COMENIUS UNIVERSITY IN BRATISLAVA

FACULTY OF MATHEMATICS, PHYSICS AND INFORMATICS

Role of theta oscillations in prefrontal cortex in semantic retrieval: tACS study

DIPLOMA THESIS

Study programme:	Cognitive Science
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Supervisor:	Mgr. Martin Marko, PhD.

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THESIS ASSIGNMENT

Name and surname: Romana Umrianová
Study programme: Cognitive Science (Single degree study, master II. deg., full time form)
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Title: Role of theta oscillations in prefrontal cortex in semantic retrieval: tACS study

Annotation: Semantic retrieval emerges through the interaction of prefrontal (PFC) and other posterior language networks. Growing evidence indicates that synchronous neural oscillations in theta-band are involved in this process. Yet, their functional role remains elusive. Neurostimulation studies have demonstrated that transcranial alternating current stimulation (tACS) can modulate endogenous brain oscillations. Therefore, tACS provides a viable approach for studying causal relations between theta oscillations and semantic retrieval.

Aim: The study will focus on the effects of transcranial alternating current stimulation (tACS) in theta-band frequency (6Hz) over the left inferior frontal gyrus on semantic retrieval measures. Identify the role of prefrontal thetaband entrainment in the controlled and automatic retrieval processing. Carry out an experimental study in healthy participants, including active/sham tACS and the assessment of semantic retrieval functions.

Literature: Polanía, R. et al. (2012). The importance of timing in segregated theta phase-coupling for cognitive performance. Current Biology, 22(14), 1314–1318.
Violante, I. R. et al. (2017). Externally induced frontoparietal synchronization modulates network dynamics and enhances working memory performance. eLife, 1–22.

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Názov: Role of theta oscillations in prefrontal cortex in semantic retrieval: tACS study
Úloha prefrontálnych théta oscilácií pri sémantickom vybavovaní: tACS štúdia

Anotácia: Vybavovanie zo sémantickej pamäti vzniká prostredníctvom interakcie prefrontálnych (PFC) a posteriórnych mozgových sietí. Výskum ukazuje, že synchrónne oscilácie v pásme théta hrajú významnú úlohu v tomto procese. Presná úloha théta oscilácií pri sémantickom vybavovaní je však neznáma. Neurostimulačné štúdie preukázali, že endogénne oscilácie je možné modulovať pomocou transkaniálnej stimulácie striedavým prúdom (tACS). tACS preto predstavuje vhodný experimentálny prístup pre zisťovanie vplyvu théta oscilácií na sémantické vybavovanie.

Cieľ: Práca sa zameriava na účinky transkraniálnej stimulácie striedavým prúdom (tACS) v pásme théta (6Hz) v oblasti inferiórnej frontálnej kôry na procesy sémantického vybavovania. Identifikujte rolu théta oscilácií pri automatickom a kontrolovaniom vybavovaní zo sémantickej pamäti. Realizujte experiment na zdravých jedincoch, ktorý bude zahŕňať aktívnu/placebo stimuláciu a posudzovanie výkonu v sémantických kognitívnych testoch.

Literatúra: Polanía, R. et al. (2012). The importance of timing in segregated theta phase-coupling for cognitive performance. Current Biology, 22(14), 1314–1318.
Violante, I. R. et al. (2017). Externally induced frontoparietal synchronization modulates network dynamics and enhances working memory performance. eLife, 1–22.

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študent vedúci práce

I hereby declare that the presented master’s thesis is original and the result of my own investigations. Formulations and ideas taken from other sources are cited as such.

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Bc. Romana Umrianová

Acknowledgments

I would like to thank my thesis supervisor Martin Marko for his valuable commentaries, assistance and guidance of my research and writing.

Abstract

Neural oscillations are crucially involved in neuronal communication and computations that are necessary for complex cognitive functions and adaptive behaviour. Semantic cognition is a fundamental system that enables semantic memory retrieval. Recent studies have demonstrated that neuronal theta oscillations in prefrontal perisylvian brain regions may play a pivotal role in binding of semantic representations. However, theta oscillations have been also associated with the involvement of cognitive control and working memory functioning which putatively support controlled semantic processing. Thus, the functional role of theta oscillations in semantic retrieval remains poorly understood. For this purpose, transcranial alternating current stimulation (tACS), an external frequency-specific modulator of endogenous cortical fluctuations, was used to modulate endogenous theta band oscillations. In the present study, we applied active and sham tACS over the left inferior frontal cortex and the contralateral supraorbitary region to entrain prefrontal theta oscillations at 6Hz (θ-tACS) over the inferior frontal cortex in 27 healthy participants. The tACS conditions were delivered in separate sessions using a pseudo-randomized and properly balanced cross-over experimental design. Participants completed tasks assessing automatic and controlled retrieval performance in three blocks within each session before, during and immediately after the stimulation. Our findings indicate that θ-tACS significantly facilitated retrieval tasks involving automatic processes (i.e., delivering free and unconstrained associations) but impaired controlled retrieval that required cognitive control (i.e., the inhibition of habitual responses and switching between semantic sets). Our study provides an important experimental evidence indicating that neuronal theta oscillation may constitute a neurocognitive mechanism for semantic binding, rather than cognitive control. We conclude that theta oscillations over left prefrontal cortex may support well-established semantic connections or strengthen their metastable activation, which enhances fluent retrieval. These conclusions should be supported by further empirical research.

Key words: semantic retrieval, prefrontal cortex, theta oscillations, tACS

Abstrakt

Neurálne oscilácie sa vo veľkej miere podieľajú na neuronálnej komunikácii a výpočtoch, ktoré sú potrebné pre komplexné kognitívne funkcie a adaptívne správanie. Sémantická kognícia je systém, ktorý umožňuje vyhľadávanie v sémantickej pamäti. Nedávne štúdie ukázali, že theta oscilácie v prefrontálnych perisylvických oblastiach mozgu môžu hrať vo väzbe sémantických reprezentácií kľúčovú úlohu. Avšak, theta oscilácie sú tiež spájané so zapájaním kognitívnej kontroly a pracovnej pamäte, ktoré zdanlivo podporujú riadené sémantické spracovanie. Funkčná úloha oscilácií theta v sémantickom vyhľadávaní teda ešte stále nie je dostatočne pochopená. Na moduláciu oscilácií endogénneho pásma theta bola použitá stimulácia transkraniálneho striedavého prúdu, externým frekvenčne špecifickým modulátorom endogénnych kortikálnych fluktuácií. V tejto štúdii sme na 27 zdravých účastníkoch aplikovali aktívny a placebo tACS na ľavú spodnú čelnú kôru a kontralaterálnu supraorbitálnu oblasť, aby sme naladili prefrontálne theta oscilácie pri 6Hz (θ-tACS) nad hornou frontálnou kôrou. Podmienky tACS boli podávané v oddelených sedeniach s použitím pseudo-randomizovaného a vyváženého krížového experimentálneho dizajnu. Účastníci absolvovali úlohy hodnotiace automatický a kontrolovaný vyhľadávací výkon v troch blokoch, v rámci každej relácie pred, počas a bezprostredne po stimulácii. Naše zistenia naznačujú, že θ-tACS výrazne uľahčilo vyhľadávanie úloh zahŕňajúcich automatické procesy (t.j. poskytovanie voľných a neobmedzených asociácií), ale narušilo kontrolované vyhľadávanie, ktoré vyžadovalo kognitívnu kontrolu (t.j. inhibíciu zvyčajných reakcií a prepínanie medzi sémantickými množinami). Naša štúdia poskytuje dôležitý experimentálny dôkaz naznačujúci, že neurónové theta oscilácie môžu tvoriť neurokognitívny mechanizmus pre sémantickú väzbu, a nie kognitívnu kontrolu. Došli sme k záveru, že oscilácie theta nad ľavým predorálnym kortexom môžu podporovať dobre zavedené sémantické spojenia, alebo posilniť ich metastabilnú aktiváciu, čo vedie k zvýšeniu plynulosti vyhľadávania. Tieto závery by mali byť podporené ďalším empirickým výskumom.

Kľúčové slová: sémantické vybavovanie, prefrontálny kortex, theta oscilácie, tACS

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1 Introduction

Pursuant to well recognised theory, fluctuating synchronous neural activity forming systematized brain processes defines the resultant behaviour and cognition. It has become increasingly evident that complex cognitive functions are linked to oscillatory phenomena within the brain, involving various frequencies and phase relations. (Muller, Chavane, Reynolds, & Sejnowski, 2018). Previous studies have demonstrated that semantic retrieval is associated with neuronal oscillations in theta band, suggesting their possible role in activation, binding, or the suppression of semantic representations, (Bastiaansen, Linden, Keurs, Dijkstra, & Hagoort. 2005)(Bastiaansen, Oostenveld, Jensen, & Hagoort, 2008). At the same time, the rhythm has been linked to the processes of executive control and working memory, which are putatively involved in controlled semantic retrieval that requires the inhibition of pre-potent but inappropriate associates or responses (Cavanagh, & Frank, 2014) (Maurer, Brem, Liechti, Maurizio, Michels, & Brandeis, 2014). The core functional role of theta oscillations in semantic retrieval remains unknown.

Transcranial alternating current stimulation (tACS) represents well-recognized approach to study the causal role of brain oscillations in cognition. The method is able to deliver weak alternating electric current to brain noninvasively and modulate internal neural oscillations in a desired way. By entraining neuronal oscillations in a specific frequency, their functional role in cognitive processing can be systematically examined. Importantly, growing evidence indicates that tACS can effectively modulate specific oscillatory signals and so substantially impact behavior (Tavakoli, & Yun, 2017). In our thesis, we will apply tACS to study theta rhythm during semantic memory retrieval.

In the first section, we will outline the existing knowledge concerning semantic memory retrieval and review available information regarding the role of prefrontal cortex (PFC) and theta oscillations in this function. Subsequently, we will describe the phenomenon of neural entrainment and outline the state of art pertaining to the use of transcranial alternating current stimulation. We will explain its suitability for application in empirical experiments studying functional roles of neural oscillatory activity. Following the reviewed literature, an empirical experiment is set to examine three hypotheses aiming to elucidate the functional role of theta oscillations in PFC in the process of semantic retrieval. Lastly, the experimental results are discussed.

2 Semantic retrieval

Great volume of general world knowledge is being accumulated during our lives. Semantic memory is a declarative memory system, responsible for the gathered information concerning objects and ideas along with lexical symbols and the concepts they represent (Battig, Tulving, & Donaldson, 1973). The stored information needs to be easily recoverable in diverse situations in order to be fully beneficial. It is encoded in a distributed, associative network. Moreover, the associations within representations are modulated by the history of their incidence, their similarity and type. Additionally, inhibitory process can be incorporated in the processing of comparable representations (Badre, & Wagner, 2002).

The stored semantic information can be accessed through the process of semantic retrieval, an important memory function operating with the meaning of objects and phenomena. It is a multi-faceted function that involves various cognitive processes, including: perception of a targeted word, online retention of the word in working memory, -recovery of the word's meaning, triggering associated mental representations and providing their conscious access (Konrad, & Engelien, 2008).

Language processing framework is generally divided into mechanisms of memory, unification and control (MUC scheme) (Hickok, & Small, 2015)(Hagoort, 2016). The memory element corresponds to (i) the language data stored and distributed in long-term memory and (ii) the processes required for the creation of representations. It is commonly linked with the activity and function of temporal cortex. The unification element corresponds to the binding of the retrieved data on a semantic, phonological and syntactic level, prioritizing the associations according to the frequency of previous experience. In the process of word retrieval, the left inferior frontal gyrus is critical in semantic binding enabling fluent verbal retrieval (Hagoort, 2016). Lastly, the control element corresponds to the chosen action of a selected response, once an appropriate semantic representation has been created after competing with other representations. Hence, cognitive control manages the intentions and guides adaptive responding. For example, it is in charge of speech permit/ inhibition according to the current context (taking turns in conversation or using appropriate language in bilingual speakers) (Ma, Li, & Guo, 2015) (Botvinick, Cohen, & Carter, 2004). The process is commonly linked with the dorsolateral prefrontal cortex area (Hagoort, 2005).

The mechanisms managing semantic retrieval is commonly divided into two distinct paths enabling the revival of meaning: automatic and controlled retrieval (Badre, & Wagner, 2002). Automatic semantic retrieval emerges when mental representations are strongly associated with the input signal (i.e., a stimulus word), which is sufficient to evoke related knowledge in a bottom-up manner, which is also called “stimulus-driven” retrieval. The automatic activation of knowledge is usually very rapid since it occurs without conscious regulation. The evoked responses are usually pre-potent, i.e., overlearned, habitual responses, and therefore may not be suitable or relevant for all situations or task demands. Contrarywise, controlled semantic retrieval is employed when the automatic stimulus-driven activation of knowledge is not sufficient for the task requirements or when the retrieval of some of the conceptual representations is affected by previous anticipation.

2.1 Neuroanatomic bases of semantic retrieval

The prefrontal cortex (PFC) is an organized system of cortical regions with distinct, but overlaying form of connectivity with practically every sensory cortical network and various subcortical systems. The interconnection creates infrastructure that enables merging of varied data required for intelligent behaviour characterised by its complexity (Miller, & Cohen, 2001). The location of PFC is convenient enough to enable the management of variety of neural processes. The PFC system also contains routes capable to communicate back to the functional systems, enabling the application of top-down process (Miller, 2007). The top-down influence supports the signals that are task-related, hence, prioritizing the relevant signals over the irrelevant ones despite their strength (Badre, & Wagner, 2002). The PFC area is developed the most in primates, species capable of adjustable and widely versatile range of behaviour. Neuroimaging and neuropsychology researches are delivering wide range of information regarding PFC properties and involved task conditions. PFC has been linked to various cognitive processes including cognitive control (Miller, & Cohen, 2001) along with memory control (Wagner, 2002) and represents an important element of the underlying network. Another crucial functional role of prefrontal cortex is its ability to integrate information. Particularly, the integration of data in the time domain (Perecman, 2018)(Friederici, & Singer, 2015). In order to implement temporal integration, the PFC must be capable to hold information in a highly accessible, “online” state and involve a selection mechanism to choose between rival options (Riès, Karzmark, Navarrete, Knight, & Dronkers, 2015)(Schnur et al., 2008). Prefrontal cortex is able to select and create unifications of information received from senses or memory (that are mostly stored in posterior brain networks) (Perecman, 2018). The evidence of the essential role of prefrontal cortex in the process of unification necessary for binding individual lexical and semantic information come from studies using neuroimaging methods (Strijkers et al., 2019).

Moreover, the left inferior frontal gyrus (LIFG), located in the prefrontal cortex is thought to be essential for different components of language processing: semantic processing, syntactic processing and phonological processing and the process of unification is realized concurrently on all of the components (Hagoort, 2005). Broca’s area is a brain region located in the left inferior frontal gyrus corresponding to the left Brodmann’s asreas 44 and 45. Anatomically, the region is bounded by the precentral and the inferior frontal sulcus and the anterior horizontal ramus of the Sylvian fissure (Devlin et al. 2003). It was firstly identified by Pierre Paul Brocka in 1861. Broca referred to the area as the “seat of speech” since a lesion in this area results in expressive aphasia (inability to produce language). It’s role in speech production has been widely acknowledged ever since, positioning the region within the main bases of language network. Various underlying components of language mechanism have been linked to Broca’s area: the sectioning of words to syllables (Indefrey, & Levelt 2004), verbal working memory (Chein, Fissell, Jacobs, & Fiez, 2002)(Chein, & Fiez, 2010) and the storage of information (Hickok, & Poeppel 2004).

The LIFG is critical for storage and retrieval of semantic information that has been once acquired and stored in semantic memory. This includes phonetic information, syntactic properties, as well as the conceptual information. Decades of research have demonstrated that LIFG is critically involved in the retrieval of words from semantic memory. It has been proposed that LIFG function in binding of lexical–semantic representations that are highly distributed over the cortex, within an appropriate context enables the emergence of verbal associations (Bastiaansen et al., 2005). The processes are embedded in regions that support also the components of memory and control that form the rest of the MUC scheme of language (Hagoort, 2016).

2.2 Neural oscillations

Rhythmic activity in the brain, observable on several temporal and spatial domains, emerges either by the communication among neurons or by the processes inside of an individual neuron. The depolarization and hyperpolarization of a membrane potential form fluctuations within individual neurons. Although, the recorded oscillations demonstrate the subthreshold fluctuations of the likelihood of firing, not the actual action potentials (Siettos, & Starke, 2016). The resonant frequencies that are able to trigger reaction vary among different neurons. The likelihood of firing is also dependent on the variable membrane state (Muller, Chavane, Reynolds, & Sejnowski, 2018). The subthreshold oscillatory activity can be also recorded from an ensemble of neurons representing the neuronal excitability of the cellular population. The current of neighbouring neurons and glia add up and affect the extracellular field states recorded from brain (Harris, Quiroga, Freeman, & Smith, 2016). Electrical dipoles generated by slow synaptic transmembrane current are involved the most, since they are not as fast as action potentials. The slower speed enables temporal summation. The recording of cortical field potentials is feasible thanks to the column alignment of pyramidal neurons. Dipoles annulate themselves when the neurons are not aligned spatially and make the spatial summation unfeasible. Overall, the comprehensive sources of field potentials has not been fully understood yet (Herreras, 2016).

In 1929 the inventor of electroencephalography (EEG), Hans Berger, recorded fluctuating electric brain activity for the very first time (Herrmann, Strüber, Helfrich, & Engel, 2016). Ever since, the fluctuations were recorded at number of frequencies on a scale from 0.05 to 500 Hz. Brainwaves are now conventionally divided into groups of different frequency bands: delta waves (1–4 Hz), theta waves (4–8 Hz), alpha waves (8–12 Hz), beta waves (13–30 Hz), gamma waves (30–70 Hz). The frequencies are derived from the frequency ranges measured by electroencephalography in humans. EEG enables the recording of field potentials by applying electrodes on scalp of a participant. The spatial clarity of the recorded signal can be affected by the diverse tissue and its conductivity filling the space between electrode and brain's source of activity. However, in more invasive recording methods, the local field potentials can be measured directly from the surface of brain or from the inside of the tissue. The most contribution is recorded from the sources that are located the closest to the electrodes and lessens with the rising distance (Cohen, 2017).

The curiosity of the functional role of the observed oscillations was present already during the Berger's research. Today, almost all of the observed cognitive processes have been associated with one, or with more than one of the established frequency bands. Neuronal binding, the function responsible for the unification of information stored in different brain networks necessary for the complex mechanism of perception, decision making and action taking, is one of the most crucial one (Fries, 2015). Brain oscillations are tightly coupled with overall brain state (e.g. awake or asleep) and moreover, with the management of neuronal outputs within sensory and cognitive processing. Great number of evidence validate the strong connection between cognitive activities and neural oscillations of various frequencies (Ward, 2003). Moreover, the causality has been demonstrated by brain stimulation methods modifying cognition by the induction of specific oscillatory bands (Herrmann, Strüber, Helfrich, & Engel, 2016), placing the neural phenomenon into a category of fundamental neurobiological processes that carry out neurocognitive computations, rather than being a mere by-product of neural spiking

2.2.1 Theta oscillations in semantic processing

The prefrontal cortex enables better decision making by overcoming routines. The neural firing patterns in the prefrontal cortex might hold the answer on ‘how’ is the process executed. In the context of semantic retrieval, the most essential oscillatory band is believed to be the theta band (von Stein & Sarnthein, 2000). The oscillating neuronal activity in the theta range (approximately 4–8 Hz in primates) is thought to realize an extensive functional integration (Solomon et al., 2017), facilitating neural communication between brain areas (cortical as well as subcortical) fundamental for language (Bastiaansen, Linden, Keurs, Dijkstra, & Hagoort, 2015) (Piai et al., 2016). Great number of evidence have demonstrated that semantic retrieval is associated with a modulation of theta oscillations and neural synchronization of various brain networks in theta band. Hence, it was suggested that theta oscillations may constitute an important neural computation enabling initiation, binding, or inhibition of lexical–semantic representations (Bastiaansen, Oostenveld, Jensen, & Hagoort, 2008) (Mellem, Friedman, & Medvedev, 2013).

However, working memory and the process of cognitive control has been also repeatedly linked to theta frequency range in the midfrontal cortex (Cavanagh, & Frank, 2014) (Maurer, Brem, Liechti, Maurizio, Michels, & Brandeis, 2014)(Cooper, Darriba, Karayanidis, & Barceló, 2016)(Albouy, Weiss, Baillet, & Zatorre, 2017), suggesting that theta synchronization may reflect a neurocognitive mechanism signaling high-order processing pertaining to the executive control function. The process is dominant especially in conditions where high processing requirements, novel stimuli or tasks, regulation of intervention, or error tracking are present (Cavanagh & Frank, 2014) (Jensen, & Tesche, 2002). In the context of semantic retrieval, theta synchronization has been involved in conditions with increased processing load (Mellem, Friedman, & Medvedev, 2013). These results could signify that theta oscillations are involved in executive control of retrieval (rather than binding of semantic representations).

2.2.2 Neural entrainment

In general, entrainment refers to the ability of distinct systems alignment. Neural entrainment refers to the brain's adaptive ability to temporally synchronize its endogenous oscillation activity of a neural network that is able to fluctuate within two states (membrane depolarization/ hyperpolarization) at a specific frequencies to an external periodic stimuli received from the environment (Herrmann, Rach, Neuling, & Struber, 2001). Hence, brain oscillations can be influenced by an external source by adjusting the properties of the internal oscillations. The internal oscillations are able to align their phases to the temporal form of the received rhythm by resetting the neural oscillations in sensory cortex areas (Morillon & Schroeder, 2015). The entrainment has been observed at various frequency bands. Additionally, the integration and management among neural networks firing at different frequency bands is possible due to the mechanism of cross-frequency coupling (CFC). CFC refers to the process where faster frequency amplitude can be altered by oscillations of a slower frequency (Aru et al., 2015). As a result, modifications within slower bands can lead to modifications in the entire system. The process of alignment can be either voluntary or involuntary and involves neural units that are able to generate autonomous periodic activity. It can be induced externally through any sensory modality. The periodic stimuli can be either visual, haptic, auditory or tactile. Nonetheless, entrainment to an auditory input has the most temporally accurate outcomes (Hove et al., 2013). Moreover, entrainment can be evoked artificially by the application of electromagnetic stimulation. The most established methods are tACS, otDCS rTMS. Our study focused on the modulation of theta oscillatory activity within the prefrontal neural networks. These networks are capable to generate oscillations independently, without the need of an external stimulation involvement. The independence differentiates this form of fluctuations from an inactive resonance phenomenon that, in order to be active, necessitates stimulation input.

Two main properties of the oscillating stimulator define the effectiveness of the entrainment of the targeted neural network. Firstly, the distance of the stimulating frequency from the targeted network. Secondly, it's the strength of the external frequency. The difference between the size of the affecting and the affected frequency determines the stimulation intensity necessary for a successful phase-locking of the network's oscillations to that of the stimulating oscillations. The network's oscillations are then modified to coincide that of the stimuli. The greater the frequency difference, the bigger is the necessary stimulation intensity to attain the same level of phase-locking and vice versa. Hence, an entrainment evoked by a mild intensity stimulation is more significant, when the frequencies of the two initial signals are similar. The level of entrainment lessens with the rising difference between them. If the difference between frequencies is big and at the same time, the intensity of the stimulation is weak, limited entrainment can occur. In this situation, the targeted network adjusts partially with resultant oscillations somewhere within the range defined by the boarders of the stimulating frequency and the initial network's frequency (Fröhlich, 2015). Hence, if we plot the strength of the stimuli with the frequency difference between the signals, the created function of level of entrainment will be delimited by an area of a triangular shape, also called Arnold tongue (Figure 1). The emerged parameter space defines the magnitude of entrainment of targeted network inversely proportional to the frequency difference and directly proportional to the strength of the stimulus.

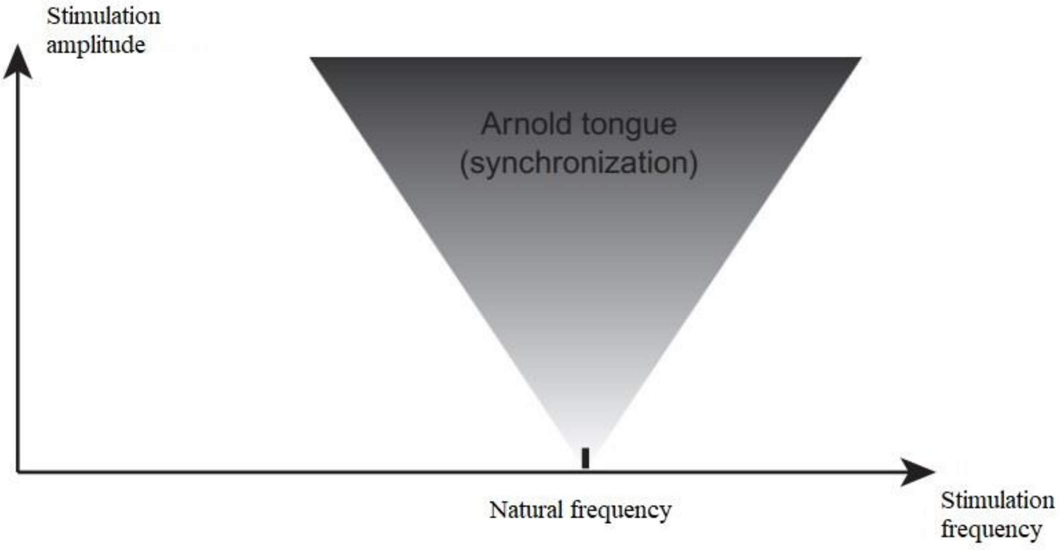

Figure 1: Arnold tongue visualizes the impact of involved parameters on neural entrainment. The resultant. Reduction in the parameter of stimulation amplitude reduces the domain of stimulation frequencies able to affect the entraining oscillator properly and vice versa (Fröhlich, 2015).

3 Transcranial electric stimulation

Treatments involving electric current applied to brain has been practiced at least as far back as in the times of Roman empire. Electric fish used as a cure for headache represents the first recorded practice of electric stimulation method (Kellaway, 1946). The methods have since been evolving, culminating throughout the last decade. The electric-fish approach has been substituted by advanced technologic tools capable of more nuanced targeting and results. Contemporary non-invasive methods based on electric stimulation aiming to modify brain activity are jointly known as transcranial electrical stimulation (tES) encompassing transcranial alternating current stimulation (tACS), transcranial direct current stimulation (tDCS) and transcranial random noise stimulation (tRNS) (Soekadar, Herring, & Mcgonigle, 2016)(Woods et al., 2016). They are inexpensive tools with uncomplicated administration, and number of potential purposes applicable in the field of neuroscience. These frequency modulators affect targeted neural tissues by invoking subthreshold polarization leading to resting membrane potential alternations. This kind of stimulation results in modifications of the neuronal firing rates or firing patterns. The current running between the electrodes pass the in-between brain structures to complete the electric circuit. The stimulation reversibly affects abilities associated with the brain area located in the cortex under and in-between the stimulation electrodes. The spatial accuracy of the stimulation is in the scope of centimeters. Nevertheless, the specificity can be induced by the application of smaller electrodes that can enhance the density of the current over the targeted area. All of the tES methods use the same hardware to deliver weak electric current to a scalp. The intensity of applied currents usually does not exceed 2 mA, but only a part penetrates the scalp and modulates the brain processes. The tES methods vary in their individual types of current waveforms, hence, the impact of their stimulation differs as well. The main parameters determining the results of tES stimulation are the applied frequency of the signal, which can be manipulated using multiple electrodes that are either „in-phase“, or „anti-phase“ and the density of the signal. Studies involving tES-evoked neuromodulation include observations of neurobiological changes as well as behavioural modulations. Number of studies have demonstrated concurrent and even outlasting modifications in neural activity of the brain, alternating the neural excitability. The effects generally persist awhile even after the stimulation is over. The aftereffects tend to last longer in settings with longer preceding stimulation session and vice versa (Antal, A., & Paulus, 2013)(Kasten, F. H., Dowsett, J., & Herrmann, 2016). Changes in cerebral blood circulation (Stagg et al., 2013), as well as in compression of neurotransmitters (Stagg et al., 2009) has been reported. In addition, studies have demonstrated behavioural modifications of cognitive processes. Therefore, tES belongs to highly recognised method in the context of neural alterations resulting in behavioural modifications. tES techniques have been well established in approaches modifying neural activity with the aim to clarify the connection of brain activity with its impact on behaviour, skill enhancement, or development of therapeutic tools. Variation of goals can be set for tES. Some of them can aim for behavioural changes, for example in sustained attention or speech production. On the other hand, goals can be set on neural changes, such as in cortical excitability. The target of our study are neural oscillations.

3.1 Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation is a type of neurostimulation that affects cortical excitability using direct electric current. This type of electric stimulation uses constant currents (i.e., the intensity or phase of current doesn’t change during the stimulation). Conventionally, one target electrode and one reference electrode are being placed on a participant’s head. This “bihemispherical“ set-up can be applied in order to produce two distinct stimulations into two parallel areas (e.g., to motor cortices – Goodwill, Teo, Morgan, Daly, & Kidgell, 2016). According to the direction of the stream, the stimulation can be either excitatory – generated by the application of the anodal current (flowing in the direction of the electrode) resulting in higher neural excitability, or inhibitory – generated by the application of the cathodal current (flowing in the direction of the brain) resulting in lower neural excitability. The anodal stimulation rises the likelihood of the emergence of action potentials by depolarizing the neurons. On the other hand, the cathodal stimulation lowers the probability of action potentials emergence by hyperpolarizing the neurons (Nitsche et al., 2008). Nevertheless, in practice, the effects cannot always be so well defined. The reaction to the polarisation is affected by various properties of the targeted cells. (Pelletier, & Cicchetti, 2014). Still, the simplification represents a well-established working hypothesis (Ehlis, Haeussinger. Gastel, Fallgatter, & Plewnia, 2016).

The method is frequently applied in researches studying the connections of behaviour and the underlying brain areas (Marini, Banaji, & Pascual-Leone, 2018)(Polanía, Nitsche, & Ruff, 2018). Furthermore, it has been proven to be a successful enhancement tool for various cognitive processes e.g. learning (Au, Karsten,Buschkuehl, & Jaeggi, 2017), motor learning

(Ciechanski, & Kirton, 2016), or attention (Vierheilig, Mühlberger, Polak, & Herrmann, 2016). tDCS has been also successfully used in the modulation in the lexical-semantic domain: stimulation over the Broca’s area lead to the enhancement of verbal fluency in healthy participants (Cattaneo, Pisoni, & Papagno, 2011), as well as in participants affected by Parkinson’s disease (Pereira et al., 2013) and stimulation over the LIFG lead to the decrement of semantic interference effect (Pisoni, Papagno, & Cattaneo, 2012).

The intricate moment linked to this method rises from the fact that each of the applied electrode have an active effect on the connected tissue. The results of the stimulation can be caused either by the anodal or cathodal electrode, or even by the mutual interaction thus, rising from the stimulation of the current flow running over the tissue between the two electrodes. Hence, the assignment of the causality can be hard to define. One of the established ways to reduce this issue is the application of smaller electrode over the region of interest along with bigger "return" electrode.

3.2 Transcranial Alternating Current Stimulation (tACS)

tACS and tDCS are analogous in number of aspects. Beside the utilization of the same hardware and comparable current strength, both of the stimulation techniques invoke the likelihood of action potentials occurrence just by amending the membrane potentials. Hence, they do not evoke them directly. Unlike tDCS, tACS employs current waveform that rhythmically shifts the direction of its flow. The current polarity periodically alternates from anodal to cathodal polarity and vice versa (Tavakoli, & Yun, 2017). The tACS waveform is traditionally administered as sinusoid. Other waveforms like sawtooth, rectangular, or boxcar are executable and being investigated (Dowsett, & Herrmann, 2016). During the sham condition the stimulation begins with an active stimulation. The stimulation than declines during ramping down phase until its completely turned off. Since the sham condition keeps all of the remaining parameters untouched, we are able of precise and rigorously controlled monitoring. (Schutter, 2016). Experimental and sham sessions can involve the same electrode placement and ramping period (in sham session, the current is turned off after the ramping up period), so the two conditions are hard to differentiate (Woods et al., 2016). In contrast to tDCS, the benefit of tACS is the ability to impact neural networks with almost unnoticeable current strength (Tavakoli, & Yun, 2017). tACS can be used to study the functional role of neural oscillations and moreover, it can be applied as a treatment for disorders where those oscillations are not working properly.

tRNS is a special instance of tACS. During this type of stimulation, the currents polarity alternations are random in a wide-ranging frequency band. tACS can be combined with direct current offset creating an oscillatory tDCS. The fusion called otDCS has the excitability-changing features of direct current stimulation (constant polarity) as well as the oscillatory features of tACS.

Transcranial magnetic stimulation (TMS) can evoke similar results of neural network changes as tACS (Rahnev, 2013). However, since tACS doesn’t involve magnetic pulses of high amplitudes, in contrast to TMS, it doesn’t evoke nausea, and especially side effects like muscle jerking that could significantly disrupt behavioural experiments involving participant’s activity e.g. keyboard responds.

3.2.1 tACS parameters

tACS stimulators typically contain current regulator that is able to respond to changes in surface resistance by fine-tuning the current strength. In studies using tACS in human participants the voltage usually doesn’t exceed the amount of 3 mA.

Number of parameters of the device’s set up have to be taken into consideration. The results can be influenced by the quantity of used electrodes, their polarity or the placement. The location of the electrodes can be set within the scalp area to target the underlying tissue, or, in case of reference electrodes, the location can be extracranial, e.g., placed on the arm. The placement of the electrodes specifies the impact of the current. Not only it determines the regions that will be affected the most, it also defines all the regions that will be involved at least on some level (Opitz et al., 2018). When the connectors are placed closer to each other, the strength of current field in the targeted tissues is smaller and vice versa. The current density is the most powerful along the rims of the electrodes (Alekseichuk et al., 2018).

The electrodes can vary in sizes thus can cover different amounts of scalp. Moreover, at an even current strength, the current density can be further modified by the size. Bigger electrodes have lesser current density and are supposedly less focal (Opitz et al., 2016). A coat of a conductive electrode paste is usually spread on each of the electrodes before attaching them to a scalp. The paste between the electrode and the targeted surface serves as an adhesive as well as it eliminates resistance.

In protocols using only two electrodes, the waveforms are in anti-phase. That means, that there is always one electrode with a positive current and one with negative current involved. In setups using more electrodes, the waveforms can be set to be in phase with each other. Thus, this approach allows us to apply either positive or negative current concurrently among a pair of electrodes.

3.2.2 Assumed mechanism of tACS effect

The process of polarity switching in tACS method supposedly results in fluctuating polarisations of neural membrane, changes in action potentials and its firing rate. Hence, it momentarily disrupts and influences the pattern of communication between neurons (Fröhlich & McCormick, 2010). The stimulation does not lead to an increase of net polarisation. Hence, in contrast to tDCS, the outcomes are not caused by changes in the level of excitability. The effects of tACS are most commonly ascribed to neuronal entrainment and phase alignment. During this process, the oscillations of the endogenous neural network are thought to align to the oscillations of the stimuli frequency (Schmidt, Iyengar, Foulser, Boyle, & Fröhlich, 2014) (Tavakoli, & Yun, 2017). Supposedly, the stimuli can thus modulate the ongoing activity of brain and cortex-related functions (Thut, Schyns, & Gross, 2011). The frequencies of the stimuli have its limitations within the restricted domain of functional brain frequencies. The stimuli frequencies outside of the domain have little or no effect.

3.2.3 Neural entrainment evoked by tACS: evidence

tACS is well known for its ability to successfully entrain neural oscillations and to link functionally connected neural networks (Helfrich et al., 2014)(Helfrich, Schneider, Rach, Trautmann-Lengsfeld, Engel, & Herrmann, 2014)(Witkowski et al., 2016). In silico, in vitro, as well as in vivo experiments have been conducted examining neural entrainment evoked by the electric fields of alternating current. Optogenetic method enabled the in vivo study of neocortical slices in mouse allowing the observation of connections between spike timing and the stimulating signal. It provided evidence of the relationship between the strength and frequency of the stimulator and the resultant neural activity. (Schmidt et al., 2014). Similar results of entrainment were reported in a study examining the effect in anesthetised rats (Ozen et al., 2010). Nevertheless, the effect was not generalised to rats that are awaken. The study examined the entrainment only on a cellular level, the supposed behavioural outcomes that are thought to arise from the interference of intrinsic processing were not confirmed in this case. Computational model of the Arnold tongue in the context of neural entrainment was supported by measurements of ferret's brains under anaesthesia (Ali et al., 2013). Overall, the mentioned studies represent empirical evidence of neural entrainment of brain activity evoked by externally applied weak alternating current stimulation. Moreover, they demonstrate the dependence of the final result on the interaction of the strength and the frequency of the stimuli as well as on the internal network dynamics.

Furthermore, neuroplastic modulations have been observed during the stimulation aftereffects (Vossen, Gross, & Thut, 2015). In humans, EEG and MEG are used to study this phenomenon non-invasively. Early studies researching neural entrainment in human participants focused on photic driving and visual entrainment (Halbleib et al., 2012; Herrmann, 2001). The results revealed a tight connection between the strength of the entrainment and the frequency difference between the visual stimulus and the visual cortex. The most significant entrainment followed stimulation that was the closest to the Eigenfrequency of the network. Studying the entrainment resulting from tACS stimulation is more technically demanding. The main obstacle represents the electromagnetic artefact emerging from the electric field and interrupting the MEG or EEG recordings. The artefact of the stimulating field has the same frequency features as the observed network. Since the ability of complete removal of the artefact is still a controversial question (Noury, Hipp, & Siegel, 2016), the possibility of incorrect data interpretation is present. Nevertheless, the left parietal area EEG theta band enhancement has been already demonstrated in a tACS study (Pahor 2014). MEG, on the other hand, is usually more resistant to the interruptions of artefacts (Witkowski et al., 2016). The phase unity between tACS and the targeted occipital network and its coherence with the initial state of inherent neural activity was demonstrated by a study measuring entrainment difference of participants undergoing the procedure with opened versus with closed eyes (Ruhnau, Neuling, et al., 2016). Amplitude-modulation of tACS represents another possible technique for artefact elimination. Theta band entrainment together with working memory decay evoked by amplitude-modulated tACS at separate theta oscillations has been studied and successfully demonstrated (Chander et al., 2016).

Lastly, functional magnetic resonance imaging (fMRI) has been applied to study the phenomenon as well. Reduced metabolic activity following visual stimulus has been showed in α-tACS study. The blood oxygenation level dependent (BOLD) has been linked to α-oscillations with a negative correlation before (Vosskuhl, Huster, & Herrmann, 2016), hence, the activity observed with fMRI offers an additional indirect proof of the tACS ability of neural entrainment. Importantly, a recent study by Violante et al. (2017) demonstrated that synchronized theta oscillations delivered into the brain using tACS can increase functional connectivity between the stimulation sites and thus can modulate higher-level cognitive processing.

Overall, number of fundamental and human neuroscience studies researching the process of neural entrainment offer empirical evidence for tACS functionality. Studying human participants is in this case inevitably more indirect and often more prone to electromagnetic deformations leading to possible misrepresentations. As a result, there are only couple of studies observing neural processes by which tACS alters human behaviour. Studying the behavioural alterations as such is more frequent.

3.2.4 Behavioural changes induced by tACS

A variety of researches engaging numerous stimulation frameworks, tasks and variables demonstrate frequency based, tACS-evoked behavioural changes in human participants.

Theta stimulation over the left parietal brain area lead to the enhancement of working memory immediately after the stimulation (Jaušovec, & Jaušovec, 2014)(Pahor, & Jaušovec, 2018) as well as to the enhancement of short term memory (Vosskuhl, Huster, & Herrmann, 2015) and to the improvement of fluid intelligence score (Pahor, & Jaušovec, 2014). Moreover, theta band induction over the midfrontal scalp region resulted in the improvement of cognitive control performance (Driel, Sligte, Linders, Elport, & Cohen, 2015). Induction of theta over the frontal cortex improved performance of reversal learning (Wischnewski, M., Zerr, P., & Schutter, 2016).

Alpha induction corresponding to 10 Hz stimulation over the left primary motor cortex resulted in the enhancement of movement, mainly in functions involving internal pacing (Wach et al., 2013). Moreover, the same type of stimulation over the right frontal and parietal cortex resulted in better performance of sustained attention tasks (Schouwenburg, Zanto, &

Gazzaley, 2017). Stimulation inducing individual alpha band over the midfrontal scalp region lead to an improvement of performance of mental rotation task (Kasten, F. H., & Herrmann, 2017). Lastly, alpha stimulation at 10 Hz over the frontal cortex increased participants score reached in test measuring creative thinking (Lustenberger, Boyle, Foulser, Mellin, & Fröhlich, 2015).

Stimulation at 20 Hz (i.e., beta oscillations) over the left primary motor cortex resulted in slower movement right after the stimulation (Wach et al., 2013). Another study applying the same frequency (20 Hz) over the same brain region (the left primary motor cortex) resulted in the improvement of motor learning (Pollok, Boysen, & Krause, 2015).

Study observing effects of gamma induction on speech perception using stimulation at 40 Hz over the bilateral auditory cortex demonstrated variance in reaction of different age groups. Younger adult participants responded with disrupted phoneme categorization, whereas the performance of older adults improved (Rufener, K. S., Oechslin, M. S., Zaehle, T., & Meyer, 2016). Enhancement of visuo-motor coordination was demonstrated by gamma stimulation at 80 Hz applied over the motor cortex (Santarnecchi, E., Biasella, A., Tatti, E., Rossi, A., Prattichizzo, D., & Rossi, 2017).

An extensive evidence proves the ability of tACS to modulate cognition. However, to our knowledge, there has been no published studies using tACS in the context of semantic retrieval, the subject of our thesis.

4 Methods

4.1 Research problem

Taken together, semantic retrieval is a complex function involving a number of distinct computations. Cognitive control, memory and semantic coupling are all being involved. In the introduction, we have argued that at least some of them are supported by the left prefrontal cortex. Theta synchronization has an evident bond with semantic retrieval. Nevertheless, the functional role of theta oscillations in the process of semantic retrieval remains unknown. We approached this issue using tACS, which represents a suitable tool for a frequency-specific modulation of brain oscillatory activity, enabling a systematic study of the causal role of brain theta oscillations in semantic retrieval.

> We hypothesized that we will be able to observe an enhancement in the associative processes if neuronal theta oscillations are functionally involved in connecting (i.e., binding) of lexical-semantic representations. Contrariwise, we would find enhancement solely in dissociative processes if theta synchronization constitutes a neuronal computation implementing cognitive control activity. Lastly, if theta oscillations moderate the shift between the stimulus-driven processing and the top-down control, we expected that tACS would modulate both, the associative and the dissociative processes, however, in the opposite direction.

4.2 Participants

Total number of 27 healthy adults (10 male; age 23 years) participated in the study in exchange of financial compensation of 25 euros. Participants were right-handed (mean score of Edinburgh Handedness Inventory was 50 or higher; Veale, 2014) and native Slovak speakers. They have not experienced any psychiatric issues nor neurologic disorders in the past and were not taking any medication throughout the duration of the experiment. The participants signed written informed consent at the beginning of the first session. The experiment was approved by the local research ethics committee and conducted in accordance with the Declaration of Helsinki. All of the participants participated in three experimental sessions overall, since our experiment was part of a larger study. Participants underwent three different conditions of stimulation (tACS, tDCS and sham) in balanced order and distributed in intervals lasting at least 6 to eliminate any potential carry-over effects. For the purpose of this thesis, only two of those sessions are evaluated (tACS and sham). Hence, the interval between the reviewed sessions (tACS and sham) was from 6 to 13 days.

4.2.1 Transcranial alternating current stimulation

The tACS was applied by a certified micro-processor-controlled current isolated stimulator (NeuroConn DC-STIMULATOR PLUS made by neuroCare Group). Conductible rubber electrodes were fixed by an EEG cap of appropriate size after head measurements were taken for each participant individually. Conductive electrode gel (Ten20, Waver and Company) was applied on the electrodes to keep them attached to the scalp. All of the participants underwent three types of tES conditions across three experimental sessions using pseudo-randomized cross-over design (3×3 orthogonal Latin square). Sinusoidal stimulation at the frequency of 6Hz with no direct current offset and amplitude of 2 mA (peak to peak) was used for the active tACS condition. The anodal electrode was 3x3 cm^2 (generating the peak current density of 0.11 mA/cm^2) in between F5, F7, FT7, and FC5 electrode sites of the 10-10 international standard system of EEG electrode placement. The return electrode was 5x7 cm^2 (generating the peak current density of 0,03 mA/cm^2) placed between the FP2 and F8 electrode sites. The phase difference among the two electrodes was 180° (see Figure 2 for more details). The stimulation started with 15 seconds of ramp-up period followed by 8 minutes of active stimulation before the initiation of the test. The stimulation continued throughout the duration of the test (10 – 12 minutes depending on the individual performance) and finished with a 15 seconds of ramp-down sequence (See Figure 3). For both of the conditions (active and sham), the electrodes were placed at the very same position. Yet, the stimulation during the sham condition lasted only for 30 seconds. Immediately after the stimulation ramped up, participants reported adverse stimulation effects using Likert scales (i.e., itching, tingling, burning, and pain) ranging from "not at all" (0) to "very much" (4). An ANOVA model revealed no statistically significant difference between the tACS conditions, $F(1,10.1) = 2.28$, $p = .145$. Also, after every stimulation, the participants were asked to rate the perceived strength of the stimulation using a Likert scale ranging from "no intensity" (0) to "high intensity" (10). The self-reported difference in stimulation intensity between the active and the sham stimulation was not statistically significant, $F(1,8.3) = 2.24$, $p = .148$, as assessed by an ANOVA analysis. This model confirmed that the sham stimulation approach was successful in blinding the participants. The mean impedance through the stimulation was 8.9 ± 5.2 kΩ.

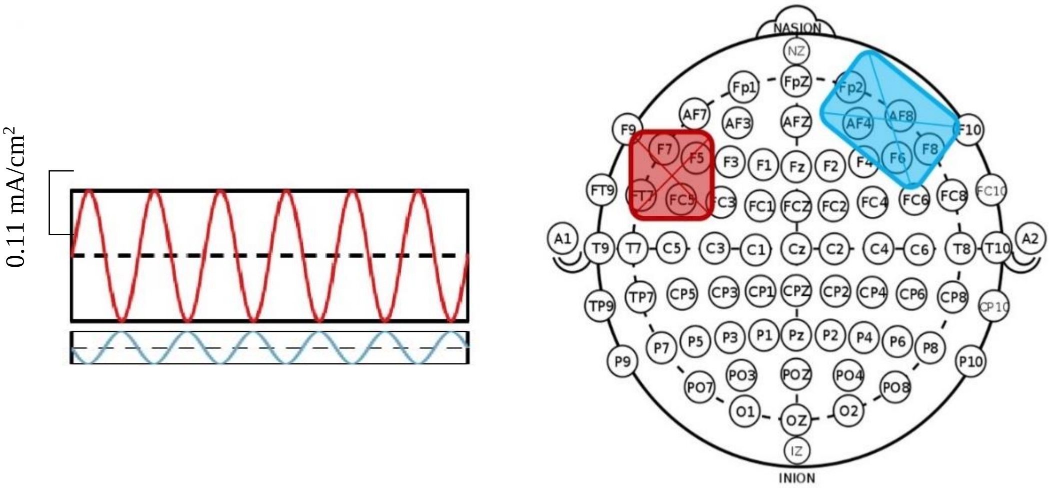

Figure 2. Placement of tACS electrodes. During the active stimulation, tACS at 6Hz was delivered throughout the duration of the stimulation. For both of the conditions (active and sham) the main electrode of 3x3 cm^2 (red square) was placed over the F7 and F3 and the return electrode of 5x7 cm^2 (blue rectangle) was placed over the Fp2 and F8 with relative phase of 180°. Note the sinus signals indicate current densities of the small target electrode (red; 0.11mA/cm2) and large reference electrode (blue; 0.03 mA/cm2).

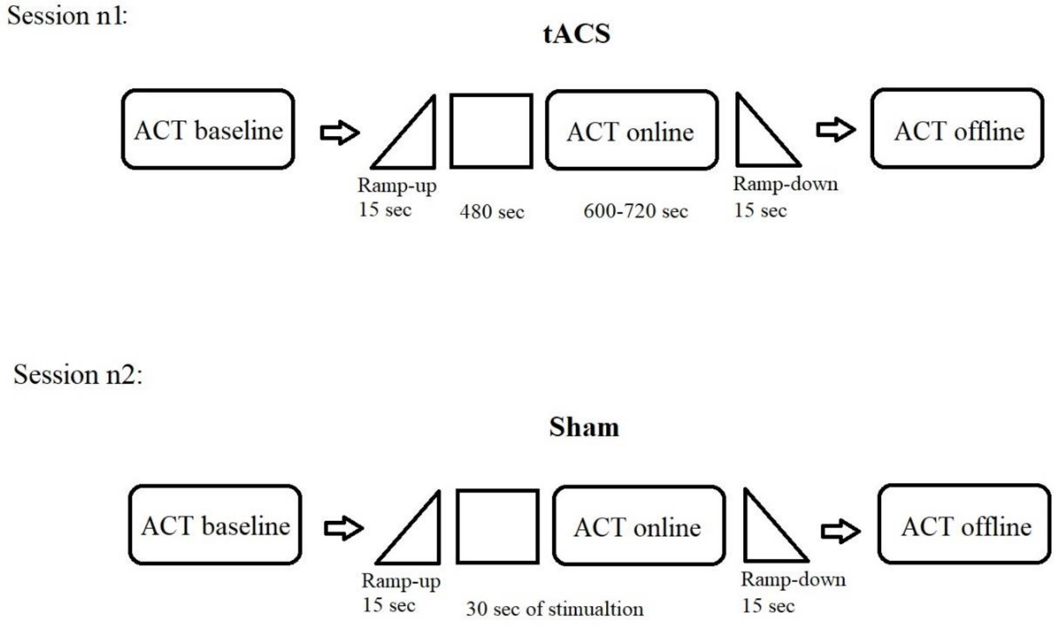

Figure 3. Timeline of the experimental procedure. Each session consisted of baseline test before stimulation (baseline block), which was followed by a test during stimulation (online block) and a post-stimulation test (offline block). Both tACS and sham condition involved ramp-up and ramp-down period, however, the active stimulation during sham condition was turned off after the first 30 seconds. The order of the sessions was randomly assigned and evenly distributed

4.2.2 Lexical semantic processing

A modification of Associative chain test (ACT; Marko, Michalko, & Riečanský, 2018) was used to evaluate lexical-semantic processing. The participants' role was to produce and type-in words following predefined rules of various types using computer keyboard. The whole test was divided into two task blocks. In the first block, participants produced chains of worlds following three distinct conditions. The test starts with a *fluency condition* assessment, asking participants to name as many words related to a predefined category as possible category (e.g., *"Vehicles: Train, Bus, Car…"*). Participants were asked to produce a list of as many words as possible through the duration of 60s. In the *associate chain condition*, the task was to create word chain so that each word was semantically associated with the preceding one (e.g., *"Flower– Pollen – Allergy – Sneeze…"*). Any unrelated word was evaluated as an error. The task lasted until the participant produced chain of 20 words

(~1 min). As in other conditions, participants were required to maintain fluent responding. In the *dissociate chain condition*, the task was to generate a word chain so that each word was not semantically associated with the preceding one (e.g., *"Frog – Health – Sand – Future…"*). Any related word was evaluated as an error by independent rater. Again, the task lasted until a chain of 20 words was completed (~2 min). In the second block, the conditions were randomized and alternating after each response: the participants were asked to switch between the *associate*, *dissociate* task and production of *random* words (random word-production condition was indicated by "*****" string of symbols). Each word-production condition was repeated 20 times (60 responses were obtained from each individual), which was divided into 2 sections with a short break in between. Each word presented in the associative task was presented also in dissociative task.

Therefore, the overall ACT assessment focused on two independent variables (factors) consisting of two conditions each: the *response type*, which can be either associative or dissociative, and the *sequence type*, which can be either fixed or alternating. Throughout all of the tasks, participants were asked to preserve fluent word flow while avoiding the repetition of already stated words. The grammatical correctness of the words was not taken into consideration in the response evaluation. At the beginning of each condition and trial, participants received a word or category (i.e., starting stimulus). The generated word was randomly selected from a list of words, which were referred to as *ACT block* (three word lists were counter-balanced across the experimental conditions). Response time was evaluated for every response word. RT measurement represented the necessary time for a response production before the initiation of keypress during responding.

Participants practiced the individual tasks during training exercises that preceded each of the ACT sequence in every session. Participants filled three tests during each session-before stimulation, during the stimulation and after the stimulation. During the online condition the ACT was initiated following the first 5 min of stimulation. The stimulation persisted throughout the whole duration of the ACT and ramped down only after the ACT was completed.

4.2.3 Control affective rates

The emotional condition of each participant was evaluated at the very beginning of each session. Participants judged their actual state with 16 Likert scales. The answering sheet consisted of 5 options ranging from 0 - “None” to 5 - “Very much”. The scales were designed to measure segments of 3 different categories: fatigue, frustration, and motivation (all scales yield high consistency, ICC > .800). Importantly, there were no statistically significant differences in the three scores across the experimental sessions, F(1,23) < 1.33, p > .244, as indicated by a repeated measures ANOVA.

4.2.4 Data processing and analysis

R language and environment (R Core Team, 2018) were used to analyze the acquired data (RStudio Team, 2018). Firstly, the RTs were examined and any response with a RT value bigger than 20s was removed from our data set (less than 0.05%). Afterwards, four independent raters checked the responses for inappropriate content (i.e., unrelated words inserted in the associative chains). Hence, the raters judged the correctness of the responses of the cleaned data. Every response was evaluated to be either correct or incorrect. The evaluation provided by the raters was then compared and every response judged incorrect by more than 1 rater was eliminated from the data set prior data processing. (less than 5% of responses were removed this way). Subsequently, the remaining responses were winsorizated because of several outlying observations (scores exceeding ± 1.5 interquartile range). A 10% quantile two-sided trimming individually for every participant, ACT block and type of stimulation was applied. The semantic variables were modeled as function of testing block (baseline, online, offline), tACS (active/ sham), and their interaction. Subsequently, linear mixed-effect models (LMEM) were computed to examine RTs and thereby to assess the tACS effects. Since following different rules in each of the tasks of ACT involves distinct neurocognitive processes, for every type of the tasks an individual LMEM was calculated (the “basic” measure). LMEMs were calculated to evaluate the scores nested within participant by approximating a random intercept for every participant (unstructured covariance matrix). LMEMs were fitted by the application of restricted maximum likelihood (REML). The Wald’s statistic and Satterthwaite approximation of degrees of freedom was used to assess the Post-hoc pairwise comparisons among different stimulations. The Tukey's honest significance test was applied to adjust the resultant *p*-values.

5 Results

Firstly, reaction times for each ACT condition was examined within the baseline testing block (before tACS treatment) sessions in order to measure the difference between *associative* and *dissociative* type of tasks and the difference between *fixed* and *alternating* type of tasks without any tACS-induced influence. Significant main effects were found with a LMEM analyses for both the *Response type*, $\chi2(1) = 1358.20$, $p < .001$ and the *Sequence type*, $\chi2(1) = 130.0$, $p < .001$ and also in their interaction $\chi2(1) = 26.11$, $p < .001$. The right panel in Figure 4 displays the significantly higher RT of the dissociative condition in contrast to associative condition. Note that the alternating condition increased response latencies in both associate and dissociate response type, but this was significant only for dissociate response type. Also, the *Category* retrieval condition was associated with lowest RT.

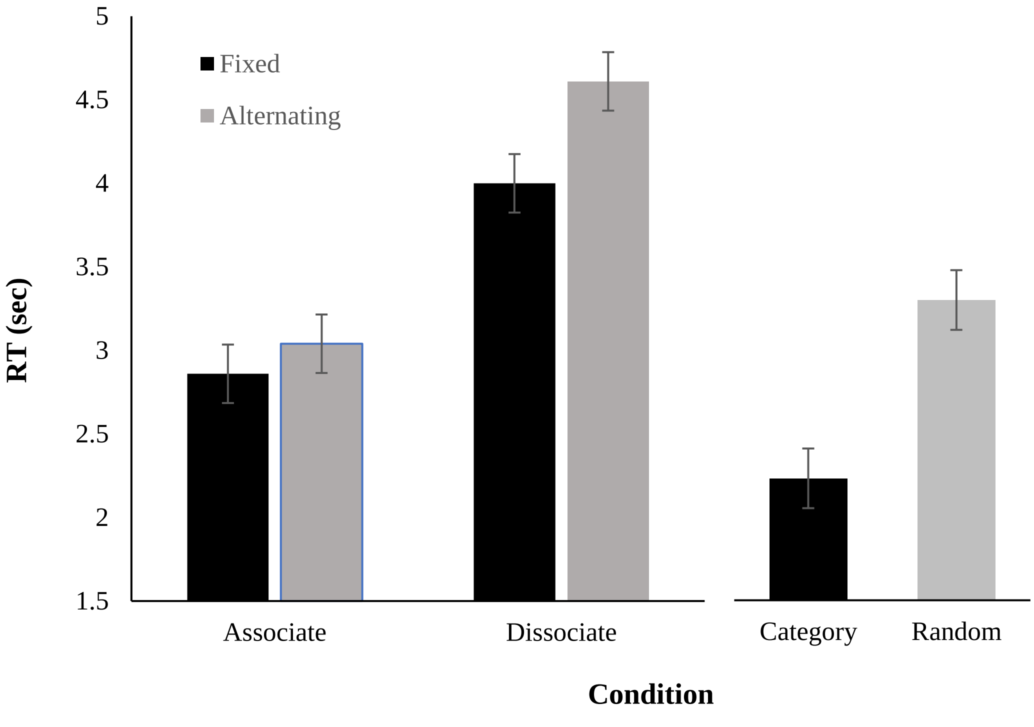

Figure 4. Mean RT (±1SE) for each ACT condition (Associative-fixed, Associative-alternating, Dissociative-fixed, Dissociative-alternating, Category – fixed, Random – alternating). The figure contains only data collected in the baseline assessment block (pre-tACS).

Secondly, the ACT measures were used to examine the effects of tACS on response times by applying the Linear Mixed-effect Models. The fixed effect of interest was the interaction between tACS (sham vs tACS) and assessment Block (baseline, online, offline). A LMEM for *associative* retrieval yielded a significant Block by tACS interaction, *F*(2, 5924) = 8.48, p < .001. A post hoc analysis revealed that the effect of tACS was statistically significant only during the offline block (see Figure 5). The LMEM for the *dissociative* retrieval yielded a significant Block by tACS interaction *F*(5723) = 17.82, *p* <.001. A post hoc analysis revealed that the effect of tACS was statistically significant both during the online block as well as during the offline block (see Figure 6). The LMEM for *category* retrieval yielded *F*(2, 2419) = 0.62, *p* = .540, showing no significant effects: neither in the online, nor in the offline assessment block (see Figure 7). Lastly, the LMEM for the *random* retrieval condition yielded a significant Block by tACS interaction *F*(2, 2946) = 9.84, *p* <.001. The tACS effect was statistically significant only during the offline block (see Figure 8).

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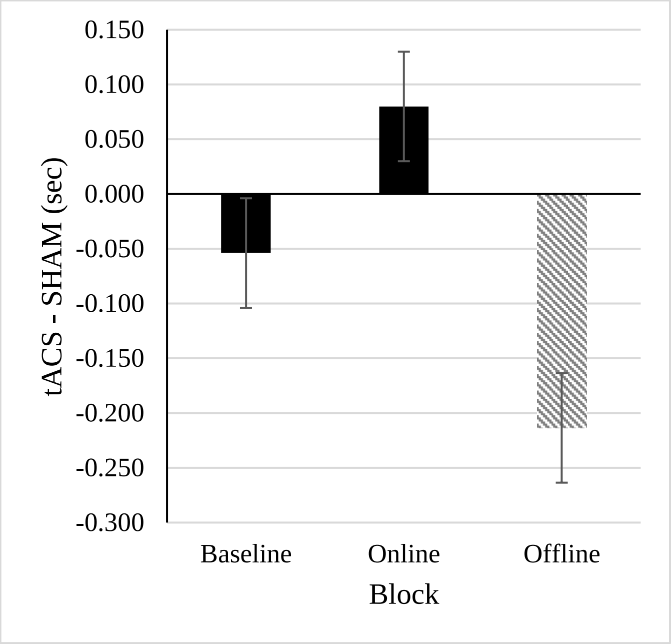

Figure 5. RTs of associative condition. The RTs improved significantly during the offline block. The RTs in online block did not change significantly. Notes: values below (above) zero indicate shorter (longer) RTs in active tACS session as compared to the sham condition; stripped columns indicate statistically significant contrast, *p* < 0.05 (Tukey HSD correction applied).

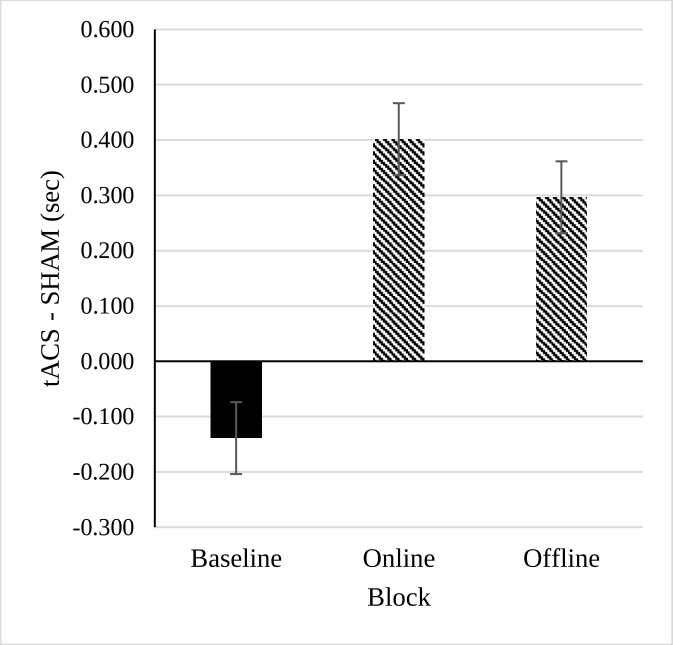

Figure 6. RTs of dissociative condition. The RTs were significantly longer both during the online and offline block (impaired performance). Notes: values below (above) zero indicate shorter (longer) RTs in active tACS session as compared to the sham condition; stripped columns indicate statistically significant contrast, $p < 0.05$ (Tukey HSD correction applied).

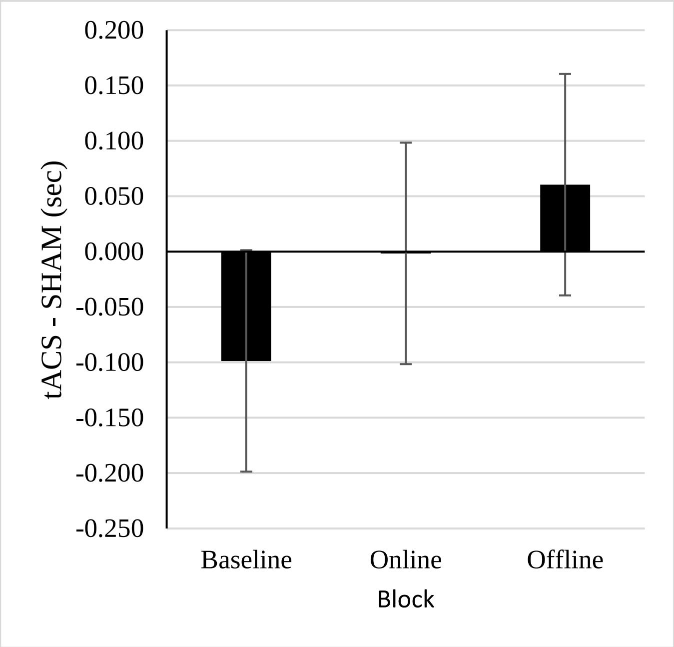

Figure 7. The RTs during the category tasks did not change significantly neither during the online, nor during the offline block. Notes: values below (above) zero indicate shorter (longer) RTs in active tACS session as compared to the sham condition; stripped columns indicate statistically significant contrast, $p < 0.05$ (Tukey HSD correction applied).

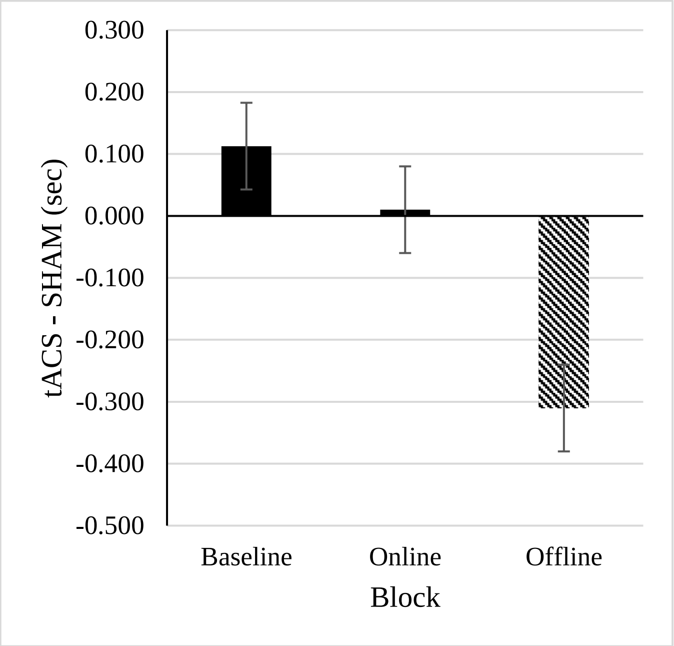

Figure 8. The RTs of random condition changed significantly only during the offline block. The online block did not change significantly. The tACS improved the performance by shortening the RTs in the offline block. Notes: values below (above) zero indicate shorter (longer) RTs in active tACS session as compared to the sham condition; stripped columns indicate statistically significant contrast, $p < 0.05$ (Tukey HSD correction applied).

6 Discussion

Previous research has demonstrated an important involvement of theta oscillatory activity in semantic retrieval. However, as this function incorporates multiple distinct processes, the precise role of theta oscillations in semantic memory retrieval was unclear. The goal of the present experiment was to shed light into the functional role of theta oscillations in semantic retrieval in healthy participants. We approached this goal using 6Hz tACS in order to support theta synchronization in the left prefrontal cortex, which has repeatedly shown theta-engagement in semantic tasks. Moreover, we used a complex paradigm enabling for a fine-grained evaluation of distinct processes, i.e., automatic and controlled, which are both involved in semantic memory retrieval. These processes were assessed before, during, and immediately after θ-tACS treatment (active or sham).

Following the previous research, we predicted that θ-tACS will significantly affect semantic retrieval performance, which was confirmed by our experimental evidence. Moreover, we predicted that θ-tACS will modulate semantic memory retrieval depending on the relative involvement of automatic versus controlled processing, as assessed by associative and dissociative tasks, respectively. In particular, we expected that, if theta plays a role in semantic activation and binding, we would see an improvement in associative measures. On the other hand, if theta oscillations implement cognitive control, we expected an improvement in dissociative measures. This processing-dependent hypothesis was also confirmed, indicating that theta oscillations presumably play a role in binding of lexical-semantic representations. This involvement is discussed in detail below.

6.1 Cognitive differences among the retrieval measures

Firstly, in order to compare the performance among the distinct retrieval tasks prior to any intervention, we evaluated the average RTs in the baseline assessment block (see Figure 4). The baseline data showed a pattern that is consistent with the previous evidence using similar assessment (Marko, Michalko, & Riečanský, 2018), supporting the notion that associative and dissociative retrieval tasks engage distinct cognitive processes. In particular, the longer response latencies observed in dissociative tasks strongly imply for an additional processing demands. In line with the previous accounts, we suggest that such demands pertain to elevated inhibitory processing: in order to produce dissociations, participants need to inhibit habitually evoked representations and responses in response to word cues. Those executive processing steps aiming to avoid incorrect, although strongly suggestive responses require time, leading to longer RTs in contrast to the associative tasks, where inhibitory steps are not involved. Neuroimaging studies observing the brain networks necessary for the initiation and the inhibition of response support this account, showing that the neural networks involved in those processes differ: although both associative and dissociative retrieval engages left inferior frontal gyrus and posterior language networks that are responsible for storing and retrieving of lexical-semantic representations (Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997), only dissociative tasks recruit additional prefrontal resources, especially in the left dorsolateral prefrontal cortex (Allen et al., 2008)(Collette et al., 2001). Importantly, this region has been repeatedly associated with working memory and executive attention (Barbey, Koenigs, & Grafman, 2013)(Kondo, Osaka, & Osaka, 2004), which further supports our conclusion that dissociative measures involve increased executive demands. Alternatively, the dissociative response latencies could be also longer because participants were not able to utilize the stimulus cues that evoke appropriate responses and guide semantic search. Therefore, the dissociative performance may be more difficult not only due to increased inhibitory demands but also due to increased demands associated with response initiation. Although the difference between associative retrieval and retrieving random words (~250 ms) clearly supports that semantic cue can facilitate the performance, this explanation cannot fully account for the RT differences between associative and dissociative measures (which is approximately 1500 ms). The removal of the cue in the retrieval of random words did not lead to substantial increase in the RT and the latencies in the dissociative condition were substantially higher compared to the latencies from random retrieval condition. The production of random words and the production of dissociations share the necessity to choose semantic cluster without the guiding cue. However, the inhibition process is not involved in the case of the random task. Based on these results, we propose, that the core process that drives the difference between dissociative and associative performance is inhibition, rather than the missing semantic cue.

Moreover, the latencies prolonged in every type of tasks of alternating sequence. The change in RT might be caused by the addition of switching processing cost, which is necessary for the switching between different task rules or conditions. This type of operation indicates the involvement of executive attention as well. Interestingly, the inhibition cost was the most significant in alternating sequence conditions and the switching cost in the tasks involving the production of dissociations, suggesting that the underlying mechanisms of those two operations might share the same executive resources at least on some level. This notion is in line with the neuroimaging studies showing that executive inhibition and executive switching engage engaging prefrontal networks (Dove, Pollmann, Schubert, Wiggins, & Von Cramon, 2000)(Ravizza & Carter, 2008).

6.2 Effects of tACS on retrieval measures

In line with our expectations, the results showed different effects of tACS on controlled (production of dissociations) versus automatic (production of associations) processing, supporting our conclusions that these tasks involve at least partially distinct cognitive operations or forms of semantic processing.

With regard to associative performance, the application of 6Hz tACS improved the performance assessed immediately after the stimulation offset (see Figure 5). Based on these findings we suggest that theta oscillations may constitute a neurocognitive mechanism that supports or implements the production of associative responses, presumably by binding of semantic features. Such a mechanism should result in enhanced retrieval fluency, which corresponds to our data. This account is in line with the findings and conceptualization from the study made by Bastiaansen and colleagues (2005).

In case of the dissociative retrieval task, the tACS impaired the performance. The RT was prolonged significantly in both online and offline assessment. Based on this evidence, we can conclude, that the induction of theta oscillations significantly disrupts the inhibition of automatic responses and switching to semantically unrelated semantic clusters. This finding is in line with the previous research showing that theta oscillations are involved in semantic binding, i.e., binding and coupling of semantic representations (Bastiaansen, 2005). Increased semantic binding could impose an additional inhibitory demand, manifesting in prolonged dissociative latencies. Interestingly, the effects of the theta oscillation induction during associative and dissociative retrieval were in the opposite direction. Since the inhibitory process aims to suppress the automatic initiation, the strengthening of the automatic initiation itself should represent a difficulty during dissociative tasks. This indicates that tACS could induce high inhibitory processing demands due to increased semantic activation and binding, thus not affecting cognitive control (i.e., inhibition) directly.

The results of the production of random responses resemble the results of the production of associations (see Figure 5 and 8) (the performance improved significantly during the session after stimulation). At the same time, the shared direction of the effect within random and associative retrieval indicates, that the retrieval processes may share, at least partially, the same underlaying mechanisms. tACS could facilitate the semantic activation improving retrieval in both, the production of associations as well as the production of random words.

Lastly, contrary to our expectations, the *category* retrieval was not significantly affected by tACS, although it clearly involves associative semantic processing. However, continuous production of words belonging to the same category can rapidly exploit the relevant semantic clusters encoded in the memory. Therefore, we propose that, as category instances are getting depleted, additional support from executive system becomes increasingly more required, contaminating the early automatic processing demands with later controlled processing demands (i.e., early and later stages of task competition may engage different profile of cognitive processes). The production of certain number of words within one semantic cluster might be improved by the theta induction, however, in the case of longer chains, the semantic cluster may not be rich enough to contain requested number of words. As a result, participant needs to engage the executive processes and effortful strategies in order to search for additional semantic information. Since associative and dissociative measures were differentially affected by tACS, this could result in a non-significant net stimulation effect (the positive tACS effect on associative processing was canceled out by the negative tACS effect on dissociative processing). Future research is required to confirm or refute this hypothesis by adjusting the length of the requested number of words.

Overall, our findings support an important role of theta synchronization during semantic retrieval, which was demonstrated by the significant changes in semantic memory retrieval due to a tACS theta-modulation. The improved associative performance is largely underpinned by stimulus-driven (primed by cue) processing involving semantic activation and activation spreading that emerges unconsciously. When the priming word triggers its semantic representation encoded in memory and tightly associated semantic connections become active. Since the relationship between two semantic associations influences the ease and extent of the automatic retrieval (Badre, & Wagner, 2002), we propose that the outcomes of theta synchronization could be caused by changes in the semantic activation. The binding of distributed lexical-semantic representations has already been the proposed a candidate for the functional role of theta activity (Bastiaansen et al., 2005)(Huth, Heer, Griffiths, Theunissen, & Jack, 2016). Based on the evaluated results, we propose, that theta oscillatory activity supports binding of semantic representations and thus modulates their activation and activation spreading within the involved semantic networks. According to this scenario, the representations with semantic connection would be reached more easily. Hence, the probability of those representations entering the short-term buffers would increase leading to more fluent automatic retrieval. On the other hand, the dissociative retrieval would require higher inhibitory resources, since the mechanism of semantic dissociation involves the suppression of the dominant associations (Wagner, 2002). Such a functional role of theta synchronization is in line with the measured behavioral data in our study.

6.3 Limitations

There is a number of limitations connected to the conducted experiment that need to be taken under consideration and the results need to be approached appropriately. First constrain pertains to the fixed stimulation frequency. A more rigorous approach would be to estimate the individual frequency peak within the theta band and customize this stimulation parameter for each individual. Hence the stimulation would apply the exact frequency that is naturally observable in the particular brain's activity (Kohli, S., & Casson, 2019). The conditions in our study did not allow for this EEG measurement, hence, each participant received the exact same stimulation frequency of 6 Hz. Although, we observed behavioural changes, the results could be enhanced (e.g. the significant change could be more pronounced) if the additional EEG sessions were included in our experimental design.

Moreover, the accuracy can be further improved by a simultaneous tACS-EEG protocol (Lustenberger et al., 2016). Such an approach would allow for a more fine-grained adjustments of the stimulation frequency depending on the feedback from EEG signal. It would also enable a more precise observation and understanding of the endogenous activity reactions (Neuling et al., 2017)(Tavakoli, A. V., & Yun, 2017). However, this method is linked to the already mentioned unsolved concerns regarding artefacts that are caused by the stimulation field and affects measured EEG signal (Noury, Hipp, & Siegel, 2016). The combined online tACS and EEG measurement is controversial, however EEG could be used during the offline session (post-stimulation). Without the application of EEG, we were not able to monitor the exact frequency changes induced by the stimulation, moreover the stimulation could also interact with other frequency bands in a complex and non-linear manner. Furthermore, it’s very probable that more oscillatory mechanisms are involved in the mechanism of semantic retrieval. Hence, the behavioural results could be the outcomes of the indirect changes of a functionally connected activities. This obstacle could be avoided in future research by the involvement of an additional controlled condition consisting of the induction of another frequency confirming the effect to be frequency specific.

Last limitation is linked to the precision of the lexical-semantic test. According to the current model of semantic cognition, the relations between semantic representations can be divided into two distinct categories. The "taxonomic" relation refers to the connection based on overlapping characteristics (e.g., cat-lion). On the other hand, "thematic" relation emerges through similarity in an accompanied situations (e.g., cat-milk) (Mirman, Landrigan, & Britt, 2017). The methodology used in the ACT was not sensitive to distinguish between these two forms of mental representations and hence, cannot evaluate them separately. This could be problematic, since the two relation types involve different brain circuits and cognitive systems.

Conclusion

Our study examined the role of prefrontal theta oscillations in semantic retrieval. The researched topic and methods presented an interdisciplinary approach combining fields of neuroscience, behaviour and the interaction of technology and human brain processes. The study is one of the pioneering research projects using neuromodulation of endogenous oscillatory brain activity within the prefrontal cortex during semantic processing. It supports the notion that theta oscillations are causally involved in the process of lexical–semantic retrieval. Moreover, the results proved an important evidence that these effects critically depend on the underlying processes that are involved in the retrieval task and retrieval demands, as the retrieval condition determined the resulting outcomes of the stimulation. In particular, the detailed analysis for response times revealed that prefrontal theta-band synchronization may play a role in binding or temporal stabilization of lexical-semantic representations. We propose, that tACS altered the accessibility of semantic representations via a modulation of the gain of semantic activation. Future research should include EEG measurements for more precise assessment of the effects. Further empirical research could lead to interventions applied in neuropsychiatric conditions.

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