emerges as a potential mechanism facilitating the integration of information across diverse brain areas, thereby supporting not only WM but also other cognitive functions [2].

Predicting WM performance based on the activity of individual neurons often proves challenging, with limited studies reporting correlations between behavioral performance and firing rate when considering continuous spiking activity as a neural measure. Notably, the majority of these studies have not identified such correlations. In contrast, evidence from both behavioral and neural measures indicates that neural synchrony serves as a more reliable predictor of working memory performance compared to other neural indices. Furthermore, experimental manipulation of neural synchronization has demonstrated its capacity to modulate WM performance [1].

## 1.2. Neural Synchronization and WM

The term 'neural synchrony', derived from the Greek words 'Syn' (meaning 'together') and 'Chronos' (meaning 'time'), takes on different meanings depending on the context. In human Electroencephalography (EEG) studies, it may denote the phase synchronization of EEG oscillations between two brain regions. Illustrated in Figure 1, phase synchrony is a fundamental neural mechanism underlying communication and plasticity, influencing various cognitive processes. As depicted in Figure 1, neural oscillations can exhibit either stable phase synchronization (left: constant phase difference) or the absence of phase synchronization (right: variable phase difference) [3].

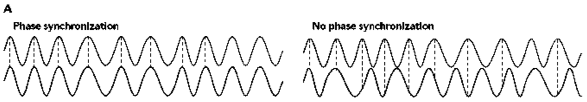

**Figure 1.** An example of the concept of phase synchronization [3]

## 1.3. The Role of the Hippocampus in WM

The increased phase locking between spikes in the alpha-beta rhythms during WM in sensory areas was reported [4]. Besides increased synchronous activities between frontal areas and the temporal cortex was another que of the role of brain oscillations during WM [5]. Recent studies showed that the hippocampus was involved in the coordination of WM-induced brain activities. The maintenance of WM information was associated with increased low-frequency activity in both the anterior and posterior hippocampus. Furthermore, they observed an increase in theta/alpha band phase synchronization (3 to 12 Hz) between the anterior and posterior subregions, indicating a correlation between WM and synchronized neural activity in these regions [6]. Also, it has been shown that the activity of neurons in the hippocampus during the encoding and maintenance is related to the workload and behavioral performance of the subject [7, 8]. However, the exact mechanism of hippocampal role in WM formation remains elusive. In this study, we want to address this issue using connectivity methods based on signals simultaneously recorded from a large number of electrodes

## 2. Materials and Methods

To analyze the functional brain network based on intracranial Electroencephalography (iEEG), we need to quantify the synchronization between the signals of different channels using suitable measures. The resulting network reflects the functional connectivity of the brain regions. The main steps for constructing and analyzing the functional brain network are preprocessing, calculating connectivity measures, shuffle correction, averaging across frames, and frequencies and comparing WM states based on resulting matrices.

### 2.1. Dataset Description

The data that was gathered by Boran and others was used in this investigation. The database includes Medial Temporal cortex (MT) iEEG signals from nine patients with drug-resistant focal epilepsy who had depth electrodes placed in anticipation of possible epileptic surgery (using on average 56 electrodes per subject). The task was done when subjects were in a normal state and did not have an epileptic seizure. Only the clinical indication was taken into consideration when choosing implantation sites. The study was authorized by the institutional ethics review board (Kantonale Ethikkommission Zürich, PB-2016-02055), and all participants supplied written informed permission. Neuropsychological tests indicated that all subjects were right-handed and had normal or corrected-to-normal vision [9].

A verbal working memory task performed by these individuals involved the visual Sternberg test, which comprised four states: fixation, encoding, maintenance, and retrieval (Figure 2). In each trial, a set of consonants was presented and had to be memorized. The set size (4, 6, or 8 letters) determined the WM workload. The stimulus presentation (encoding period, 2 s) was followed by a delay (maintenance period, 3 s). After the delay, a probe letter was presented, and subjects indicated whether the probe letter was contained in the stimulus [9].

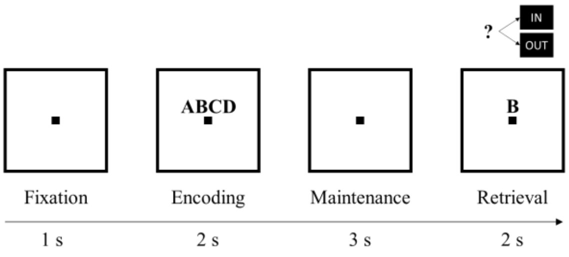

**Figure 2.** Modified Sternberg task [9]

### 2.2. Pre-Processing

The preprocessing of iEEG signals involved a series of essential steps, including noise removal, segmentation into 600-millisecond time windows with 200-millisecond steps, and notch filtering at 50Hz using a 35th-order FIR filter. Furthermore, signal down-sampling from 2 kHz to 200 Hz was performed to alleviate computational complexity. In the following, the common electrodes among the subjects were selected as the set of studied electrodes. The selected electrode set comprised 40 electrodes distributed across five brain regions: Left Anterior Hippocampus (AHL), Amygdala (AL), Entorhinal Cortex (EC), Left Posterior Hippocampus (PHL) and Right Posterior Hippocampus (RHL); eight electrodes in each area.

### 2.3. Connectivity

The connectivity measures can be divided into two categories based on their ability to detect how brain regions interact. Functional Connectivity (FC) measures analyze statistical relationships between signals, but they don't show causation. Effective Connectivity (EC) measures, on the other hand, reveal causal connections between signals [10]. Studies with a primary focus on the anatomical aspect also explore another type of connection known as structural connectivity. Structural connectivity involves the physical connections between neurons, often referred to as 'neuroanatomical' connections, which include the white matter connections in the brain [11].

### 2.4. Phase Locking Value

Quantification of the connection between pairs of iEEG channels was performed using the Phase Locking Value (PLV) metric. The PLV metric can be calculated between signals X and Y by employing (Equation 1), taking into account parameters such as the number of time points (N) and the relative phase ($\Delta\varphi\_rel$) between X and Y.

The phase of each channel was computed through a wavelet transform employing 42 distinct central frequencies. Subsequently, the resulting phase signals underwent the same windowing procedure as previously described (Equation 1):

$$PLV(X,Y) = \left|\frac{1}{N}\sum_{n=1}^{N} e^{i\Delta\varphi_{rel}(t_n)}\right| \quad (1)$$

The phase difference between two signals indicates how synchronized the pair of electrodes is, and this is quantified by the PLV index. PLV, ranges from 0 to 1. A PLV of 1 means that the phase difference remains constant throughout the time series, while a PLV of 0 means that the phase difference is evenly distributed from 0 to 2π. Essentially, PLV assesses how the phase differences are spread across the range of [0, 2π]. A higher PLV value suggests that the time series has a smaller range of phase differences within the unit circle [0, 2π]. For example, the phase of two signals that are highly synchronized is shown in Figure 3, and the PLV value of 0.87 is obtained.

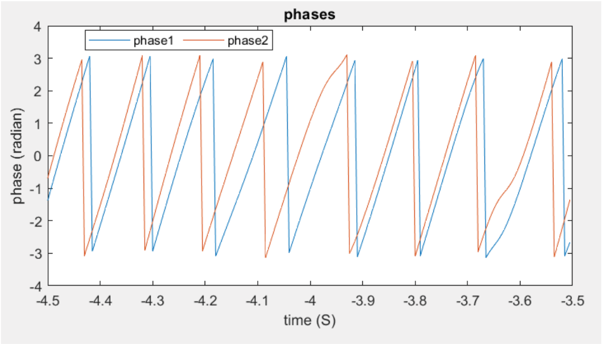

**Figure 3.** An example of calculating the PLV of two signals, in this example PLV equals 0.87

## 2.5. Averaging

For enhanced data interpretation, a two-tiered averaging approach was applied to the resulting PLV matrices. Firstly, temporal averaging was employed, grouping the 32 valid time frames into 4 distinct segments: fixation, encoding, maintenance, and retrieval. Subsequently, a second level of averaging involved the consolidation of 42 frequencies into 6 meaningful frequency bands: delta (1 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 12 Hz), low beta (12 – 21 H), high beta (21 – 30 Hz), and gamma (30 - 90 Hz).

Following the described windowing procedure (outlined in 2.2), the dataset yields a total of 38 frames. The initial three windows exclusively capture the fixation state, while windows 4 and 5 encompass both fixation and encoding states. To maintain the integrity of information within distinct working memory states, future analyses will involve the exclusion of windows that straddle different states. Additionally, 32 out of the 38 windows exclusively correspond to a single state, facilitating time averaging for subsequent analyses.

## 2.6. Shuffle Correction

To address the influence of frequency changes on PLV values, shuffle correction was performed as follows; shuffled PLV values were calculated for each pair of electrodes at each specific frequency and in each frame, with 50 repetitions, in each repetition, the index vector of the trials was randomly permuted and the PLV index was calculated between the pairs for the permuted signals. Then, the averaged PLV value obtained from the permuted trials was considered the PLV shuffled value of that repetition. Subsequently, the average PLV shuffled values for each pair at every frequency were subtracted from the corresponding actual PLV values at the same frequency. This process aimed to mitigate random effects and enhance the robustness of the study's findings.

## 2.7. Compare WM States

In the following, the statistical comparison between encoding and maintenance, at three significance levels of 0.05, 0.01, and 0.001, was done by Will Coxon Sign Rank statistical test to reach the significant decrease or increase of PLV values from encoding to maintenance states for all the pairs of brain regions.

This significant difference was considered if, in addition to the significance of the difference between encoding and maintenance, at least one of these states had a significant difference with the shuffled value.

In our analysis, we first assessed the presence of significant differences in PLV values between electrode pairs during encoding to maintenance states for all the subjects and sessions. Each area was equipped with 8 electrodes; hence, we computed the total number of significant PLV differences between pairs of areas, spanning from the encoding phase to the maintenance phase.

To facilitate interpretation, we normalized these values by dividing them by the total number of pairs, thereby yielding a range of values between 0 and 1. The resulting values, along with their respective edge connections, were presented for visualization.

## 3. Results

The WM-induced oscillatory activity of the MT cortex was calculated using the PLV metric. This index returns a value between 0 and 1 as output, which indicates the degree of phase synchronization between two signals (details are described in 2.3.1). To remove noisy factors of PLV values, shuffle correction was performed (details are described in 2.5). Figure 4 shows the PLV values for a sample pair which has significantly higher synchronization than shuffled PLV values.

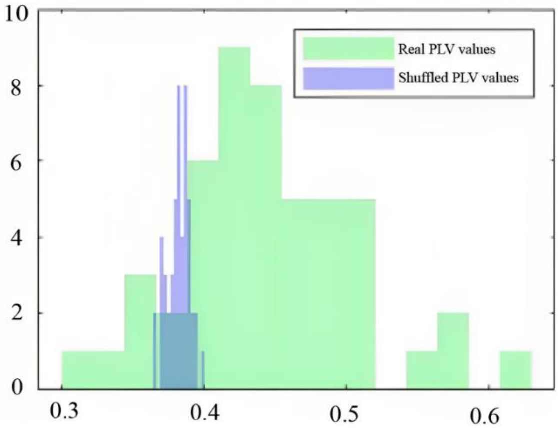

**Figure 4.** An example of distributions of real and shuffled PLV values for two channels in the amygdala and Entorhinal Cortex, for encoding frame at the low-beta band, is illustrated. The green histogram represents the real PLV values, while the blue, depicts the shuffled PLV values

In Figure 5 also, the percentage of values of the PLV value pairs that were significantly different from the corresponding values in the shuffled values are observed at three levels of significance. These pie charts are drawn for all frequency bands, examined frames, and subjects.

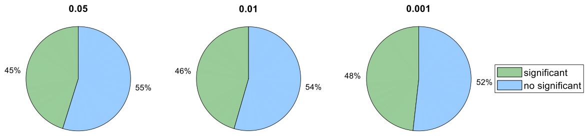

**Figure 5**. Percentage of significant differences between shuffled PLV and real PLV values

A comparison was also made between different states of working memory, and the highest neuromodulation of working memory was in the connection between the entorhinal cortex and the amygdala in the high-beta frequency band. The histogram of shuffle-corrected PLV distributions of encoding and maintenance between two electrodes in these areas in the beta frequency band is shown in Figure 6.

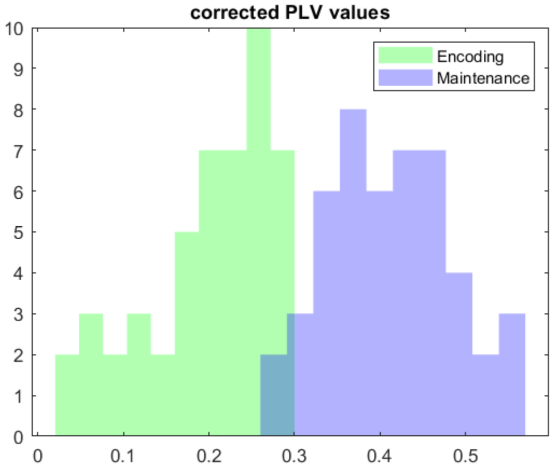

**Figure 6.** An example of shuffle corrected PLV values for a sample pair of electrodes in the amygdala and entorhinal cortex

Finally, a quantitative conclusion was made between all the electrodes of the brain regions for all subjects and we reached the graphs of Figure 7. These graphs show the percentage of the average number of pairs with significantly different PLV values between encoding and maintenance (T-test, significance level of 0.01).

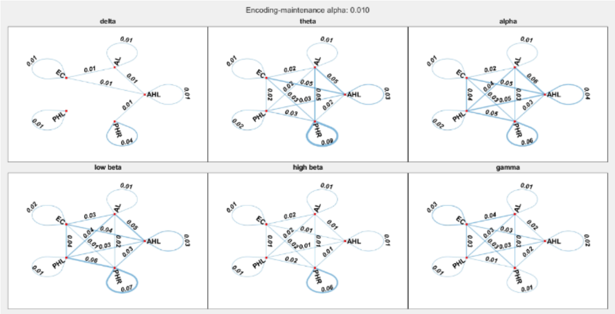

**Figure 7.** PLV comparison of encoding and maintenance states: five brain regions, six frequency bands. The thickness of the lines indicates the significant relative number

Figure 8 and Figure 9 separately show the significant increase and decrease of PLV values during the encoding phase compared to that of the

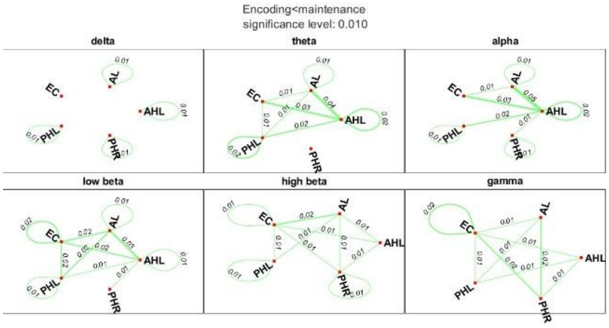

**Figure 8.** Graphs of the percent average number of pairs with significantly enhanced PLV values during the encoding phase in comparison to the maintenance phase

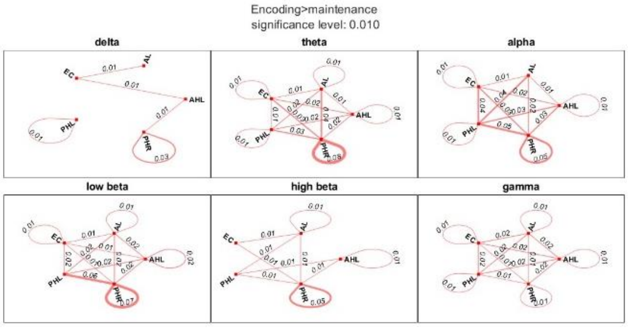

**Figure 9.** Graphs of percent average number of pairs with significantly reduced PLV values during the encoding phase in comparison to the maintenance phase

maintenance phase. It can be seen that in general, synchronization at low oscillations (delta), and high oscillations (gamma) are weak, however, theta, alpha, and low beta rhythms are responsible for the most modulation of WM in the stages of encoding and maintenance. In particular, the most modulation is in the theta rhythm, between the electrodes within the PHR region (which is often related to the reduction of PLV). Also, a decrease in PLV between the right and left posterior hippocampus areas is evident in alpha and low-beta rhythms. On the other hand, an increase in PLV between the AHL region and two regions of the amygdala and entorhinal cortex is observed in theta/alpha oscillations.

Distinct modulation patterns emerge in working memory phases, notably in theta rhythm within the PHR region. Decreasing in alpha and low-beta rhythms are observed between left and right posterior hippocampus areas, while increased theta/alpha oscillations reveal intricate synchronization dynamics between AHL and amygdala/entorhinal cortex regions.

Finally, it can be said that the increase of PLV within the AHL region and between this region and the amygdala and entorhinal cortex, as well as the decrease of PLV within the PHR region and between this region and the PHL region in theta/alpha frequency rhythms and to some extent low beta can modulate the maintenance of information during working memory.

Unlike the results of [12], in this study, a decrease in phase synchrony between the anterior and posterior regions in theta/alpha bands was observed during maintenance. In another study, it has been shown that the direction of information flow between the posterior and anterior hippocampus can be related to the subject's performance (correct and incorrect answers) [12]. Our study gains a deeper insight into the neural mechanism underlying this process of working memory. As the importance of connections between the amygdala and the hippocampus was mentioned in previous studies [13], our study provided a detailed neural mechanism in terms of reduction or enhancement of phase synchrony between these two areas by distinct brain oscillators. Unlike the results of [12], in this study, a decrease in phase synchrony between the anterior and posterior regions in theta/alpha bands was observed during maintenance. It has been shown that the direction of information flow between the posterior and anterior hippocampus can be related to the subject's performance (correct and incorrect answers) [12]. Our study gains a deeper insight into the neural mechanisms underlying this process of working memory.

## 4. Discussion

This article provides partial validation of the prior study's discoveries regarding neural synchronization between the hippocampus, entorhinal Cortex, and amygdala within the theta, alpha, and beta bands during WM. Exploring the notable distinctions between the escalation and reduction of PLV values during encoding versus maintenance stages unravels intriguing patterns, as depicted in Figure 8 and Figure 9. An overarching trend surfaces, indicating that connections at delta and gamma oscillations exhibit comparatively weaker modulation than other rhythms.

Within the intricate landscape of WM modulation, the theta, alpha, and low beta bands emerge as pivotal players, wielding substantial influence during both the encoding and maintenance phases. The theta frequency, in particular, takes center stage, showcasing maximal modulation between electrodes within the PHR, aligning with a concurrent reduction in PLV. Furthermore, a discernible dip in PLV manifests between the right and left posterior hippocampal areas.

Conversely, a contrasting narrative unfolds as an upswing in PLV is observed in the theta/alpha oscillations characterizing heightened synchronization. This phenomenon is notably observed between the AHL and two distinct regions. the amygdala and entorhinal cortex. Such orchestrated neural activity implies a coordinated effort during specific stages of working memory processing.

The dynamic interplay of theta, alpha, and low beta rhythms underscores their unique roles in the orchestration of working memory. The nuanced shifts in PLV between specific brain regions illuminate the complexity of neural networks engaged in encoding and maintaining information. This study not only unveils the frequency-specific intricacies of working memory modulation but also prompts further investigation into the functional implications of these observed patterns, paving the way for a deeper understanding of the neural underpinnings of working memory processes.

It should also be noted that due to the limitations of invasive recording which needs opening the skull and driving the electrodes into the cortex, few datasets record the iEEG of the human brain. The used dataset has recorded activities of different brain areas using a high number of electrodes. This has made it possible to obtain more comprehensive information about the mechanism of WM processing compared to previous studies.

This study, in particular, examined the directional connections inside the MT lobe of the brain with the help of the PLV index, in future studies, it is suggested to use the rest of the methods of examining brain connections to check the results. The use of other indexes such as the Phase Locking Index (PLI), Phase Amplitude Coupling (PAC), etc., or the use of the Laplacian filter can reduce the effect of Volume Conduction between electrodes. Also, the use of directional methods can provide a better insight into the flow of information between different areas. Also, investigating the coupling between iEEG-EEG, iEEG-spike can also be used to find out neural mechanisms of interaction between neurons and oscillatory activities within the MT cortex and across different brain regions like frontal and posterior cortices during working memory.

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