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BRIEF COMMUNICATION

Slow Theta tACS of the Right Parietal Cortex Enhances Contralateral Visual Working Memory Capacity

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Abstract

Recent research suggests alteration of visual working memory capacity by modulation of parietal theta frequency via transcranial alternating current stimulation (tACS). However, it remains to be clarified whether this effect is partly driven by co-stimulation of prefrontal cortex and subcortical structures. It was hypothesized that focal tACS over the parietal lobe without additional prefrontal or subcortical stimulation should lead to similar effects as reported in the literature. Healthy, young participants were tested on a visual working memory paradigm while receiving either focal parietal tACS at 4 Hz, at 7 Hz or sham stimulation. Focal right posterior 4 Hz tACS led to increased working memory capacity strictly for the visual hemifield contralateral to stimulation. Exclusive stimulation of posterior cortex by 4 Hz tACS replicates effects recently reported in literature, confirming that stimulation of the prefrontal cortex or subcortical structures are not a primary driver of these observations.

Keywords Focal tACS · Modulation of brain frequencies · Nesting of oscillations · Theta:gamma coupling

Introduction

According to a popular theoretical framework (Lisman and Idiart 1995; Jensen and Lisman 1996; Lisman and Jensen 2013) multiple items are transiently stored in working memory (WM) by nesting of fast (gamma) brain oscillations into slow (theta) brain waves (see also Sauseng et al. 2018 for discussion). Thereby, the number of gamma cycles that can be integrated into each theta wave is considered as a limiting factor for WM capacity (Jensen and Lisman 1996, 1998). Recently, causal evidence for this theoretical framework has been provided by two transcranial alternating current stimulation (tACS) studies (Vosskuhl et al. 2015; Wolinski et al. 2018; for a comprehensive review see; Turi et al. 2018). While slowing-down of theta frequency in parietal cortex (allowing for more gamma cycles being nested into the resulting slower theta waves) increased WM capacity (Vosskuhl et al. 2015; Wolinski et al. 2018), speeding-up theta frequency via parietal fast theta tACS led to decreased WM performance (Wolinski et al. 2018). In both studies tACS targeted parietal sites with return electrodes placed at supraorbital (Wolinski et al. 2018) or frontal sites (Vosskuhl et al. 2015). However, these electrode montages do not lead to spatially particularly precise stimulation. Thus, one could argue that the obtained results can potentially be biased by (i) very distributed cortical stimulation including parietal as well as prefrontal cortex or (ii) even subcortical structures directly stimulated by a parietal electrode with a return site on the forehead (Chhatbar et al. 2018). Here we investigated whether focal tACS over right parietal cortex (certainly without any stimulation of prefrontal cortex and less likely direct stimulation of subcortical areas) would lead to comparable results to those by Wolinski et al. (2018). Based on the assumption that the previously reported effect actually is driven by modulation of parietal theta activity, we hypothesized that, compared to sham stimulation, focal parietal tACS at a slow theta frequency (4 Hz) would lead to increased visual WM performance; whereas focal

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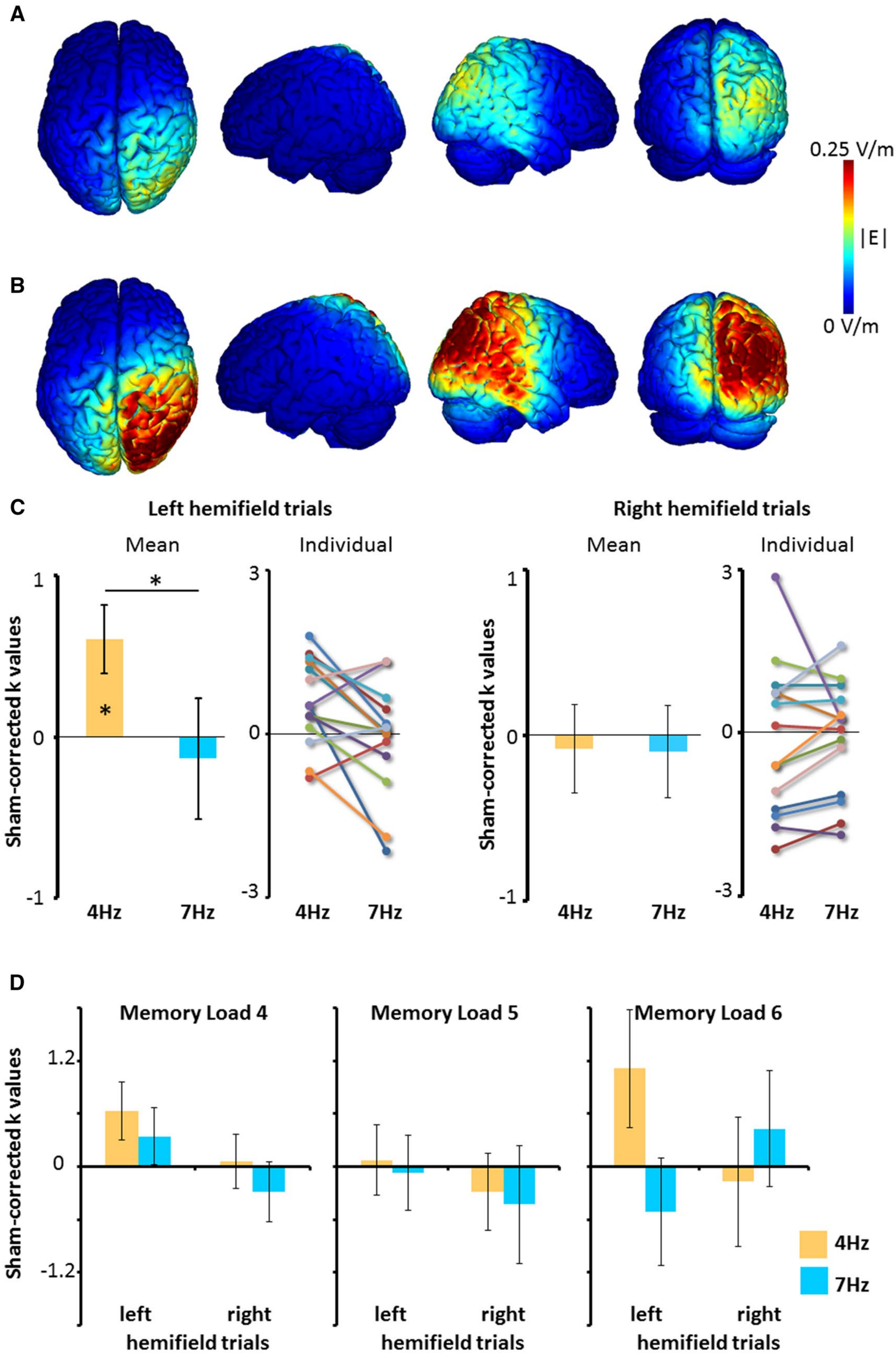
A
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0.25 V/m
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Left hemifield trials
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1
0
-1
3
0
-3
*
*
4Hz
7Hz
D
Memory Load 4
Memory Load 5
Memory Load 6
Sham-corrected k values
1.2
0
-1.2
left
right
hemifield trials
4Hz
7Hz

◂**Fig. 1** Electric field distribution estimates for experiment 1 (**a**) and experiment 2 (**b**) based on a montage with the stimulation electrode over electrode site P4 and three return electrodes at sites Oz, Cz and T8. In experiment 1, stimulation intensity was at 1000 µA peak-to-peak, in experiment 2 it was at 2000 µA. **c** In experiment 2 there was a significant increase in WM capacity k with tACS at 4 Hz compared to sham stimulation only for trials with memory targets presented in the contralateral, left visual hemifield. No such effect was obtained for right visual hemifield trials. 7 Hz tACS did not decrease WM capacity. **d** Increased WM capacity in the hemifield contralateral to stimulation was largely driven by effects on trials with a memory load of six, i.e. a condition in which six visual items had to be retained in WM

parietal tACS at faster theta frequency (7 Hz) would lead to decreased WM capacity.

Materials and Methods

Experiment 1

Participants

A priori power analysis based on results reported by Wolinski et al. (2018) suggested a sample size of at least 12 participants. 20 participants were recruited for experiment 1; two volunteers dropped out of the study without giving reason. The remaining sample of 18 healthy, young participants (11 females; all but three participants right handed) had a mean age of 29.8 years (SD = 8.3), normal or corrected vision and did not meet any exclusion criteria for tACS. All participants gave written informed consent, and the study was approved by the LMU Faculty 11 ethics review board.

Experimental and tACS Stimulation Protocol

As in Wolinski et al. (2018) a visuo-spatial WM delayed match-to-sample task was used. In each trial a brief central cue pointing to the left or to the right was presented followed by 100 ms presentation of four, five or six colored squares (factor MEMORY LOAD) presented in each visual hemifield (factor HEMIFIELD). Participants were instructed to retain only the items presented in the cued visual hemifield for 900 ms and then compare them to a probe item. In each of three tACS stimulation sessions (4 Hz tACS, 7 Hz tACS, sham stimulation; factor CONDITION) 60 trials of the task were run (20 trials per memory load, with memory targets in the left and right visual hemifield in 50% of trials each).

While participants performed the WM task they received tACS over the right parietal lobe using a NE® starstim multichannel tACS device. A 19.6 cm² stimulation electrode was mounted over EEG electrode site P4, and three 4.9 cm² return electrodes were set equidistant from the stimulation electrode (at positions Oz, Cz and T8). This way a highly focal stimulation of the right posterior parietal lobe was achieved as indicated by electric field distribution estimates calculated in NIC 2.0 software (see Miranda et al. 2013; Wolinski et al. 2018 for details and supplementary material for further information and limitations) and depicted in Fig. 1a. In three different sessions on different days tACS at 4 Hz or at 7 Hz with a peak-to-peak stimulation intensity of 1000 µA, or sham stimulation was applied. As a measure of WM capacity parameter k (k = (z(hit rate)–z(false alarm rate))*set site; see Cowan (2001) for details) was calculated for each memory load, hemifield and stimulation condition, separately. For statistical analysis k values were sham-corrected, i.e. k values from the sham stimulation condition were subtracted from 4 Hz and 7 Hz k values, respectively. Data were analyzed using a three-way repeated measures ANOVA with factors CONDITION (4 Hz, 7 Hz), MEMORY LOAD (4, 5, 6 items) and HEMIFIELD (left, right).

Experiment 2

Participants

16 participants were recruited; again, two volunteers dropped out of the study without giving reason. The remaining sample of 14 healthy, young participants (12 females; all right handed) had a mean age of 21.9 years (SD = 5.9), normal or corrected vision and did not meet any exclusion criteria for tACS. All participants gave written informed consent, and the study was approved by the local ethics review board.

Experimental and tACS Stimulation Protocol

Exactly the same experimental and tACS stimulation protocol and data analysis strategy was applied as in experiment 1 with the exception that stimulation intensity was set to 2000 µA to obtain an electric field strength in parietal cortex comparable to that reported in Wolinski et al. (2018). As can be seen in Fig. 1b this lead to far stronger but also slightly less focal stimulation of right parietal lobe compared to experiment 1.

Results

For experiment 1 no significant main effects or interactions were obtained (all Fs < 1.5, all ps > 0.246; see Supplementary Material Table S1 for details). In experiment 2, on the other hand, the CONDITION*HEMIFIELD interaction [the most important result reported by Wolinski et al. (2018)] at least showed a trend towards a relevant effect ($F_{1/13} = 3.39$, $p = 0.089$, $\eta^2 = 0.21$), with a significant increase in sham-corrected memory capacity estimate k for the 4 Hz condition ($t_{13} = 2.82$, $p = 0.007$, $d = 0.75$) and a significant difference to 7 Hz tACS ($t_{13}=2.67$, $p=0.01$, $d=0.71$) in left hemifield trials only (Fig. 1c). The two-way interaction, however, was entirely driven by trials at memory load 6 (see Fig. 1d). This was evident from a significant three-way interaction CONDITION*HEMIFIELD*MEMORY LOAD ($F2/16=3.48$, $p=0.046$, $\eta^2=0.21$) which was followed up by two-way ANOVAs for each memory load separately. Only for memory load 6 a significant interaction CONDITION*HEMIFIELD ($F1/13=6.84$, $p=0.021$, $\eta^2=0.35$) was obtained. Statistical analyses were additionally run on HIT and FA rates; results for HIT rates resemble those for k-values reported here, whereas no stimulation-related effects were found for FA rates (see Supplementary Materials for details).

Discussion

In experiment 2 we obtained similar effects as reported by Wolinski et al. (2018). However, there have been two major differences. First, in the current study we only found evidence for increase of WM capacity by 4 Hz tACS, but no WM decline caused by 7 Hz tACS (although, analysis of HIT rates for memory load 6 show a tendency towards WM capacity decrease during 7 Hz tACS). It might be that modulation of theta frequency towards slower oscillations is easier to achieve than shifting theta frequency towards the alpha range, rhythmical activity that is clearly dominant in amplitude in the human parietal cortex. Another possibility could be that on average in our sample individual theta frequency was closer to 4 Hz than to 7 Hz. Modulating individual theta frequency towards the closer stimulation frequency of the two should require less energy. In this respect, future research combining neurostimulation (TMS/tACS) with concurrent EEG/MEG recordings is imperative to shed light on the precise neurophysiological underpinnings accounting for the interaction between neurostimulation montages, and effective behavioral impact. And second, the obtained effect was only driven by the most difficult trials with six items to retain. The latter finding is in good agreement with studies that also report increase of WM performance by tACS in the theta frequency range if the task is challenging for the participants (Violante et al. 2017; Tseng et al. 2018). It is unlikely that stimulation effects were attenuated at lower memory loads due to a ceiling effect, since participants performed clearly below ceiling even in the easiest condition of memory load 4 (see supplementary materials). In experiment 1 no modulation of WM capacity was achieved. Most likely this was because of the very low intensity of tACS applied in this experiment. Participants in experiment 1 were significantly younger than in experiment 2 ($t_{30}=3.03$, $p=0.005$). However, it is unlikely that this might have led to no detected effect in experiment 1 as if anything, tACS has been reported more effective in older than in younger healthy subjects (Antonenko et al. 2016; Rufener et al. 2016; Fresnoza et al. 2018).

In conclusion, similar results as reported by Wolinski et al. (2018) can also be obtained without any direct stimulation of prefrontal cortex and most likely without substantial stimulation of subcortical structures. Relatively strong stimulation of parietal cortex (at the cost of focality), however, seems necessary.

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