

Rhythmic TMS in the theta frequency over the right parietal cortex modulates
contralateral visuospatial Working Memory capacity.

Nina Straub

Matrikelnummer: 12259570

2. Fachsemester Psychologie B. Sc.

Empira I SoSe 2021

Abgabedatum: 02.09.2021

Zeichenzahl: 16427

Department Psychologie, LMU München

Abstract:

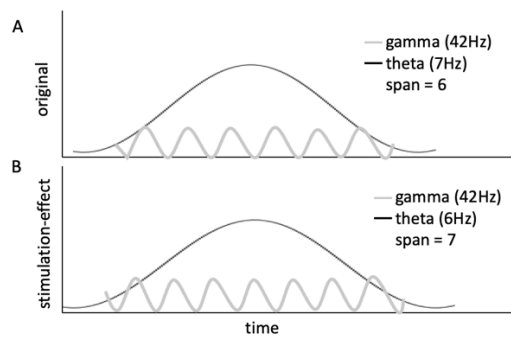
Visuospatial Working Memory (WM) capacity is thought to be limited by the length of theta brain oscillations and the number of gamma cycles that can be nested in them. This theory, known as theta-gamma-coupling, implies that modulating theta frequency can enhance or reduce WM capacity. Recent studies used transcranial alternating current stimulation (tACS) to modulate theta frequency testing this hypothesis. However, the found effects might be confounded by co-stimulation of the prefrontal cortex and other brain regions. To test the theory with more temporal and spatial precision, rhythmic transcranial magnetic stimulation (TMS) was used to modulate parietal theta frequency during retention of a visuospatial WM task. While stimulation in a slow frequency (4Hz) should enhance WM capacity, faster (7Hz) stimulation should have the opposite effect. Results showed significant effects in both enhancing and reducing WM capacity and are another piece of evidence supporting the theta-gamma-coupling theory.

Introduction

The capacity of visual Working Memory (WM) is known to be limited to about 4 to 6 items. The theta-gamma-coupling theory proposes that this is due to the nesting of fast gamma brain oscillations ($>30\text{Hz}$), each representing one item, into slower theta oscillations (4-7Hz) binding them together during the retention interval (Lisman & Idiart, 1995; Lisman & Jensen, 2013). Every theta cycle, memories, represented by a gamma cycle, are repeated and kept active. According to this theory the number of gamma cycles that can nest into one theta wave is the limiting factor of the WM capacity. (Fig. 1)

Figure 1:

Schematic of the theta gamma coding theory



Note: (A) Gamma waves nest into theta wave of individual length. Max. number of items is 6 in this case.

(B) Neural stimulation could manipulate theta frequency and increased max. number of items, in this case to 7.

Recent studies tested this theory by using tACS stimulation to manipulate the frequency of the theta wave and in consequence enhance or reduce WM capacity. The results of these studies were mixed, but all at least showed a trend supporting the theory (Bender et al., 2019; Vosskuhl et al., 2015; Wolinski et al., 2018). As tACS stimulation is limited in its spatial precision it might be that results of these studies are confounded by stimulating not exclusively brain areas associated with WM but distributed cortical regions and subcortical structures (Albouy et al., 2018).

Our aim was to test the theory but trying to focus stimulation more precisely on the parietal cortex, especially the Intraparietal Sulcus (IPS) which is known to be involved in retaining information in WM processes (Champod & Petrides, 2007). Therefore we designed a similar experiment as the ones already conducted but using rhythmic transcranial magnetic stimulation (TMS) to manipulate the theta frequency. TMS is a brain stimulation technique using small but strong rapidly changing magnetic fields to modulate neuronal activity. It has a higher spatial and temporal precision compared to tACS, thus making it possible to focus stimulation better on the parietal cortex.

We hypothesise that parietal TMS applied in a slow theta frequency (4Hz) during retention leads to a higher visuospatial WM capacity in the hemifield contralateral to the TMS compared to a baseline condition (5.5Hz). Parietal TMS in a faster theta frequency (7Hz) should show the opposite effect of a lower WM capacity. The WM capacity of the hemifield ipsilateral to TMS should not show any difference compared to baseline condition.

Method

Due to the Covid-19 pandemic no real data for this experiment could be aggregated, results and discussion are based on simulated data. For the links to preregistration, script of statistical analysis and raw data see Appendix A.

Participants:

Recent studies found different effects for the interaction of condition and hemifield (Bender et al., 2019; Wolinski et al., 2018). The mean of in these experiments found effects was taken for a power analysis using MorPowr. A 2x2 ANOVA analysis with $\eta^2 = 0.219$, $\alpha = 0.05$ and power of 0.8 suggested a total sample size of 30 participants. A one-sided, one-sample t-test power analyses using an effect size of Cohen's $d = 0.44$ (Wolinski et al., 2018) suggested a total sample size of 34. Excluded from the study were colourblind people, since the visual task required ability to distinguish colours. A standard TMS-safety-screening was undertaken beforehand. Age was supposed to range between 18 and 35.

Based on this we tested 38 people. Two were excluded later from analysis as they were above 35 years old. The remaining 36 healthy, young participants (24 male, 10 female, 2 diverse, all right-handed) had a mean age of 21.33 years ($SD = 2.38$). All participants were volunteers, were recruited over blackboard notices and gave written consent. The study was approved by the local ethics review board and was in line with the declaration of Helsinki.

Experimental Paradigm:

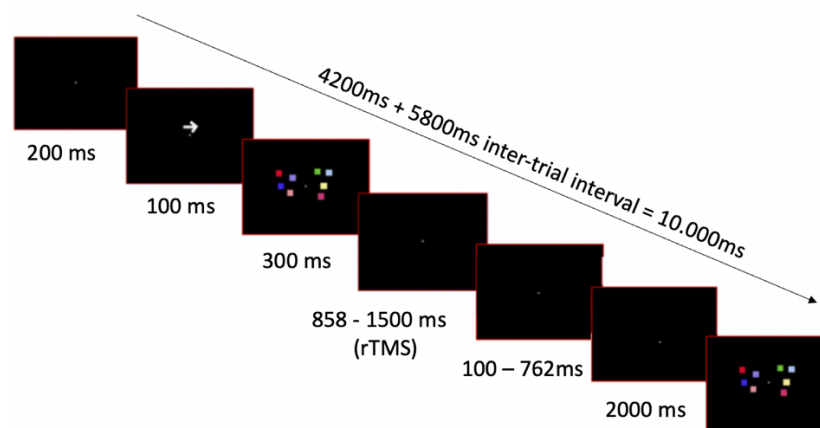
For measuring visuospatial WM capacity the same delayed match to sample task as in Wolinski et. al. (2018) and Bender et. al. (2019) was used. Sets of coloured squares are presented in the left and the right visual hemifield (factor Hemifield). The visual load, e. g. number of squares presented, ranges from 4 to 6 items between trials. Colours of the left and right arrays are different, the number of squares is the same on both sides for each trial.

The task started with a fixation cross on the screen. (19-inch CRT View Sonic G90fB monitor, resolution of 1024 x 768, 100 Hz refresh rate, placed approximately 80 cm from the observer.) In each trial the sets of coloured squares were presented for 100ms. An arrow showed prior to the squares (200ms) indicated if the right or left sets should be memorised.

This was followed by a retention interval of 1900ms, after which a set of squares was shown again on screen for 2000ms. The participant had to decide if the colours of presented squares on the cued side were the same or different than before by pressing the left or right button of the mouse, respectively. Each trial was followed by a 5750ms to 5850ms long inter-trial interval. Each trial was altogether 10.000ms long. Figure 2 shows the temporal structure of the task.

Figure 2:

Temporal structure of the delayed match-to-sample task



Rhythmic TMS parameter

Rhythmic TMS was applied over the right Intraparietal Sulcus (P4 according to the EEG 10-20 system) during the retention interval of each trial using a PowerMAG 100 research TMS stimulator with a double coil PDM 70 by Mag&More®. P4 was found for each participant by measuring the distance between nasion toinion and between preauricular points, then calculating percent steps using the EEG 10-20 system to find the desired location. The retention interval showing just the fixation cross on screen started with a 300ms buffer, following the TMS stimulation applying 6 pulses in either 4Hz, 7Hz or 5.5Hz frequency (factor Condition). Due to the different speed of pulses the stimulation time varied in its length, for either 1500ms (4Hz), 858ms (7Hz) or 1092ms (5.5Hz), respectively. The retention interval was 1900ms in total in every trial, consequently the buffer at the end ranged from 100ms up to 762ms depending on length of stimulation time.

4Hz and 7Hz stimulation was performed to test the hypothesis of theta oscillations effecting WM capacity, 5.5Hz was chosen as baseline condition being in the middle of the other stimulation frequencies.

Procedure

After participants filled out the screening form and signed the informed consent, the individual motor threshold of each participant was found by applying TMS over the estimated hand area of the motor cortex. The applied intensity of stimulation was low in the beginning and increased until the fingers twitched, showing that the individual motor threshold was reached. Intensity was decreased again until the twitch was no longer found in 5 out of 10 pulses. The stimulation in the experiment was performed on the 80% level of this individual motor threshold. Participants performed two practice blocks of the delayed match to sample task of 16 trials each. One without TMS stimulation and the following one with TMS stimulation to get to know the task as well as the feeling of performing it during stimulation.

After this procedure the experiment itself started. 4 blocks of 60 trials were presented. As one trial takes 10.000ms, each block lasted for 10min, resulting in 240 trials and 40min in total. In each trial another frequency of TMS pulses was applied. To avoid sequence effects, the frequency of stimulation given was randomised, resulting in 80 trials for each of the three frequencies. The software used for conducting the stimulus presentation was Presentation 0.71 by Neurobehavioural Systems, Inc. Between each block participants were able to take a break for several minutes.

Data preprocessing and statistical analysis:

A logfile for each participant and block was created containing reaction times and if responses were correct. Participants with continuous response times below 200ms or just clicking one button were excluded. In double-responses first response was used, missing data was observed carefully if it was still useful for analysis.

From this raw data hit-rates (right answer) and false-alarm rates (wrong answer) and set size were extracted. WM capacity was measured using a K-value, a standardised measure defined as $K = S * (H - F)$, where H is the hit rate, F the false alarms and S the set size (number of items presented in the trial). One single K-value was calculated for each participant and stimulation condition (4Hz, 7Hz, 5.5Hz) across all memory loads (4, 5, 6 items). (Appendix B.)

Baseline-corrected K-values were calculated by subtracting K-values of the 5.5Hz from K-values of the 4Hz and 7Hz stimulation factor. Before performing inference statistical tests, data was observed in a histogram to test the statistical requirement of normal distribution.

Data of one subject showed consistently strong negative K-values. This being highly unlikely, it can be assumed that there was a confusion of the right and left mouse button for response. To save data, the K-values for this subject were inverted.

A repeated measure 2x2 ANOVA with the factors Hemifield (left, right) and Condition (4Hz and 7Hz stimulation) was used on the K-values to analyse the interaction between Hemifield x Condition. As this interaction proofed significant, post-hoc one-tailed t-tests were performed testing the baseline corrected K-values for both 4Hz/7Hz Condition and left/right Hemifield against 0 to analyse direction of the interaction. T-tests for left hemifield trials should be both significant while t-test for right-hemifield trials should not be significant. If this would be the case, results would support our hypothesis.

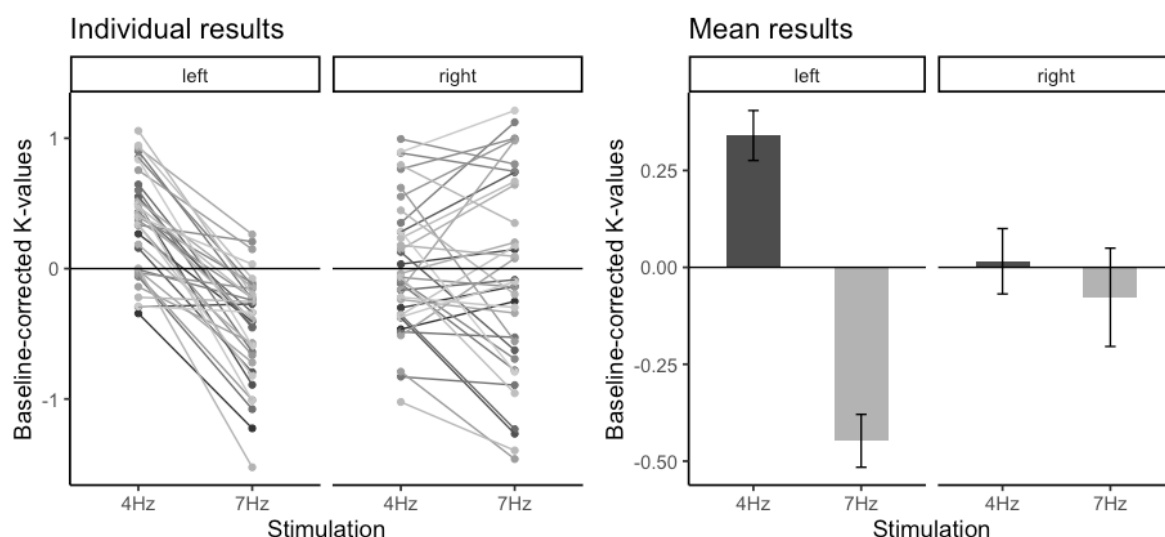
Results

Descriptive analysis:

The mean for baseline corrected K-values was positive in the 4Hz stimulation and left hemifield condition (mean = 0.342, SD = 0.385). In the other conditions means were negative (7Hz and left: mean = -0.439, SD = 0.419; 4Hz and right: mean = -0.039, SD = 0.505; 7Hz and right: mean = -0.122, SD = 0.755).

Figure 3

Individual differences and means of K-values



Note: Baseline-corrected K-values for each combination of Condition and Hemifield. The left graph depicts individual K-values of all 36 participants, the right graph depicts means of K-values from each condition. Significant differences were observed between 4Hz and 7Hz stimulation in the left Hemifield condition. No significant differences were found between 4Hz and 7Hz stimulation in the right Hemifield condition.

Confirmative analysis:

Results for repeated measures ANOVA were in line with the hypothesis, that there will be an interaction between the factors Hemifield and Condition: Analysis showed a main effect of the factor Condition ($F(1, 35) = 48.06, p < .001, \eta^2_{\text{par}} = .579$) and a significant interaction between Condition x Hemifield ($F(1, 35) = 42.14, p < .001, \eta^2_{\text{par}} = .546$) (Appendix C). The main effect of the factor Hemifield did not reach significance ($F(1, 35) = 0.04, p = .848, \eta^2_{\text{par}} < .001$). The following one-sample *t*-tests against 0 confirmed expectations that the slow 4Hz stimulation enhances contralateral WM capacity relative to the baseline condition ($t(35) = 5.28, p < .001$, one-tailed; Cohen's $d = 0.88$) while the faster 7Hz stimulation reduces contralateral WM capacity relative to baseline condition ($t(35) = -6.56, p < .001$, one-tailed; Cohen's $d = -1.09$). Further analysis of the trials ipsilateral to stimulation (e. g. in the right visual hemifield) showed neither for 4Hz nor for 7Hz Condition significant effects (4Hz: $t(35) = 0.189, p = .426$, one-tailed; Cohen's $d = 0.031$; 7Hz: $t(35) = -0.61, p = .273$, one-tailed; Cohen's $d = 0.1$). (Fig. 3)

Discussion

In this study we were able to show that applying TMS over the IPS during retention in a slow theta frequency (4Hz) can enhance WM capacity while faster theta frequency (7Hz) reduces WM capacity. These findings are in line with our hypothesis and previous findings. The results can be explained by the theta gamma coupling theory.

Using TMS for manipulating theta frequency had several advantages to the previous studies using tACS. Due to the higher spatial resolution of TMS we are able to exclude several alternative explanations, e. g. that effects are due to activation of distributed cortical and even subcortical regions. The better temporal resolution of TMS made it possible to apply stimulation just during the retention interval and randomize different frequencies between trials, which is not possible with tACS.

The higher precision of TMS might explain why our results are in contrast to previous studies significant in both directions and show stronger effects.

One might still argue that the results are some kind of unspecific artefact, for example that the faster 7Hz stimulation condition was more uncomfortable than the slower 4Hz condition, thus resulting in a lower WM capacity. Although this is a valid argument, it can be easily rejected: If the difference between 4Hz and 7Hz is just due to stimulation being differently uncomfortable, difference in WM capacity would also be significant in the right Hemifield condition. This is not the case. A similar logical answer could be given to the

objection that when stimulating on the right parietal cortex, it might be that the head was shifted somewhat by the coil, thus making it easier to see the items presented in the left hemifield. If this were the case, no difference in the data of 4Hz and 7Hz would show but a main effect of the factor Hemifield, which turned out to be not significant.

Although this kind of arguments can be resolved, our study has limitations that could be valid alternative explanations of the results found: Most severely, no control of manipulation was performed. Although previous studies have shown that TMS is able to manipulate theta oscillations (Li et al., 2017) it might also be the case that we did not manipulate frequency but rather the amplitude of theta oscillations and this somehow stronger in the 4Hz condition than during the 7Hz condition. Future research could exclude this alternative explanation by recording EEG in addition to TMS. Furthermore, there is a risk that we did not actually stimulate the targeted IPS in each participant: Firstly, we just measured the location by using the EEG 10-20 system, which gives an approximate but possibly flawed estimate. A more precise way would be to find the exact location of the IPS in a MRI scan, although it is questionable if this effort would be worth the benefits. Secondly, the coil could have been shifted from the location during the experiment. In addition, we did not measure the individual baseline of the theta frequency in each participant (done by Vosskuhl et al., 2015) but used a general baseline of 5.5Hz, thus possibly reducing effects in participants with a rather long or short individual theta. Although less likely than in tACS, we cannot fully exclude that TMS led to remote effects in other brain regions.

Further experiments controlling for alternative explanations and possible other theoretical proposals will be necessary to be able to better understand the basic mechanisms underlying the cross-frequency-coupling of different brain oscillations. (For discussion of alternative theories concerning theta gamma coupling see Sauseng et al., 2019.) Future research could widen the perspective to not just retention of information in the visuospatial WM but on processes during encoding and retrieval of information as well as other entities of the WM like the auditive functions.

Despite the limitations it is justified to conclude that the results of our experiment are yet another piece of evidence supporting the theta gamma coupling theory proposed by Lisman and Idiart (1995). We were able to show that modulation of the theta frequency has an effect on WM capacity. Although the absolute effect is small it might be enhanced in the future and contributes to a better understanding of how Working Memory works.

Literature:

- Albouy, P., Baillet, S., & Zatorre, R. J. (2018). Driving working memory with frequency-tuned noninvasive brain stimulation. *Annals of the New York Academy of Sciences*. <https://doi.org/10.1111/nyas.13664>
- Bender, M., Romei, V., & Sauseng, P. (2019). Slow Theta tACS of the Right Parietal Cortex Enhances Contralateral Visual Working Memory Capacity. *Brain Topography*, 32(3), 477–481. <https://doi.org/10.1007/s10548-019-00702-2>
- Champod, A. S., & Petrides, M. (2007). Dissociable roles of the posterior parietal and the prefrontal cortex in manipulation and monitoring processes. *Proceedings of the National Academy of Sciences of the United States of America*, 104(37), 14837–14842. <https://doi.org/10.1073/pnas.0607101104>
- Li, S., Jin, J.-N., Wang, X., Qi, H.-Z., Liu, Z.-P., & Yin, T. (2017). Theta and Alpha Oscillations during the Retention Period of Working Memory by rTMS Stimulating the Parietal Lobe. *Frontiers in Behavioral Neuroscience*, 11, 170. <https://doi.org/10.3389/fnbeh.2017.00170>
- Lisman, J. E., & Idiart, M. A. (1995). Storage of 7 +/- 2 short-term memories in oscillatory subcycles. *Science (New York, N.Y.)*, 267(5203), 1512–1515. <https://doi.org/10.1126/science.7878473>
- Lisman, J. E., & Jensen, O. (2013). The Theta-Gamma Neural Code. *Neuron*, 77(6), 1002–1016. <https://doi.org/10.1016/j.neuron.2013.03.007>
- Sauseng, P., Peylo, C., Biel, A. L., Friedrich, E. V. C., & Romberg-Taylor, C. (2019). Does cross-frequency phase coupling of oscillatory brain activity contribute to a better understanding of visual working memory? *British Journal of Psychology (London, England: 1953)*, 110(2), 245–255. <https://doi.org/10.1111/bjop.12340>
- Voskuhl, J., Huster, R. J., & Herrmann, C. S. (2015). Increase in short-term memory capacity induced by down-regulating individual theta frequency via transcranial alternating current stimulation. *Frontiers in Human Neuroscience*, 9, 257. <https://doi.org/10.3389/fnhum.2015.00257>
- Wolinski, N., Cooper, N. R., Sauseng, P., & Romei, V. (2018). The speed of parietal theta frequency drives visuospatial working memory capacity. *PLoS Biology*, 16(3), e2005348. <https://doi.org/10.1371/journal.pbio.2005348>

Appendix:

Appendix A.)

Under the following links can be found

- Preregistration: <https://osf.io/kvd9e/>
- Codebook: <https://osf.io/ufypj/>
- Demographic data of participants: <https://osf.io/bn3vw/>
- Experimental data of participants: <https://osf.io/czqrt/>
- Script for statistical analysis: <https://osf.io/ah4ed/>

Appendix B.)

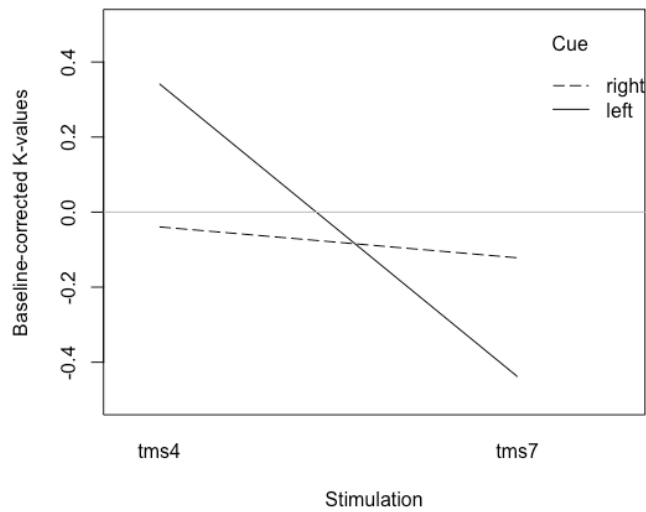
Presenting different memory loads reduced the possibility of a floor or ceiling effect. We did not differentiate between memory loads in our statistical analysis as it does not contribute to test our hypothesis, although testing results with the additional factor of memory load could be used for different hypothesis.

E. g. Bender et al. (2019) found that the significant three-way interaction between Condition x Hemifield x Memory Load was entirely driven by trials of a memory load of 6 items.

Our data could be analysed in a similar way to find if the significant effect we found is due to the same condition as in Bender et. al. (2019). To be able to do this K-values would need to be calculated separately for each memory load during data pre-processing. In consequence, the ANOVA would contain not two but three factors: Hemifield (left, right), Condition (7Hz, 4Hz), Memory Load (4, 5, 6 items).

Appendix C.)

Interaction plot of the factors Hemifield x Condition



Note: This plot shows visualizes the interaction between the two factors Hemifield x Condition. While the graph of the right hemifield condition has hardly any slope, the slope of the graph of the left hemifield condition is clearly visible. Baseline-corrected K-values are positive in the 4Hz stimulation condition and negative in the 7Hz stimulation condition.