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As a manuscript

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METHODOLOGICAL APPROACHES IN INVESTIGATING THE CONTRIBUTION OF THE HIPPOCAMPUS IN ASSOCIATIVE EPISODIC MEMORY FORMATION

Summary

of the dissertation for the purpose of obtaining academic degree

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PUBLICATIONS AND APPROBATION OF RESEARCH

This thesis comprises following studies:

First-tier publications[1]

1. Vorobiova A. N., Pozdniakov I., & Feurra M. (2019). Transcranial direct current stimulation effects on memory consolidation: timing matters. eNeuro, 6(3).
2. Pozdniakov, I., Vorobiova, A. N., Galli, G., Rossi, S., & Feurra, M. (2021). Online and offline effects of transcranial alternating current stimulation of the primary motor cortex. Scientific Reports, 11(1), 1–10.

Second-tier publications[2]

3. Vorobiova, A. N., Fedele, T., Pavone, E. F., Sarnthein, J., Imbach, L., & Feurra, M. (2022). Hippocampus-Located Processing Speed of Contextual Information Is Associated with Its Congruence to the Previously Developed Schemas. Zhurnal Vysshei Nervnoi Deyatelnosti Imeni I.P. Pavlova, 72(3), 360–369.

Other relevant publications:

4. Vorobiova, A. N. (2022). Intracranial EEG in Episodic Memory Research: Possibilities, Limitations, Results. //The Russian Journal of Cognitive Science. **(in press)**.

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[1] First-tier publications include papers indexed in the Web of Science (Q1 or Q2) or Scopus (Q1 or Q2) databases, as well as peer-reviewed collections of conferences that appear in CORE rankings (ranks A and A*).

[2] Second-tier publications are papers published in journals included on HSE's list of high quality journals or indexed in the Web of Science (Q3 or Q4) or Scopus (Q3 or Q4) databases, as well as peer-reviewed collections of conferences appearing in CORE rankings (rank B).

Conference reports

25th Annual Meeting of the Organization for Human Brain Mapping (OHBM 2019). Rome, Italy. *June 9-13, 2019*

2018 International Conference on Learning and Memory. Huntington Beach, California, USA. *April 18-22, 2018*

Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation. Barcelona, Spain. *March 5-8, 2017.*

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List of abbreviations

CT – computed tomography

EEG – electroencephalography

ERP – evoked response potential

fMRI – functional magnetic resonance imaging

HC – hippocampus

iEEG – intracranial electroencephalography

LTM – long-term memory

M1 – primary motor cortex

MEG – magnetoencephalography

MEP – motor evoked potential

mPFC – medial prefrontal cortex

MRI – magnetic resonance imaging

MT – motor threshold

MTL – medial temporal lobe

NIBS – non-invasive brain stimulation

sEEG – stereo electroencephalography

tACS – transcranial alternating current stimulation

tDCS – transcranial direct current stimulation

TES – transcranial electric stimulation

TMS – transcranial magnetic stimulation

INTRODUCTION

One of the most important cognitive mechanisms that provides flexible regulation of behavior is the ability to compare and integrate the subject's background information about the world with novel information constantly coming from outside. The importance of prior knowledge or schema representation in facilitating memory encoding, consolidation, and retrieval has been well-established in research. The hippocampus (HC) plays a crucial role in integrating information across different brain networks during memory processes (Geib et al., 2017; Moscovitch et al., 2016; Nadel & Moscovitch, 1997; Squire & Zola-Morgan, 1991). Recent studies have also highlighted the involvement of the medial prefrontal cortex (mPFC) in establishing connections between object representations based on their congruence with prior knowledge or similarity to each other, thereby enhancing memory functions.

In this study, we aimed to investigate the potential of non-invasive brain stimulation (NIBS) techniques to modulate the functioning of the episodic memory network. Specifically, our focus was on suppressing the activity of the mPFC, which is a core hub within this network, in an attempt to downregulate deeper brain structures otherwise inaccessible for NIBS. NIBS techniques are largely used for studying cognitive processes and their neural underpinning in a causal manner by allowing a transient and reversible modulation of neural activity in a given brain region. Indeed, such techniques as transcranial magnetic stimulation (TMS) and transcranial electric stimulation (TES) allow to establish causal relationship between cognitive function and particular cortical regions.

TMS, however, came out inefficient to bring evidence to reject or support our hypothesis about causal involvement of the mPFC to associative memory processing. As a next step, we considered TES for the same purpose of mPFC activity modulation. Transcranial direct current stimulation (or micropolarization) is a widely used method to study neurocognitive functions. However, according to the findings of a recent meta-analysis, transcranial direct

current stimulation (tDCS) studies on long-term memory in healthy subjects have demonstrated statistically non-significant or weak effects (Galli et al., 2019). This can be attributed to the high heterogeneity of tDCS protocols employed, such as variations in stimulation intensity and duration, as well as potential temporal mismatches between the tDCS effect and the process under investigation (Vorobiova et al., 2019).

On the other hand, the usage of transcranial alternating current stimulation (tACS) allowing for modulation of endogenous oscillatory activity, was very appealing. Online effects of tACS are well known, however, our experimental paradigm required for an offline stimulation technique, for there is no evidence for time-locked tACS effects. It is a rather novel method, and we explored its possibilities in a full-scale combined TMS-tACS methodological study on motor cortex excitability. This precursory part was necessary as a groundwork, because testing tACS effects on motor cortex excitability allows to record direct electrophysiological response from muscle to check for reliability of tACS effects per se, which is impossible with cognitive tasks. Our study did not reveal any significant offline effects of tACS on motor cortex excitability. This result, though of high methodological value per se, leaned us to disclose the usage of tACS in our study of associative memory. Thus, we have decided to adopt a challenging but more accurate technique, such as stereoelectroencephalography (sEEG) as the most suitable alternative method for investigating a deep structures like the hippocampus.

To date, sEEG remains the number one provider of detailed information about dynamics of electrophysiological activity of the human HC involved in the memory functions (Johnson et al., 2020; Johnson & Knight, 2015). However, the implementation of this method for the purposes of a fundamental neurocognitive research has a number of potential limitations and disadvantages (Henin et al., 2019; Parvizi & Kastner, 2018; Youngerman et al., 2019). We reviewed the main results in the field of episodic memory mechanisms obtained with the stereo-electroencephalography (sEEG) method, as well as its basic principles, advantages

and limitations. Finally, using sEEG, we recorded the hippocampal local field potential in human subjects performing an associative memory encoding task.

Episodic memory is a memory for person's own life events in a specific spatial and temporal context (Ranganath, 2010; Tulving, 1993). Starting from Bechterev's description of clinical cases (Бехтерев, 1994) and Milner and Scoville's seminal study of patients with hippocampal resection (Milner, 1972; Milner et al., 1968, 1998; Scoville, 1954; Scoville & Milner, 1957), clinical and neurophysiological evidence served as a foundation for the theoretical inferences about structure and mechanisms of episodic memory. Further development of neuroimaging techniques gave rise to the new insights about neural underpinning of the long-term memory system. Nowadays the episodic memory is assumed to be supported by the distributed network of cortical and subcortical structures, including hippocampal formation, prefrontal and posterior parietal cortices (Buckner et al., 1998; Buckner & Koutstaal, 1998; Burke et al., 2014; Kim, 2011; Long & Kahana, 2015; Paller & Wagner, 2002). It is suggested that the medial temporal lobes (MTL) structures (including the hippocampus, rhinal cortex, amygdala and parahippocampal gyrus) are responsible for the initial formation of the memory trace (Damasio et al., 1985; Milner et al., 1968; Preston & Eichenbaum, 2013; Scoville & Milner, 1957), whereas the neocortex, specifically the medial prefrontal cortex (mPFC) is involved in the binding of details and events into coherent memory trace within a given context (Brodt et al., 2016; Eichenbaum, 2017; Moscovitch et al., 2016; Sestieri et al., 2017; Squire, 1992). Moreover, cortico-hippocampal circuits allow for the construction and reconstruction of episodic events based in semantic structures and within its detail-rich context, i.e. providing an access to the interrelated representations (Behrens et al., 2008; Blumenfeld & Ranganath, 2007; Ghosh & Gilboa, 2014; Moscovitch & Winocur, 2002; Preston & Eichenbaum, 2013).

Cognitive neuroscience of memory is a challenging area of research, for various reasons. Episodic memory is a reconstructive process unfolding in time and charging a large network of brain areas. For this reason, it requires for the research methods with high temporal and

spatial resolution. Due to technical limitations for studying the human MTL, this brain area is not yet investigated at the same level of specificity as for the non-human animal models.

NIBS techniques, such as transcranial magnetic stimulation (TMS) and transcranial electric stimulation (TES) are well-established methods for studying cognitive processes and their neural underpinning. NIBS is an umbrella term for methods which, by virtue of different non-invasive mechanisms, allow a transient and reversible modulation of neural activity in a particular brain region. Thus, they have advantage over other neuroimaging techniques, moving from correlative approach to establishing of causal relationship between a given brain region and its function. TMS affects brain tissue by generating strong electric field which elicits an electric current depolarizing neuronal membranes, thus inducing action potentials in cortical structure directly under the induction area (Wagner et al., 2007). A series of TMS pulses of specific frequency allows for safe short-term stable modulation (facilitation or inhibition) of cortical excitability (Huang et al., 2005; Rossi et al., 2009). TES, in turn, uses weak electric current to modulate brain activity, shifting its excitability by direct current stimulation, or entraining endogenous rhythmical activity by alternating current (tACS).

Intracranial EEG (iEEG) is the main technique that provide high spatial and temporal resolution human memory data from the MTL. This method provides research opportunities that are inaccessible for non-invasive neuroimaging techniques (Chiong et al., 2018). Typically, iEEG involves patients with implanted stereotaxic electrodes due to the drug-resistant epilepsy. The number of electrodes in non-epileptic tissues depends on the total amount of electrodes and their position. Generally, it is assumed that up to 80% of contacts are located in non-epileptic brain tissue (Parvizi & Kastner, 2018). A stereo-EEG electrodes records local field potentials, i.e. compiled neuronal (and other electrophysiological) activity with millimeter spatial and millisecond temporal resolution (Buzsáki et al., 2012; Parvizi & Kastner, 2018). High signal to noise ratio (compared to the scalp EEG and magnetoencephalography (MEG)) increases observed effect sizes and allows to conduct

studies with relatively small sample size. However, this method presents several difficulties proceeding from the participants' clinical state. Typical limitations of an iEEG research include:

1) suboptimal physical and psychological state and engagement of participants due to seizures, pain, medication intake, fatigue, disturbances in the sleep-wake cycle, which only allow to conduct cognitive studies with a low amount of trials and relatively simple experimental design.
2) the experimenter's lack of full control over the environmental conditions during the experiment;
3) artifacts caused by the hospital equipment, patient's movements, or interictal activity that results in significant data leakage;
4) limited time of patients' availability due to the risk of infection and signal deterioration over time (Henin et al., 2019);
5) limited access to patients and small sample size (Youngerman et al., 2019);
6) heterogeneity of samples by diagnosis, age, sex, handedness, etc.;
7) influence of focal epileptic activity on the normal physiological activity (Henin et al., 2021), as well as possible functional (Alessio et al., 2013; Sidhu et al., 2013; Wilson et al., 2015; Witt et al., 2014; Witt & Helmstaedter, 2012) or structural (Bonilha et al., 2015; Buckmaster, 2010; Taylor et al., 2015; van Diessen et al., 2013) abnormalities in the epileptic brain;
8) limited spatial coverage of the brain by the implantation scheme (Johnson et al., 2020; Parvizi & Kastner, 2018);
9) additional massive data leakage due to an ambiguous status of the hippocampus: on the one hand, it is often a target for the stereo-electroencephalography (sEEG) as a potential candidate for the seizure onset zone, on the other hand, only data from the non-epileptic hippocampi could be used for the research purposes, whereas an

assumption of the hippocampus as a source of epileptic activity can be rejected only after surgery.

Therefore, an additional experimental control, as well as customized approach to data analysis and interpretation are required at all stages of iEEG-research, from study design to the data interpretation.

In summary, we identified the following gaps in this field of research, which we addressed in a series of studies: 1) previous studies robustly demonstrated the role of stimuli congruence to their memorization, but no studies causally addressed underlying brain mechanisms of this process; 2). Results of the NIBS memory studies are mixed and controversial, so additional methodological study is required to identify optimal stimulation parameters allowing to modulate memory functions; 3) no study of the human hippocampal electrophysiological activity was performed to investigate its involvement in the processing of information of various congruence.

Provisions for the defense

1. As highlighted by our methodological study, 10 and 20 Hz tACS with intensity 1000 μA applied over M1 doesn't induce significant offline effects.

2. The sEEG method is a valuable but highly demanding tool of episodic memory research, as highlighted by our review paper. The main methodological problems are related to the clinical status of the subjects and the operationalization of LTM.

3. Direct registration of the electrophysiological activity of the human hippocampus indicates the involvement of the hippocampus in the cognitive processing of complex contextual information, both congruent and incongruent to previously formed semantic knowledge. The processing of information that is congruent to previously formed semantic knowledge is accompanied by an earlier activation of the hippocampus compared to the processing of information that requires the establishment of new associative links.

OVERVIEW

Here we summarize results of research comprising this thesis. In the first part (Study 1) we completed a methodological study aiming to disentangle online and offline effects of tACS and discussed potential limitations of TES for the purpose of this area of research. In the second part (Study 2) we performed an overview state-of-the-art in the iEEG research dedicated to the episodic memory and ran an iEEG experiment to check the hypothesis about HC response to the association of various congruence.

Study 1

The physiological mechanisms associated with the effects of transcranial alternating electric current stimulation (TES) effects currently a topic of debate within the academic community. One of the methods, transcranial alternating current stimulation, implies entrainment of the endogenous cortical oscillatory rhythms with external sinusoidal potentials. Whereas online (e.g., ongoing) tACS is known to induce robust effects on cortical excitability, the offline effects of tACS are less investigated. We investigated the online and offline effects of tACS in two double-blind, placebo-controlled experiments (Pozdniakov et al., 2021). The identification of offline effects of the tested protocol would enable its future application for modulating endogenous rhythmic activity in the episodic memory network, particularly through the modulation of hippocampal activity.

Neuronavigated transcranial magnetic stimulation (TMS) targeting the primary motor cortex (M1) was utilized as a means to assess changes in cortical excitability. During the experiments, participants received M1 TES at frequencies of 10 Hz (alpha), 20 Hz (beta), and sham stimulation (30 seconds of low-frequency transcranial random noise stimulation; tRNS), in randomized and counterbalanced order.

Participants

All subjects (Experiment 1: N = 24, 15 females, mean age: 21.9, SD: 4.2; Experiment 2: N = 19, 10 females, mean age: 21.1, SD: 2.7) were right-handed volunteers without history of

neurological or psychiatric disorders, gave their written informed consent and compensated financially for their time. At the end of each experimental session subjects answered a questionnaire about tACS side effects (Russian version of the questionnaire by Fertonani et al. (2015)). After the experiment subjects were debriefed and asked to make a guess whether they received active or sham stimulation during each of the three tACS blocks. Participants were blind to the stimulation condition, as was indicated by a questionnaire results.

Combined tACS-TMS

tACS was delivered online in Experiment 1 and offline in Experiment 2. In the online experiment tACS conditions (10 Hz, 20 Hz, sham) were accompanied by TMS-induced measurement (combined tACS-TMS), and in the offline experiment tACS was followed by TMS.

Corticospinal excitability was measured by single pulse TMS-induced motor evoked potentials (MEPs). MEPs were recorded using electromyography (EMG) from the first dorsal interosseus muscle (FDI). As a baseline measurement, in the online experiment two blocks of MEPs were recorded before and after three combined tACS-TMS blocks. In the offline experiment each session consisted of two blocks of MEPs before (baseline) and seven blocks of MEPs after tACS. tACS conditions (10 Hz, 20 Hz, sham) were randomly assigned to participants across three sessions. For the offline experiment these sessions were spaced apart by a minimum of three days to allow for an adequate washout period and to minimize any carryover effects between the different tACS conditions.

In order to determine the optimal TMS intensity an individual threshold of motor cortex excitability (MT) was found for each participant. Single pulse TMS was applied to M1, starting from central sulcus to more anterior and lateral areas in order to find a hot spot, starting with intensity of 45% of maximum stimulator output. After finding a hotspot, intensity of TMS was gradually decreased in order to define MT.

tACS was administered using a battery-operated current stimulator (BrainStim, EMS Medical, Bologna, Italy) with two sponge electrodes (5 × 7 cm). The target electrode was positioned over M1. The reference electrode was placed over the ipsilateral shoulder. 10 Hz and 20 Hz tACS protocols were applied online for a total of 4 min per block (Experiment 1) or offline for 15 min (Experiment 2). Sham stimulation consisted of 30 s of low frequency transcranial random noise stimulation (tRNS) between 0.1 and 100 Hz. tACS was administered at an intensity 1000 μA (peak-to-peak) with a maximum current density of 14.3 μA/cm2 per electrode, with phase difference 0°. Fade in and fade-out times were set to 10 s to ensure a smooth transition. A number of studies have demonstrated the presence of stable online effects of tACS on the motor cortex at an intensity of 1000 μA and a frequency of 20 Hz (Cancelli et al., 2015; Feurra et al., 2011, 2013; Guerra et al., 2016; Heise et al., 2016). In the present study, the same intensity of tDCS was employed to replicate previously observed online effects and to investigate the offline effects induced by this protocol. It should be noted that tACS at a different intensity can elicit opposite effects (Moliadze et al., 2012), highlighting the potential for studying both its online and offline effects as a promising direction for future research.

Data analysis

EMG signal processing was performed using MATLAB R2014a (The MathWorks Inc., Natick, MA, USA), and statistical analysis was performed using R 3.6.0 (The R Project for Statistical Computing, Vienna, Austria). After high-pass and a notch filtering (50 Hz) MEP peaks were recognized within a window of 20–62 ms from the TMS pulse and underwent semi-automatic artifact rejection procedure. First, artifact MEPs (preceded by the extra noise or muscle activity with amplitude higher than > 0.1 mV) were manually and blindly to the experimental condition rejected through visual inspection. Furthermore, MEPs were automatically rejected if they met at least one of these criteria: 1) peak-to-peak amplitude less than 50 μV, 2) latency jitter more than 2 ms from a median latency in the baseline condition, and 3) peak amplitude (negative or positive peak of MEP) less than the amplitude

of the noise outside the 20–62 ms time window. Then we logarithmized peak-to-peak amplitudes and calculated 10% trimmed mean for each stimulation block. Finally, we normalized individual logarithmized and averaged data to baseline.

A one-way repeated measures ANOVA with stimulation condition as the independent variable (20 Hz, 10 Hz, and sham), and the logarithmized MEPs change as the dependent variable was used to reveal any significant differences between stimulation conditions. The Greenhouse–Geisser correction was applied to correct sphericity violations, and post hoc Tukey HSD comparisons were performed in case of significant differences. Then *p*-values were corrected for multiple comparisons using Bonferroni correction.

Results

In Experiment 1, we replicated previous evidence showing a small but robust online effect of 20 Hz tACS on the TMS-induced MEPs amplitude, compared to 10 Hz tACS and sham. In Experiment 2, we did not find any significant MEPs change after either the 10 Hz or the 20 Hz stimulation tACS at any interval within the range of 0 – 50 min after stimulation cessation. These findings support the hypothesis that tACS modulates cortical excitability only during online application, at least when delivered on the scalp overlying M1 at the intensity of 1000 μA. A detailed exploration of factors that can moderate TES effects on episodic long-term memory (LTM) is of high interest due to the clinical potential for patients with traumatic or pathological memory deficits and with cognitive impairments. Additionally, we discuss findings by Marián et al. (2018) recently published in *Cortex* within a broad context of brain stimulation in memory research. We have concluded that despite the high potential of using tDCS within different temporal windows associated with various stages of memory consolidation, the study possesses several characteristics (such as the selection of stimulation site, montage, and statistical design) that impede the accurate interpretation and further application of the obtained results. Thus, our commentary emphasizes the importance of considering stimulation parameters when

assessing the effects of TES in general, and the specific parameter of stimulation timing in studies related to long-term memory.

Methodological commentary

Additionally, we addressed methodological issues of TES application such as timing, site of stimulation, electrode montage and stimulation parameters (intensity, duration) in a commentary to the recent study of Marián et al. (2018) that demonstrated a disruption of long-term retention of remote memory after application of TES to the prefrontal cortex. Moreover, we computed the electric field distribution by utilizing a realistic finite element model based on the montage applied in an experiment conducted by Marián et al. (2018), where the anode was placed on F4 and the cathode on Cz (according to the International 10-20 EEG system) incorporated in SimNIBS 2.1 free software (Thielscher et al., 2015).

Study 2

The second study involved patients with drug-resistant epilepsy undergoing sEEG monitoring and employed an associative memory task (Vorobiova et al., 2022).

Participants

Six German-speaking patients (five women, mean age 31, all right-handed) undergoing 24-hour invasive SEEG monitoring took part in the study. SEEG monitoring and data acquisition were carried out at the University Hospital of Zurich, Switzerland. During preoperative SEEG monitoring, patients received levetiracetam, lamotrigine, brivaracetam, and lacosamide at doses determined by the attending epileptologist. All patients underwent detailed pre- and postoperative neuropsychological examination, which included, among others, assessment of general cognitive abilities (IQ), attention and cognitive control (Go/NoGo and Stroop tests), memory (verbal (VLMT) and visual tests (RDVLT) learning tests), and speech production. Only patients whose level of cognitive performance was satisfactory or above, based on the pre- and post-operative neuropsychological screening,

were selected for participation in the study. All patients gave their written informed consent. Study protocol was approved by the local ethical committee (protocol № PB 2016-02055).

Stereoelectroencephalography

SEEG was acquired with ATLAS (Neuralynx, www.neuralynx.com) recording system with sampling frequency 4 kHz using AD-Tech (AD-Tech, www.adtechmedical stereotaxic electrodes. Electrodes localization was performed by superimposing pre-op MR image with the post-op CT image and manually marked out in the patient's native MR space by the surgeon (iPlan Stereotaxy 3.0, Brainlab, Germany). For the purposes of the current study only the hippocampal electrodes were selected for the analysis (25 contacts on 13 electrodes, see **Fig 1, A-B**). An example of the location of a stereotaxic electrode is shown in **Fig. 1, C**.

Study Design and Procedure

The study used a modification of the experimental model designed and used in the study by van Kesteren et al. (2013), who also kindly provided a set of stimuli for the experiment. The stimuli set consisted of 185 pairs of pictures ("object–context "). Each pair of pictures was unique, i.e., presented to the subject only once. The pairings were matched such that 10% were "congruent" (e.g. "book-library"), 80% were "medium congruent" (e.g. "earplugs-living room"), and 10% were "incongruent" (e.g., "ball-laboratory").

Participants were instructed to rate a set of object-context pairs according to their degree of "congruence": "how well does this object fit the context; how likely is it that you would see such an object in such a context in real life?" During each trial, the subject was presented with a fixation cross for 350 ms, followed by a blank screen for 100 ms. This was followed by simultaneous presentation of a pair of pictures ("object–context") for 2500 ms. Then, after a blank screen (100 мс), a visual analogue scale was presented and the subjects had to use a computer mouse to mark the congruence of each pair from "Doesn't fit" to "Fits well". A blank screen was again presented, for 1500 ms, the next trial then beginning. The visual analogue scale was a 100-point scale visually perceived as continuous. Thus, the subject

assessed the congruence of each pair on a 100-point scale. Furthermore, all pairs of stimuli were divided into three groups, according to the subjects' responses: "Incongruent" (with scores of 0-33 points), "Intermediate" (34-66 points), and "Congruent" (67–100 points). Stimulus presentation and recording of subjects' responses were carried out using the E-Prime 2.0.10.147 program (Psychology Software Tools, Pittsburgh, PA). The design of the behavioral task is shown in **Fig. 1, D**.

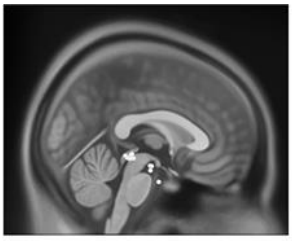
Data analysis

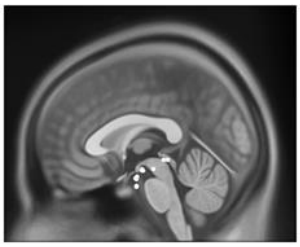
Signal processing and statistical analyses of behavioral and SEEG data were performed in the MatLab programming environment (version R2017b) using custom scripts and specialized toolboxes. SEEG preprocessing was performed using the Brainstorm toolbox (Tadel et al., 2011). The sampling rate of the original signal was decreased to 200 Hz using the cascade resampling algorithm. The common reference electrode for recordings was located in the white matter of the brain. The total averaged potential from all contacts was used as reference in the subsequent analysis. SEEG data were then visually inspected for the presence of epileptic discharges and other artifacts. Samples and channels containing artifacts were excluded from further analysis, such that the final analysis included 25 channels and 73% of samples. The signal was then divided into stimulus-related epochs from –2000 to 3000 ms relative to the moment of stimulus presentation. Samples recorded from each lead in each patient were pooled and included in further analysis as belonging to one "pseudo-patient".

Further analysis of SEEG data was performed using the FieldTrip toolbox (Oostenveld et al., 2011; http://fieldtriptoolbox.org). Local field potential amplitudes in the samples corresponding to each experimental condition were normalized to the average value of prestimulus activity (from –1500 to –100 ms) and averaged in the range 0-2000 ms from stimulus presentation. ERPs were calculated using absolute amplitude values, as when combining data from multiple subjects it is impossible to establish the position of the signal source with respect to each of the recording contacts. Pairwise comparisons between

experimental conditions, were made using Student's t-test for independent samples. Significant differences between experimental conditions were identified using the Monte Carlo method with 500 permutations. The significance level for all tests was $p < 0.05$.

A

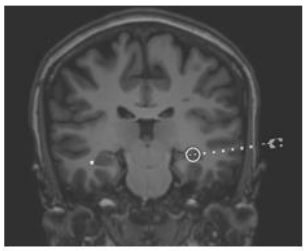




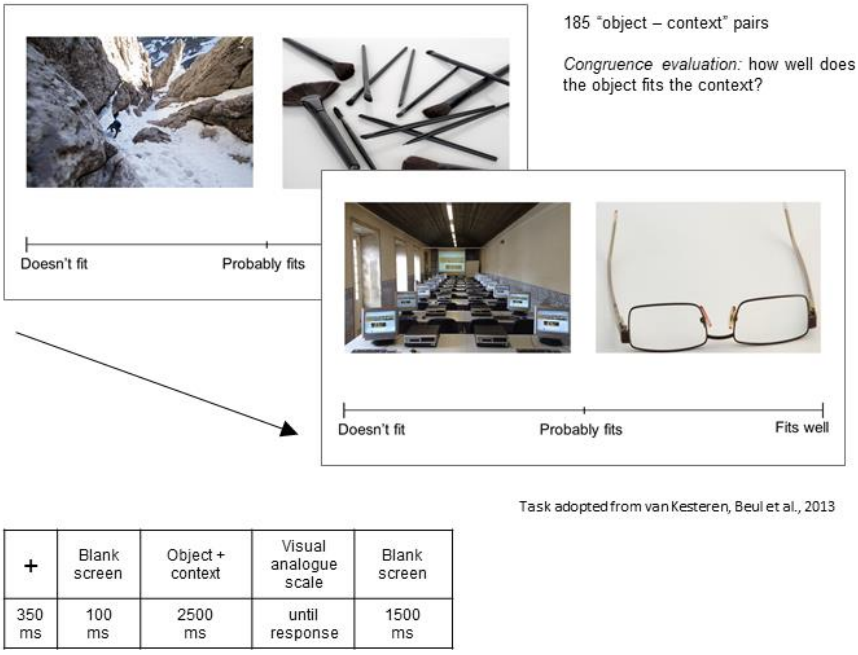
B

ID	N electrodes	N contacts
1	2	2
2	5	8
3	2	5
4	1	2
5	2	3
6	3	5

C



D



+	Blank screen	Object + context	Visual analogue scale	Blank screen
350 ms	100 ms	2500 ms	until response	1500 ms

Figure 1. A Contacts included in the analysis (n = 25) in the left and right hemispheres marked on the MNI template in the projection of the sagittal section of the brain. **B** Numbers of electrodes and contacts included in the analysis. **C** An example of stereotaxic electrode emplacement on a coronal section of the brain. The illustration shows a postoperative CT

image of the patient's brain superimposed on a preoperative MRI image. Contacts located in the hippocampus are circled. **D** Behavioural task design.

Results

Firstly, we presented arguments for the iEEG method as a key method allowing for the investigation of time-frequency dynamics of episodic memory-related HC activity and described its advantages over other neuroimaging techniques, as well as human lesion studies and non-human animal models.

Secondly, we performed an extensive systematic review of iEEG studies of episodic memory. We analyzed the relevant literature to identify commonalities and discrepancies in observed neural correlates of encoding and retrieval of single-item and associative information, focusing on 1) their temporal dynamics, 2) oscillatory patterns, 3) episodic memory operationalization, 4) functional dissociation within the MTL structures. We outlined that theta-gamma activity in the hippocampus plays crucial role for the memory functions, where theta oscillations coordinate activity of distinct brain regions, and gamma activity supports local information processing, supposedly, by encoding perceptive/conceptual features. We concluded that the brain mechanisms involved in episodic LTM require further investigation to differentiate the role of the partitions of the HC and to clarify their functional interaction. However, most of the studies are focused on the relatively basic episodic memory phenomena, which is substantially related to the limitations of the sEEG.

Finally, we addressed the hypothesis that hippocampal evoked responses (ER) obtained on processing existing associations familiar to humans would be different from those obtained when an association needs to be established for the first time.

The obtained results show that the hippocampus is involved in the processing of information about the congruence of the subject to the context. The processing of information that is congruent to previously formed semantic knowledge is accompanied by an earlier activation

of the hippocampus compared to the processing of information that requires the establishment of new associative links (**Fig.2**).

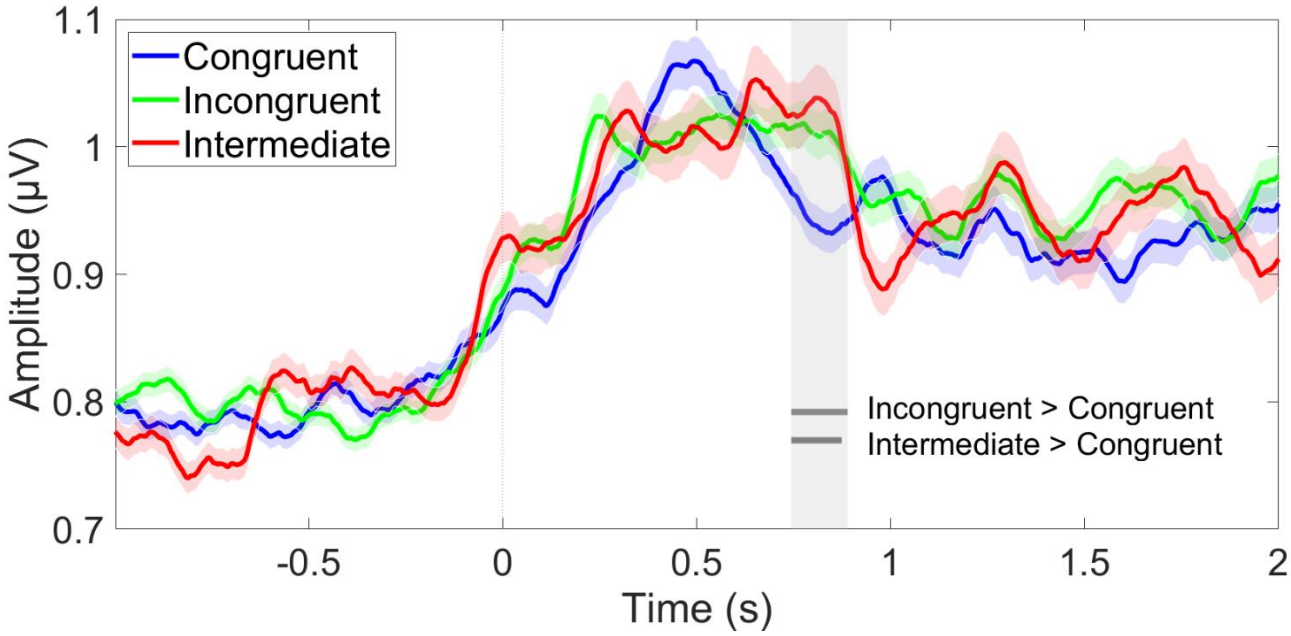


Figure 2. Average absolute local field potential amplitudes for each group of stimuli. The signal is smoothed with a time window of 100 ms. The shaded areas around the curves show the standard error of the mean (SEM). The horizontal bars below the graph show the time intervals in which the absolute value of the amplitude for "congruent" stimuli was significantly ($p < 0.05$) lower than the amplitudes for "incongruent" and "intermediate" stimuli. The pre-stimulus activity level is non-zero, as averaged absolute amplitudes are used.

CONCLUSION

Key results

In the present work, we attempted to apply non-invasive brain stimulation techniques to modulate function of episodic memory network by suppressing activity of one of its core hubs, the medial prefrontal cortex (mPFC), thus downregulating deeper brain structures otherwise inaccessible for NIBS. An aforementioned part also included a methodological study aimed to define optimal parameters for the NIBS stimulation.

Furthermore, we conducted a review addressed possibilities and limitations of intracranial electroencephalography for the human episodic memory research and delineated main results obtained by this method. Based on the results of review, we hypothesized that congruence-mediated processing is reflected in the hippocampus activity. We used intracranial EEG recordings with depth electrodes in epilepsy patients to test this hypothesis. The results suggest that more rapid processing of congruent information by the HC, compared to non-congruent information, thus, supporting our hypothesis.

Scientific novelty and significance of the results

The results of our project provided contribution to the field of theoretical models of episodic memory which allows clarifying interpretation of experimental results. Moreover, in a commentary paper we highlighted several corollaries of these models that could account for inconsistencies of previously obtained evidence, thus, criticizing application of tDCS to the long-term memory studies.

In the same vein, our project provided an important contribution to the methodological discussion regarding NIBS application to studying brain functions. Specifically, we provided a comprehensive evidence about online/offline tACS effects, thus, indicating direction to the scientific community in causally addressing brain mechanisms of cognitive functions. It should also be noted that our review and empirical research are one of the first ones in Russia

addressing sEEG as a method of fundamenthal cognitive research (in addition to its' default diagnostic purposes).

We addressed associative memory as an item-context binding process, as opposed to more simplified item-item approach. Our sEEG ERP study provided the first evidence that the human hippocampus processes congruent, or schema-linked, information faster, than incongruent or unrelated.

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