

Kognisyonun Ritimleri

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10.EKLER

EK-1: Impact Paragraph

The studies carried out within the scope of this doctoral thesis investigated the functional role of different brain oscillations associated with human memory processing. Importantly, our conceptual and technological approach enabled us to modulate neural oscillatory activity with measurable impact on both, neurophysiological assessments of neural oscillations as well as cognitive performances in various memory tasks. This has direct implications for developing therapeutic neuromodulation techniques capable of addressing cognitive deficits in patients in whom these cognitive deficits are linked to disease-specific altered brain oscillatory mechanisms as showcased here with the example of Parkinson's Disease.

Neuromodulation may in first instance be conceptualized as any method capable of affecting the ongoing, normal functioning of the brain via external interventions. In fact, pharmacological treatments (drugs), rehabilitation interventions, and psychotherapies are also considered forms of neuromodulation in that sense. However, in many cases, these approaches may turn out to be inadequate and/or have limitations in terms of feasibility, tolerability, or clinical efficacy. In these cases, neuromodulation technology using non-invasive electric or electromagnetic brain stimulation methods may be a suitable and desirable nonpharmacological alternative. While the modern concept of transcranial (through the skull) electrical stimulation is relatively young (about 20 years), there is a century of history behind the idea of using electrical stimulation to alter brain activity. Non-invasive electrical brain stimulation is based on the principle of manipulating the brain by modulating neural activity of the brain through the electrical current applied through the skull (4–7).

Low intensity electrical stimulation methods as utilized in this thesis can affect the activation of neuronal networks, but they are not strong enough to initiate non-existent neuronal activity. In contrast, their working mechanism is based on the modulation of existing neural activation. Although all forms of this low intensity non-invasive electric methods of brain stimulation can modulate brain activity and therefore cognition-behavior in general, the underlying working mechanisms are different and therefore the selection of the appropriate method is important in order to achieve the desired change in brain activity and behavior. Therefore, considering the

aims of this thesis based on investigating the oscillatory. In particular, considering that we here focused on the functional role of neural oscillatory activity for saucerful cognition in healthy and diseased participants, we here investigated the potential of using transcranial alternating current stimulation (tACS) as a technique which allows rhythmic stimulation at a certain frequency (e.g., 7 Hz), in order to specifically intervene with the oscillatory activity of the brain. TACS is able to deliver sinusoidal currents at the desired frequency to alternate ongoing brain oscillations in the targeted direction. (5,8,9,301). The stimulation applied by alternating current is thought to modulate the excitation (firing) times of neurons (nerve cells). The altered exposure of synapses (connections between neurons) to the altered electric field is thought to cause changes in biochemical mechanisms that lead to short-term synaptic plasticity (12). This external manipulation of ongoing brain oscillations by tACS can affect the cognitive processes based that are associated to these brain oscillations. If so, this technique could prove to have a large impact across various scientific and clinical applications as it provides the experimental possibility to regulate and control brain oscillations through external intervention. The clinical potential cannot be overestimated as this may be developed into a therapeutic tool for many pathologies (osilopathies) whose deterioration pattern is known to be reflected in brain oscillations. The aim and impact of this thesis is clearly positioned within this framework.

In this thesis, firstly, the specific contribution of brain oscillatory responses (especially slow frequency $< \sim 8$ Hz responses) to memory sub functions are examined in healthy volunteers and the contributions of delta and theta frequencies to working memory encoding strategies are revealed. Moreover, it has been shown that in healthy individuals, by using tACS, electrical stimulation at individual theta frequencies calculated from the individuals' own EEG data can affect their behavioral performance beyond the stimulation period itself (after effect). Moreover, the possible oscillatory mechanisms that may underlie this behavioral performance enhancement have been studied to help understand the relationship between brain oscillations and cognitive functions on a more general level. The results show that, not surprisingly given the complex and dynamic working mechanism of the brain, the effect of neuromodulation (both on behavior and on brain oscillations) are not as linear as expected. Concretely, we could reveal that tACS may induce an enhancement in memory performance in

healthy volunteers not when tACS is applied at the individual theta peak frequency, but rather at a frequency aimed at slowing down the individual theta frequency. However, in terms of neurophysiological effects this slowing down tACS approach did not cause changes in ITF as expected, but rather caused the connectivity between the stimulated brain regions to be modulated within a larger widely distributed frontoparietal network. Interestingly, assessing oscillatory alterations in Parkinson's patients with mild cognitive impairment, we also unraveled abnormal oscillatory connectivity features in the EEG data as being associated with the cognitive impairment. When we look at these results, they seem to complement the findings we have obtained experimentally from healthy volunteers.

In sum, the studies described in this thesis provide new fundamental insights into the functional roles of specific oscillatory frequencies in the context of human memory processing, demonstrate the capability of tACS to modulate these neural oscillations as well as memory performance, causing tACS-induced cognitive enhancement that persist even after the tACS stimulation has been discontinued (tACS after effects), and showcase the potential of using EEG-informed tACS to individualize the stimulation frequency such that slowing down the individual peak frequency can cause changes in network connectivity and memory improvements. These findings are undoubtedly very promising for clinical use in appropriate pathologies. Accordingly, the results seem to be important in terms of developing potential treatment approaches for diseases in which cognitive performances are affected, in addition to the scientific perspective it provides in terms of understanding the rhythms of cognition.

EK-2: General Summary

In a series of studies we here aim to test and modulate the functional relationship between brain oscillations and cognitive processes, induce cognitive after effect of electroencephalography (EEG)-informed individualized transcranial alternating current stimulation (tACS) in the context of memory and learning, and investigate the therapeutic potential of noninvasive neuromodulation techniques in patients suffering from cognitive impairments associated with pathological alterations in oscillatory brain activity. To this end, we recorded EEG in both, healthy and diseased human participants during the performance of various cognitive tasks. In the first study, we revealed that event-related delta and theta oscillations play a specific functional role for the optimization of cognitive performance with both differentially contributing to different encoding strategies during the digit span-backward working memory task. Namely, delta responses evoked by items in each series matched the ‘serial position curve’, with higher delta power being present during the first and last items as compared to items presented in the middle of a series. Theta responses, in contrast, rather resembled a neural correlate of a chunking pattern. This EEG study contributed to our understanding of the neural oscillatory mechanisms underlying multiple item encoding, directly informing recent efforts towards memory enhancement through targeted oscillation-based neuromodulation. In a next step, we then used tACS to experimentally modulate these oscillatory activities and assess the induced effect on brain oscillations and memory performance. We could show that theta tACS applied at the individual peak frequency of theta (ITF) most effectively modulated spontaneous oscillatory theta activity but had not measurable effect on memory performance. In contrast, tACS stimulation applied slightly below this individual peak theta frequency showed to be better capable to improve memory performance. Importantly, this beneficial cognitive effect of tACS applied at a slightly lower frequency than ITF was observed to persist even after stimulation and was associated with tACS-induced changes in EEG frontal-parietal connectivity. Finally, in a clinical study on patients suffering from Parkinson's Disease with mild cognitive impairment (PD-MCI), impaired anterior-posterior functional connectivity caused by abnormal EEG delta-theta oscillations was revealed during a visual oddball task. Collectively, these studies highlight the importance of delta-theta oscillations for cognitive

processing in the domain of memory, and demonstrate that these oscillations can be effectively modulated using tACS leading to measurable cognitive enhancements that persisted even after tACS stimulation was discontinued (tACS cognitive after effects). We also revealed pathologically altered functional connectivity patterns within theta-delta oscillations to be associated with cognitive impairment in PD-MCI patients. The results of this thesis may therefore pave the way for developing new neuromodulation-based treatment approaches for improving cognitive deficits in patients suffering from disorders with underlying oscillatory deterioration patterns.