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Role of neural oscillations modulating long term potentiation to Alzheimer's Disease

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Abstract. Neural oscillations are key in forming long-term memory. Theta and gamma oscillations have particularly gained substantial interest over the year for their involvement in memory formation. Theta-Gamma Coupling (TGC) has proven to be critical in memory formation processes. However, the relationship between neural oscillations and molecular synaptic mechanisms, including Long Term Potentiation (LTP) and Long-Term Depression (LTD) has yet to be fully understood. Furthermore, the modulation of neural oscillations has emerged as a novel way of treating Alzheimer's Disease (AD) and Mild Cognitive Impairments (MCI). Various methods have been exploited, including optogenetics and Deep Brain Stimulation (DBS). While offering promising results including enhanced memory performance and restored brain oscillations, such modulation's applicability to clinical trials in human and potential side effects are still in doubt. In this review, we elucidated on the link between LTP and oscillations, assessed the various neuromodulation techniques introduced by recent studies and also provided insights into future research directions to optimize these present methods of neural modulation.

Keywords: neural oscillations, theta-gamma coupling (TGC), Alzheimer's Disease.

1. Introduction

Our ability to learn and remember things hinges on multiple brain mechanisms, amongst which contains neural oscillations- the synchronized neural activity in single or multiple brain regions. There are two major frameworks in the neuroscience field- the single neuron representation, which focuses primarily on the intrinsic properties of individual neurons and the neural network representation, which entails a group of neurons creating a common electric field and potential [1]. Neural oscillations consist of rhythmic neuronal activities of varying frequency bands: delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (14–25 Hz), and gamma (30–100 Hz). Oscillations can be explained by both of these representations. In a single neuron, oscillations are regular, repetitive firings of action potentials. In neural networks, oscillations arise from the coordinated activity of multiple interconnected neurons. This includes cross-frequency coupling (CFC) of higher-frequency amplitude to the phase of activity at lower frequency, or phase-amplitude coupling (PAC). Theta oscillations have lower frequencies than gamma oscillations and they spread wider spatially. Therefore, theta oscillations have been hypothesized to play a role in forging connectivity across different brain regions [2]. Theta-gamma phase-amplitude coupling (TGC) in particular is the most heavily studied form of CFC.

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Growing number of studies have shown that successful episodic memory formation requires certain contextual encoding in the core memory network [3]. The magnitude of TGC can predict the success of memory encoding [4]. The evidence points to the modulatory role of oscillations in inducing long term potentiation (LTP) and long term depression (LTD) [2, 5]. Alzheimer's disease (AD) is a prevalent disease among the elderly. As a subtype of dementia, AD commonly manifests as a gradual cognitive decline, including memory loss and degradation of spatial abilities. AD is characterized by alterations in brain structures and connectivity. The pathological accumulation of beta-amyloid (Ab) is usually observed in AD patients. Significant reduction in phase-amplitude coupling (PAC) has been observed in Alzheimer's disease (AD) and mild cognitive impairments (MCI) [6]. It has been proposed that oscillatory patterns may serve as biomarkers for Alzheimer's disease in Down Syndrome. Another question ensued is whether monitoring and restoring neural oscillations can function as an approach to rescue memory in AD. Here we describe the interplay between neural oscillations and LTP mechanisms. Next, in review of recent works on recording and manipulation of neural oscillations, we propose a possible framework in treating Alzheimer's Disease based on current research.

2. Neural oscillation in AD

2.1. Theta and gamma oscillations play a role in memory encoding

Despite ample evidence that establishes the role of theta and gamma oscillations in memory formation, conflicting results have been reported regarding the change in oscillatory power which lead to successful memory formation. Interestingly, studies focusing on theta band oscillations change during memory formation have reported contradictory findings. While most electroencephalography (EEG) studies often suggest that higher theta power and activities are associated with successful memory encoding [7], other studies suggest the opposite, whereby a decrease in theta activities take place in memory formation [8]. One possible explanation from [8] is that since theta oscillations are of a relatively low frequency, desynchronization of neurons allows more segregated, task-specific firings. Therefore, neural assemblies can code for a higher amount of information. In the context of working memory which encompasses increasing memory loads, there will be higher demand for processing and temporary storage capacity for incoming information in multiple neural assemblies.

An exception to this, however, is that researchers observed increased theta oscillations in a sequence encoding task. When test subjects were asked to memorize a list of items in order, they showed increased theta activity [9]. The researchers poised that while local neural assemblies fired in the gamma frequency represent individual items, multiple gamma oscillations are nested within a slower theta oscillation. The chronological order of gamma oscillations within the theta oscillation is indicative of the actual order of external item stimuli. Hence, it may be proposed that change in theta activities in memory encoding is task-dependent, given that some investigating associative memory also observed increased theta activity [10].

The previous study shed light on the significance of theta-gamma coupling (TGC) in the memory formation process. It is well-accepted that theta-gamma PAC supports sequence order memory, an integral part in episodic memory [9, 11]. When neurons are phase-locked in gamma oscillations, neural firings are organized into precise time windows within the gamma oscillation. This subsequently promotes spike-timing dependent potentiation (STDP). On the other hand, LTP and LTD will be induced depending on whether the neural activity takes place at the peak or trough of theta oscillations. Gamma oscillations are 'nested' within theta oscillations - several gamma oscillations exist within one cycle of theta. On a molecular level, inhibitory interneurons acting on slow GABAa receptors, which contribute to generation of theta oscillations, also act on fast GABAa receptors that correspond to gamma oscillations [12]. At the peak of theta oscillations, most of the neurons in the region are functionally inhibited, which means there is less noise in the environment and hence neurons are more sensitive to incoming action potentials [2]. Stimulation at the peak of theta oscillation induces LTP, while LTD is induced if stimulation is delivered at the trough [13].

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Two pieces of research work showed that when drug treatments inhibited LTP, either by blocking the N-methyl-D-aspartate receptor (NMDAR) [14] and G-protein-gated inwardly rectifying potassium (GIRK) channels [15], theta-gamma coupling during high-frequency stimulation were weakened. This may underlie unsuccessful memory formation and suggest a casual role between LTP and oscillations. However, it is unsure whether it is the lack of LTP that prevented oscillation or altered oscillations impaired LTP or both.

2.2. Alterations in oscillatory pattern is found in Alzheimer's Disease

Progressive reduction of oscillatory power is a commonly observed neuropathological alteration in AD. Termed as 'neural slowing', increased power of lower frequency oscillations (delta and beta) coupled with reduced power of higher frequency oscillations (alpha, beta and gamma) is consistently observed in AD subjects. Magnetoencephalography (MEG) was used to confirm that the magnitude of the slowing effect is spatially distinctive [16]. The most severe slowing effect is correlated with regions with greater amyloid-β burden, which is often observed in the bilateral middle temporal cortex (MTC), inferior parietal cortex (IPC), medial temporal, dorsolateral prefrontal and cerebellar cortices. These regions form a neural network which is crucial in many cognitive processes. A separate MEG study indicated that tau pathology is higher in regions where spectral power of all oscillations is lower, albeit within a relatively small sample size (n=7) [17]. This is corroborated by evidence suggesting that pathological tau reduces both single neuron activity and neural synchronization, possibly by weakening synaptic connections and inducing synaptic loss [18].

Episodic memory formation requires exchange and transmission of information across different brain regions containing multiple aspects of the contextual information. CFC plays a crucial role in synchronizing the firing across multiple neural assemblies. It is hence no surprise that the theta-gamma PAC in AD patients is weaker compared to healthy elderly, as shown in an EEG study [6]. In AD mice models, theta-gamma PAC is significantly disrupted in the subiculum before a significant level of Amyloid-beta emerges [19]. Based on these observations, attempts have been made to use neural oscillations as biomarkers to identify patients with MCI and AD. Two classifiers were trained to interpret theta-gamma PAC values and amplitude coherence measured with EEG [20]. The classifiers successfully distinguished the test subjects. Compared to traditional biomarker identification using amyloid-β and pathological tau, this method is non-invasive and less likely to incur damage to the patient during sampling. It may also be more convenient to screen the progression of the disease for patients over time.

Another research reported lower theta activity in the frontal lobe but increased theta activity in the temporal-parietal lobe in early-stage AD [21]. This suggests that in early stages of AD, the activities of the temporal-parietal lobe may be enhanced to compensate for the functional decline of the frontal lobe. This may provide an explanation as to why some forms of plasticity and memory are only affected in later stages of AD [22]. It may be possible that the aberrant oscillations in AD patients disrupted necessary neural rhythms for induction of LTP, and therefore leading to cognitive impairment. However, more research will be needed to inspect the underlying mechanisms that link these dysfunctional neural processes.

2.3. Modulation of neural oscillations can improve memory performance

There are two major tracks of research aiming at neural modulation for memory enhancement. The first one works by developing brain-machine interfaces (BCI) and Machine Learning Algorithms to collect data of neural oscillations and classify them into brain states. This can be used to identify the periods in which memory formation is most likely to be successful. The second one is relatively more popular. That is, using Deep Brain Stimulation (DBS) or Optogenetics to manipulate neural oscillations. This approach is often used in the context of cognitive decline, where normal neural oscillations are disrupted. This section will examine both approaches, including relevant case studies and analysis.

Using BCI [23], researchers found that successful episodic memory encoding is associated with an increase in high-frequency oscillatory activity and a concurrent decrease in low-frequency activity. In a

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free recall task, they first recorded theta and alpha oscillations that took place preceding successful memory encoding using Intracranial Electroencephalography (iEEG). This was set as the pre-stimulus oscillatory marker for future reference. Word representations are triggered by neural activities that cross the threshold of the reference. The result showed that word stimuli delivered at the appropriate timing are usually better remembered than when delivered at random timings.

Deep Brain Stimulation (DBS) is a method of neural modulation that has been widely used as a therapy for Parkinson's disease. Electrical pulses delivered at the internal globus pallidus (GPi) and the subthalamic nucleus (STN) disrupt neuronal firing and enable patients to restore natural movement. A recent research interest revolves around using DBS techniques to modulate neural oscillations. By delivering stimulation that synchronizes with oscillations of certain frequency bands, oscillatory rhythm can be restored in patients with cognitive impairments. This often leads to changes in memory performance. However, due to heterogeneity in the condition of tests and protocols used, studies have reported inconsistent results.

In one study, researchers implanted stimulating electrodes in 4-month-old APP/PS1 mice, a model of preclinical AD [24]. DBS at 100 μA, 10Hz and 90μs was delivered for 1h per day in 21 days which increased the power of theta and gamma oscillations. The target region was the entorhinal cortex (EC). The post-stimulation mice showed significant improvements in spatial learning and memory performance, raising it to the level comparable to wilt type (WT) mice. Interestingly, the level of hippocampal Aβ plaque levels also decreased after the stimulation, coupled with increased hippocampal neurogenesis.

Another approach using optogenetic gamma stimulation has also shown to improve memory performance in AD mouse models [25]. 40 Hz laser light paced neuronal firing in the hippocampus at the gamma frequency band. When stimulation was turned on during a spatial memory task, the mice performed better than the control group. This study has also demonstrated the significance of stimulation parameters specification. While both belong to the gamma frequency band, stimulation at 80 Hz did not achieve the same effect as stimulation at 40 Hz. Notably, this experiment has also proved optogenetics as a viable method to enhance theta power, albeit at a lower frequency.

Extending this research to long-term stimulation at 40 Hz in human participants with mild cognitive impairment (MCI), [26] designed a trial using combined auditory and sensory gamma flicker. The flicker takes place at 40 Hz and is maintained for 1 hour over a period of 4 weeks or 8 weeks. The results showed no significant difference in Aβ level before and after stimulation. However, the functional connectivity between the posterior cingulate cortex (PCC) and precuneus (PCu) was enhanced, together with downregulation of proteins involved in neural immune responses. What distinguishes this study from the rest is that the stimulation did not substantially increase the power of gamma oscillations, instead, a decrease was observed, presumably due to a homeostatic response after repeated flicker stimulation.

Transcranial alternating current stimulation (tACS) was applied in another study to ameliorate AD symptoms in transgenic AD mice [27]. In the experiment, the test group received tACS at 40Hz at the bifrontal lateral lobe for 2 consecutive weeks to restore gamma oscillations. After stimulation, the slope of field-Excitatory Postsynaptic Potential (fEPSP) increased significantly, indicating higher level of success of LTP induction. However, this effect was only measured for 60 minutes. Coupled with the negative results obtained regarding changes in neuroplasticity-related protein levels, the effect of such stimulation is likely to be limited in the lasting duration.

3. Discussion

While the above studies have presented impressive results in their success of modulating neural oscillations, the underlying mechanism remains unclear. A common limitation of the reviewed research is their short test duration. The impact was often assessed over a restricted time period, thereby casting uncertainty on the long-term effectiveness. Follow-up studies can be done to investigate changes in memory performance when the stimulation is no longer sustained. This refers to a period longer than the current duration of experiments, such as the 21-day period in the DBS study [27].

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In particular, 40 Hz gamma entrainment has evoked much interest among researchers. This is partially due to the fact that 40 Hz gamma oscillations are believed to be crucial in memory processing and other cognitive tasks. Nevertheless, in the actual context of a brain, neuron firings are synchronized at different frequencies and cross-frequency coupling is taking place constantly. How to avoid altering oscillations in other frequency bands while manipulating oscillations within one region would be an outstanding question to future research. Further, one promising direction of future study can be done on observing neuromodulatory effects if theta frequency stimulation is delivered separately, or together with gamma stimulation.

Inconsistencies have arisen from two studies looking into pathological Aβ levels after 40 hz stimulation. While the invasive method used in [25] reported lowered Abeta levels, this effect was not observed in non-invasive stimulation in [26]. This distinction may stem from the failure of the latter in increasing gamma oscillation power in the participants, reinforcing the role of gamma oscillation in controlling the molecular microenvironment within the brain. What remains unclear is through which mechanism can enhanced gamma oscillations reduce Aβ levels.

Lastly, regarding invasive stimulation methods, two key determinants of success of neuromodulation are the accurate placement of electrodes and the stimulation parameter. As mentioned in [26], sham trials of the sensory stimulation led to increased Aβ levels, which limits the possibility of carrying out such tests in human participants. By the same token, the memory-enhancing effect in [23] was only significant in 6/10 sessions, suggesting that there could be variable memory encoding processes that may be irrelevant to theta/alpha oscillations. Stimulation applied must be carefully designed to minimize unwanted side effects due to interference with existing brain oscillations by externally induced oscillation. This will lead to the extension of using the same stimulation parameters tests for human participants.

4. Conclusion

As indicated in the various studies, it is evidence-based that theta and gamma oscillations play a key role in regulating LTP formation and memory-related mechanisms. The mutual dependence between oscillations and LTP suggests that the presence of both are vital in memory. Characteristic pattern changes in neural rhythms can be utilized to indicate early onset of AD for more effective prevention. While the intricacies of synchronized neural networks still awaits further elucidation, present studies illuminate a promising avenue to ameliorating AD symptoms through neuromodulation of brain oscillations. Various methods including DBS, tACS, optogenetics and can be refined to better manipulate neural oscillations. Finally, in view of the potential side effects and risks inherent within these methods, a cautious approach must be adopted to ensure that any neuromodulation on human participants is based on scientifically rigorous, replicable results in animal models.

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