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COMPARISON OF TMS-EVOKED EEG POTENTIALS
BETWEEN WAKING AND NREM SLEEP STATES

Seminary work

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Running head: TMS of V1 and LOC in waking and NREM sleep

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Comparison of TMS-evoked EEG potentials
between waking and NREM sleep states

Abstract

We experience the sleep-wake cycle on a daily basis, but what related underlying processes change in the brain? Using electroencephalography (EEG), the spread of the evoked potentials of non-sensory task-independent transcranial magnetic stimulation (TMS) to the occipital areas V1 or lateral occipital cortex in waking and non-rapid eye movement (NREM) sleep was compared in the study. We hypothesized that a) right-hemisphere slow negative potentials evoked by V1 TMS are reduced in NREM sleep, and b) stimulating different target sites leads to different activation patterns. Results showed significant interactions between different regions and states of consciousness in influencing the evoked EEG activity, suggesting different activation patterns in response to TMS when sleeping or awake. The data confirms and extends previous results.

Keywords: TMS/EEG, V1, lateral occipital cortex, consciousness, connectivity.

Running head: TMS of V1 and LOC in waking and NREM sleep

TMS-i poolt tekitatud EEG potentsiaalide võrdlus
ärkveloleku ja unestaadiumi tingimuste vahel

Kokkuvõte

Me kogeme igapäevaselt une-ärkveloleku tsüklit, kuid millised seotud alusprotsessid muutuvad ajus? Kasutades elektroentsefalograafiat (EEG-d), võrreldi käesolevas töös mittesensoorse ülesandest sõltumatu oksipitaalse V1-le või lateraalsele oksipitaalsele korteksi piirkonnale rakendatud transkraniaalse magnetstimulatsiooni (TMS) poolt esile kutsutud potentsiaalide levikut nii ärkvelolekus kui ka aeglase silmaliigutuste (NREM) une ajal. Püstitasime hüpoteesid, et a) oksipitaalse V1 piirkonna TMS tekitab paremas hemisfääris NREM une ajal vähemal määral väljendunud aeglaseid negatiivseid potentsiaale, ning b) erinevate piirkondade stimuleerimine viib erinevate aktivatsioonimustriteni. Tulemused näitasid olulisi interaktsioone erinevate piirkondade ning teadvusseisundite mõjude vahel EEG aktiivsusele, viidates erinevatele aktivatsioonimustritele vastuseks TMS-le sõltuvalt sellest, kas stimulatsioon toimus katseisiku magades või ärkvelolekus. Andmed kinnitavad ja laiendavad varasemaid tulemusi.

Märksõnad: TMS/EEG, V1, lateraalne oksipitaalne korteks, teadvus, ühenduvus.

Läbiv pealkiri: V1 ja LOC TMS ärkvel ning NREM une seisundis

Introduction

Loss of consciousness is the hallmark feature of human sleep, but until the present time relatively little is known as to why it fades every single night. According to philosopher David J. Chalmers, questions about consciousness can be divided into „easy“ and „hard“ problems. The easy problems (e.g. the difference between wakefulness and sleep) are those (eventually) explainable by standard methods of cognitive science (through computational or neural mechanisms), while the hard problems (such as the conscious *experience* itself) seemingly resist similar approaches (Chalmers, 1995). Yet some believe consciousness can be fully understood by simply solving all the „easy“ problems, so no additional „hard“ problem even exists (Dennett, 1996). Many modern researchers have focused their efforts to unravel the conscious experience through the exploration of the neural correlates of consciousness (NCC). In one view, these are “the minimal set of neuronal events and mechanisms jointly sufficient for a specific conscious percept” (Koch, 2004, p. 9). Many have studied NCC-s with respect to high-frequency (fast) oscillations in recorded activity level (Crick & Koch, 1990; Melloni et al., 2007; Steriade, 2000). Others have turned their attention to the possibility of slow cortical potentials as the markers of consciousness (Birbaumer, 1999; Devrim, Demiralp, Kurt, & Yücesir, 1999; He & Raiche, 2009; Stamm, Aru, & Bachmann, 2011). In the current study the second line of research is pursued.

One prominent way to investigate causal effects in different states of consciousness is to study the sleeping brain in a task-free experimental setup with non-invasive transcranial magnetic stimulation (TMS) (Jahanshahi & Rothwell, 2000; Stamm et al, 2011; Pascual-Leone, Bartres-Faz, & Keenan, 1999). By safely stimulating the cortex with a magnetic field, TMS allows researchers to investigate the communication between different cortical brain regions without unwanted peripheral effects (Ferrarelli et al., 2010). Combining TMS with electroencephalography (EEG) recording enables to map the spread of the electric activity induced by the administered TMS impulse in the surface layers of the brain (Komssi & Kähkönen, 2006). This combination allows to examine different theories of consciousness in various states (Stamm et al., 2011). One of these theories, which has been investigated by combining TMS and EEG, is the integrated information theory, which states that the quantity of consciousness corresponds to the amount of integrated information generated by a complex of elements (Tononi, 2008). In strongly simplified terms, more information

integration in the system might equal more consciousness. Previous TMS experiments combined with EEG recordings in waking and sleep have shown various effects - breakdown of effective connectivity and loss of variability in cortical activation patterns in sleep, among others (Esser et al, 2005; Esser, Hill, & Tononi, 2009; Massimini et al., 2005, 2010; Rosanova et al., 2009). It is also known that TMS pulses evoking slow waves in NREM sleep are unable to do so during wakefulness (Massimini et al., 2007). Another study found that in NREM sleep rostral right pre-motor cortex TMS response did not propagate far beyond the stimulation site (compared to waking conditions) (Massimini et al, 2005). From these results one can suggest that a breakdown of cortical effective connectivity may be an underlying feature of loss of consciousness and might, thus, remotely support the information integration theory of consciousness (Tononi, 2008).

TMS manipulation with EEG recordings in task-free waking and sleep conditions for the study of consciousness therefore warrants further investigation. TMS has so far been primarily used for motor cortex stimulation (Overgaard, Nielsen, & Fuglsang-Frederiksen, 2004). In the present study, EEG data in response to TMS to different visual areas (V1 and lateral occipital cortex, LOC) in waking and sleep are collected and examined. V1 as a stimulation site has been successfully used elsewhere (Stamm et al., 2011). To the author's knowledge, LOC has not been stimulated with TMS in sleep states before. The region was chosen as a target location for its known role in visual object processing (Grill-Spector, Kourtzi, & Kanwisher, 2001; Mullin & Steeves, 2011) and activation in REM-sleep (Braun et al., 1997). Importantly, in contrast to V1, LOC has direct connections with the prefrontal cortex (Crick & Koch, 1995), thus different activation patterns following V1 and LOC stimulation can be expected. Also, the visual cortex with its long neuroanatomical cortical distance from frontal regions offers a chance to explore long range brain region interactions and effective connectivity, thereby enabling to investigate the theoretical approach suggested by others (Massimini et al, 2005; Tononi, 2004).

The strong methodological overlap with previous work by Stamm et al. (2011) also allows to assess the reproducibility of those results. This is important in the light of present-day discussions around the importance of scientific replication and the concern that some basic science findings can not be replicated at all (Open Science Collaboration, 2012). Stimulating

the left or right occipital V1, Stamm et al. (2011) found a decrease of relative negativity in the right hemisphere under NREM conditions. The effect was strongest in the right-frontal region.

Considering all the above, the present study establishes two general hypotheses. Firstly, right hemisphere slow negative potentials evoked by occipital V1 TMS are reduced in NREM sleep compared to wakefulness (reproducing the results of Stamm et al., 2011). Secondly, although TMS stimulation of V1 and LOC create different activity patterns, the difference between the waking and NREM conditions will be the hemisphere-specific slow negative potentials in both instances.

Materials and methods

Participants

Eight healthy subjects (5 female, 3 male, mean age 23.9, age range 21-32) participated in the study. All of them were right-handed, non-smokers, sober and fully rested before the study and did not report any history of sleeping disorders nor caffeine use prior to the experiment. All participants were screened for adverse effects of magnetic resonance imaging (MRI) and TMS, were fully briefed about the study beforehand and signed an informed consent form. The experiment was approved by the Ethics Review Committee on Human Research of the University of Tartu and was carried out in compliance with the Declaration of Helsinki.

Design

A pilot study with three subjects was conducted prior to the main experiments. The goal of these sessions were to find the optimal sleeping conditions in the laboratory (time, temperature, position of the chair, configuration of the EEG electrodes, lighting conditions, TMS sound masking). No EEG data from the pilot study was used in the final analysis. One of the participants in the pilot study also took part in the main experiment. There, subjects were laying horizontally and with closed eyes on the chair of the EEG/TMS set, with a custom-made head-rest allowing a comfortable position on the right side of the body.

The subject came to the laboratory at 21.00. After the preparation of the EEG cap, the subject

was allowed to start falling asleep at around 23.00. The subjects wore ear plugs and masking noise was played through nearby speakers to minimize the confounding effects of the TMS click (Nikouline, Ruohonen, & Ilmoniemi, 1999). The main experiment consisted of up to 18 stimulation blocks (8 wakefulness, 8 NREM and 2 REM). Sleep was defined on-line as the presence of sleep spindles and slow high-amplitude waves on the EEG recording (Hori et al., 2001; Ogilvie, 2001). Each block consisted of 50 trials of TMS with a 4-second (occasionally longer) pause between each stimulation, the whole block lasting a total of about 4 minutes. TMS pulses were delivered either to the left LOC or to the left V1 in an ABAB design between blocks and counterbalanced across participants when applicable. The TMS target locations (Figure 1) were obtained from similar TMS experiments (Chouinard, Whitwell, & Goodale, 2009; Cohen, Cross, Tunik, Grafton, & Culham, 2009; Kim, Biederman, & Juan, 2011; Mullin & Steeves, 2011; Pitcher, Duchaine, Walsh, Yovel, & Kanwisher, 2011; Stamm et al., 2011) and marked on the EEG cap with the aid of Navigated Brain Stimulation (NBS) (Nexstim Ltd) and individual MRI images acquired earlier. There was a pause of varying length between each block, during which the TMS coil was repositioned and EEG gel added to the electrodes. Some 3-minute resting state recordings with no stimulations were also made during this time. The experiment ended around 02.00. A total of up to 900 trials were recorded for each subject. All experiments (with the exception of one) were conducted by the author of this seminary work.

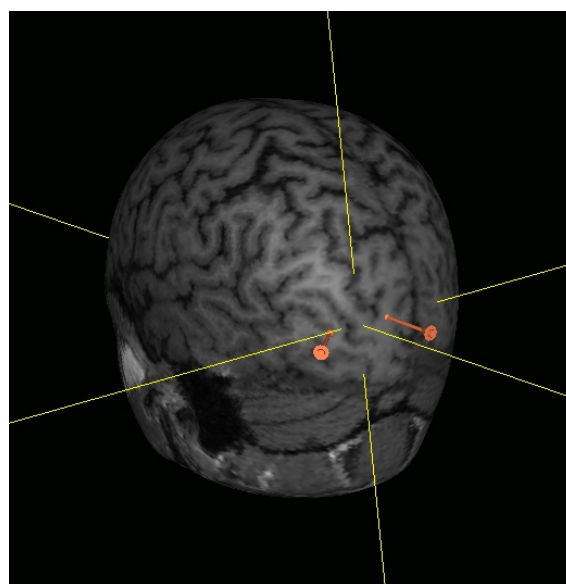


Figure 1. Representative locations of occipital TMS sites in 3D space, as assigned with the help of NBS. Brown pins from left to right: left LOC and left V1.

One subject in the main experiments only attained brief periods of light sleep and was therefore excluded from later data analysis. Also, REM sleep was very rare across all subjects in the laboratory setting, so the REM condition was left out of the final analysis. From the remaining 5 subjects and 4 conditions (state of consciousness (wake, NREM) and stimulation area (V1, LOC)) at least 86 trials per person per condition (mean 134) were collected.

Apparatus

MRI-assisted NBS system was used to locate the two stimulation sites (with an error less than 2 mm), which were then marked on the EEG cap. For the sake of comfort of the sleeping subject, the NBS system was not used during the trials. Ear plugs and masking noise (pre-recorded clicks) were used to eliminate the subject's perception of the TMS coil's click and to prevent contamination of TMS-evoked potentials. The room was darkened in order to prevent confounding the effects of TMS pulses with the effects of visual sensory stimulation. TMS pulses were delivered by a biphasic figure-of-eight coil (wing diameter of 70 mm). Stimulation intensity was 50% of the maximum output of the stimulator and corresponded to a maximum estimated electric field on the target of about 50 V/m. EEG was recorded by Nexstim eXimia EEG-system with a cap of 60 carbon electrodes and a TMS-compatible amplifier (Nexstim Ltd). All EEG signals were referenced to an additional reference electrode placed on the middle part of the forehead and sampled at a sampling rate of 1450 Hz. The signal was amplified with a gain of 2000 and with hardware based band-pass filter of 0.1-350 Hz. Electrooculogram electrodes were placed on the left side of the subjects face to detect eye movements.

Data analysis

Data analysis was performed in Fieldtrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) running under Matlab R2012a (Mathworks, Inc.) and in IBM SPSS Statistics 16. EEG data was filtered with a 30 Hz low pass filter and epoched around the TMS-stimulation event (-500 to 1000 ms). The time interval used for baseline correction was set at -100 – 0 ms as measured with regards to TMS stimulation onset. All EEG data were visually inspected for ocular and muscle artifacts, strong alpha waves and electrodes containing noise. Trials containing artifacts were rejected and noisy electrodes were repaired by interpolating their

average from 3-4 neighboring electrodes. EEG channels were divided into three regions. The regions of interest (ROI-s) corresponded to those from Stamm et al. (2011) and were frontal (electrodes AF1, F1, F4, F7, FP1, AF2, F2, F3, F8, FP2, AFZ, FPZ), central (C1, C3, C5, FC1, FC3, FC5, C2, C4, C6, FC2, FC4, FC6, FCZ, CZ) and parietal (CP1, CP3, CP5, P1, P3, P7, CP2, CP4, CP6, P2, P4, P8, CPZ, PZ). To analyze event-related potentials (ERP-s), each ROI was further divided between left and right hemisphere (leaving out the midline electrodes). A $2 \times 2 \times 2 \times 3$ (state of consciousness, site of stimulation, hemisphere, ROI) repeated measures ANOVA was used to calculate the differences and interactions between all the conditions in the time frame 400-1000 ms. Where necessary, the Greenhouse-Geisser correction for sphericity was applied. Topographic voltage maps were plotted for 0-50 ms and after every 150 ms thereafter (until 800 ms) for both hemispheres.

Results

Different stimulation sites (V1/LOC) or states of consciousness (wake/NREM) separately did not produce significantly different patterns of brain activity in response to the TMS pulse ($F(1,4) = .047$, $p = .840$ and $F(1,4) = .804$, $p = .421$, respectively). As expected, the voltages in the ROI-s differed significantly ($F(2, 8) = 10.31$, $p = .029$) with the activity being more positive over the central and parietal electrodes (Figure 2). Analysis of hemispheric effects also showed a significant difference ($F(1, 4) = 9.157$, $p = .039$). As can be seen from the amplitudes in Figure 3, the TMS-induced electrical activity in the stimulated left hemisphere was stronger. Most importantly, there was a clear interaction between ROI and state of consciousness ($F(2, 8) = 11.149$, $p = .005$). In the waking condition the stimulation caused moderate activity spread across the whole brain, while in the NREM condition the frontal ROI exhibited more relative negativity. The parietal ROI electrodes registered strong positive waves in NREM, showing a more localized spread of TMS induced activity compared to waking (Figure 2). The same conclusions can be made from the topographic voltage maps (Figure 4).

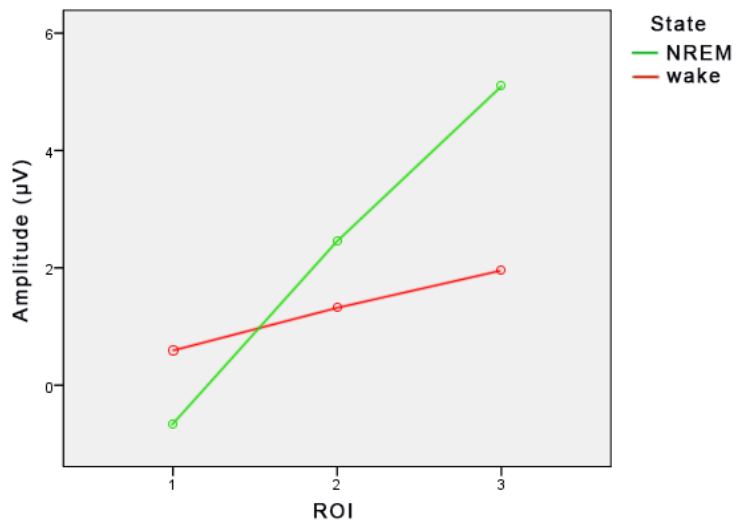


Figure 2. The interaction between state of consciousness and ROI (1 – frontal; 2 – central; 3 – parietal) in determining the EEG response.

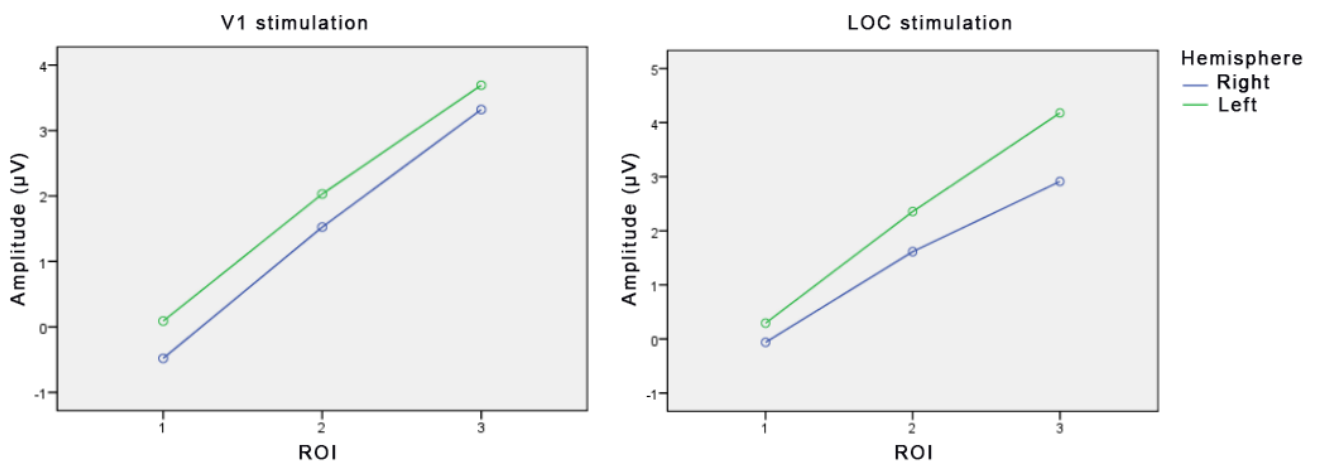


Figure 3. EEG activity showing the interaction between hemisphere, stimulation target location and ROI (1 – frontal; 2 – central; 3 – parietal).

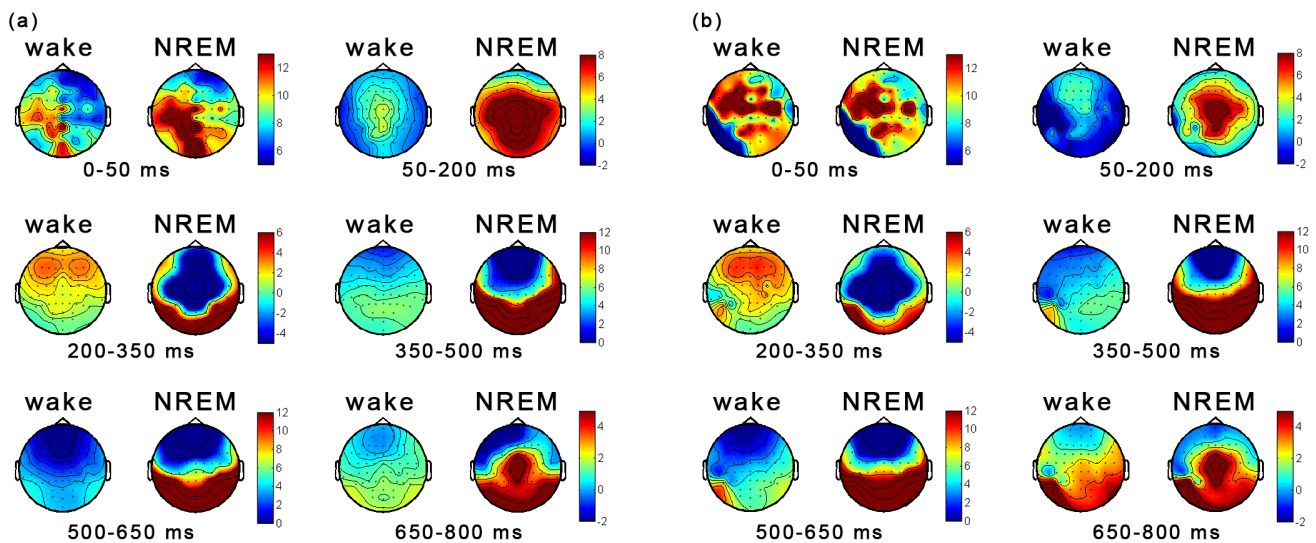


Figure 4. Topographic voltage maps averaged for all electrodes when stimulating V1 (a) or LOC (b). The time frame is 0-800 milliseconds (ms). The voltage colour bar units are in microvolts (μV).

Regarding the second hypothesis, there was an interaction between ROI, hemisphere and stimulation target location ($F(2, 8) = 15.85, p = .009$) (Figures 3, 4 and 5). V1 and LOC stimulation produced different effects in ROI-s, with more relative negativity in the right hemisphere and the effect being stronger for the parietal electrodes after LOC stimulation. The ROI x hemisphere interaction was also statistically significant ($F(2, 8) = 5.859, p = .049$), but this can be expected from the experimental plan, whereby stimulations were only administered to the left hemisphere. The main differences and similarities across all the conditions can also be seen on the ERP plots (Figure 5).

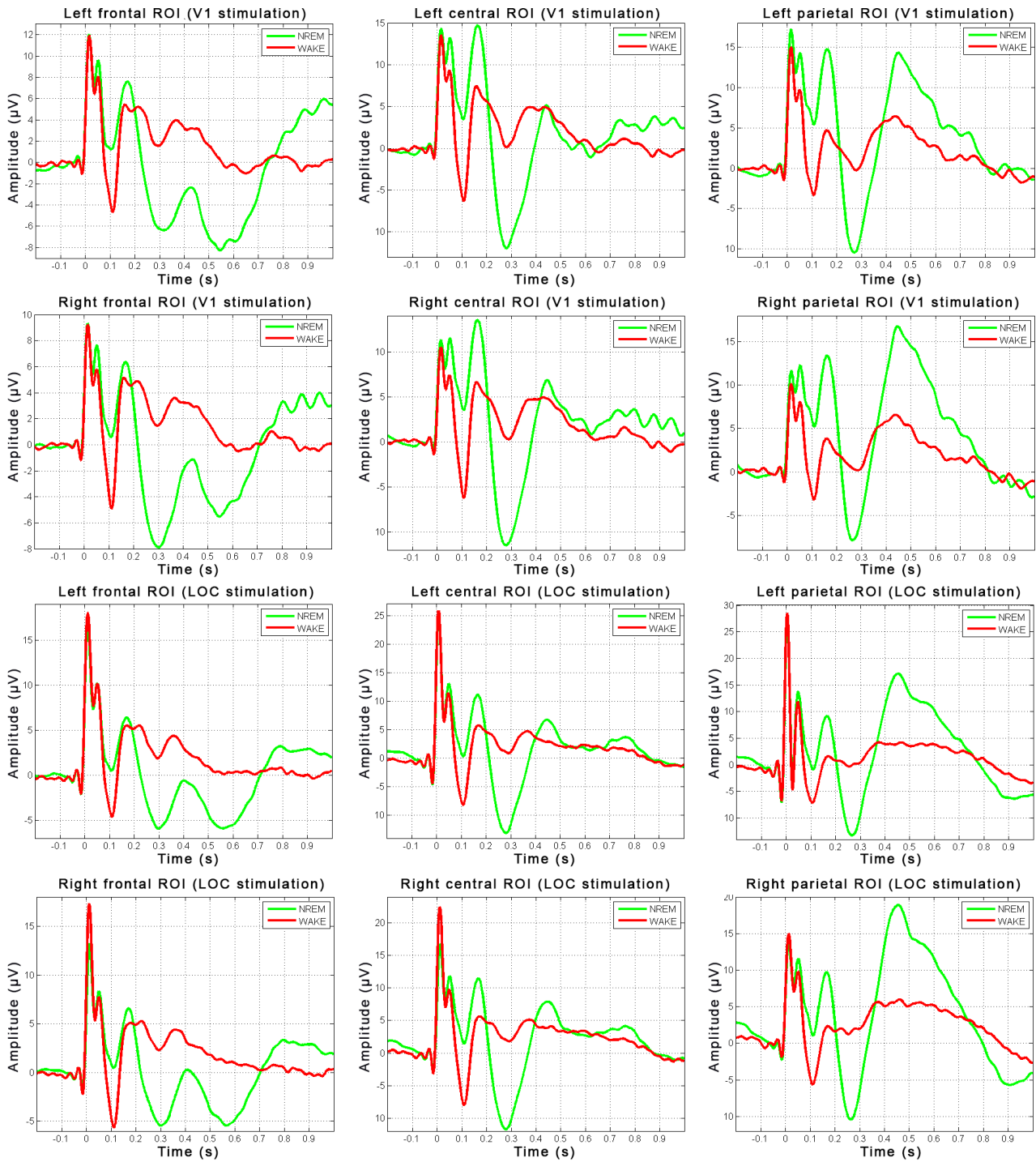


Figure 5. ERP plots for every ROI and stimulation site combination. The time frame is -200 to 1000 ms. TMS onset is at 0 ms.

Discussion

TMS/EEG combination was used to study the effects of different states of consciousness and stimulation sites on the connectivity of the cortex. It was hypothesized that right hemisphere slow negative potentials evoked by occipital V1 TMS would be reduced in NREM sleep compared to wakefulness. We also suggested that different stimulation sites would differ in terms of evoked slow negative potentials.

While Stamm et al. (2011) found a significant interaction between the hemisphere and the state of consciousness over all ROI-s, the main result of the current study was the interaction between ROI and state of consciousness (Figure 2). As the parietal electrodes registered stronger positive waves in NREM compared to waking, the spread of TMS-evoked activity in sleep was more localized (see also Figure 4). These data fit well with previous findings (Massimini et al., 2005) and partially confirmed the first hypothesis – the effects of states of consciousness were indeed region-specific and waking state is associated with region-specific relative negative potentials. However, in contrast to Stamm et al. (2011), in our study, the relative negativity related to consciousness was not confined to the right hemisphere, but was rather more pronounced on the parietal electrodes. Interestingly, no general main effect of the state of consciousness was found either in the present study or in the work of Stamm et al. (2011). State of consciousness has region-specific effects on TMS-evoked activity propagation. It is unclear why this specificity arises and why the region-specific activation patterns were different in the present study and the study of Stamm et al. (2011). Noticeable differences to the aforementioned article were stronger ERP components (Figure 5) in the current study. A possible explanation for this is that a stronger TMS stimulation (estimated at ~50 V/m compared to ~25 V/m from Stamm's work) was used. The stronger responses might also be attributed to deeper sleep stages in the present data, as the experimenter tried to avoid collecting trials from the beginning of the very first sleep stage.

When visually comparing the ERP plots from V1 stimulation conditions to those from Stamm et al (2011), a few conclusions can be drawn. The patterns of waking state peaks and valleys are similar, when the stronger stimulation parameters of the current study are neglected. NREM potentials, however, are very different, with our calculated ERP-s being clearly more

negative and much bigger in amplitude. The findings contradict those of Stamm et al. (2011) in respect of the frontal regions in the analysis of the current study showing *increased* late negativity. When looking at the differences in ERP components between V1 and LOC TMS conditions, it can be seen that LOC stimulation produced a much stronger initial response in both hemispheres. Another effect is the slight decrease of relative negative potentials in frontal ROI-s when LOC is stimulated. These region-specific differences of V1 and LOC stimulation were evident in the significant interaction between the stimulation target, the electrode hemisphere and the electrode region. However, these effects were not dependent on the state of consciousness. Thus our second hypothesis - that LOC and V1 stimulation lead to different activation patterns while the effect of conscious state is the same, was also partially confirmed. Although, based on the study by Stamm et al. (2011), we had hypothesized that the difference between the states of consciousness after stimulating both target regions would be the hemisphere-specific negativity, in both cases we observed region-specific relative negativity as the marker of the state of consciousness.

The present study may have suffered from many confounding factors. First, there were only five subjects in the experiment and thus the results have very little statistical power. Second, due to inter-individual difference in brain anatomy or cortex morphology, it is not absolutely certain that V1 and LOC areas were actually stimulated, as no *functional* MRI mapping was performed prior to the experiment. During the experiment the TMS coil may have moved to an inaccurate position as the use of precise real-time NBS navigation was not possible. Also, TMS coil vibration could have resulted in the movement of the electrodes, causing direct-current shifts in the signals of the electrodes near the coil, muscles twitches, and involuntary eye blinks (Komssi & Kähkönen, 2006). The TMS pulse may have also been contaminated with expectations of the subject, as the stimulation was mostly administered with a fixed four-second interval. This could be very troublesome for our study, as the expectations could cause a contingent negative variation potential in the brain when awake (Tecce, 1972) and be absent when the subject sleeps, resulting in a noticeable difference in the EEG recording. Sleep stage classifications may have also contained errors due to the lack of polysomnographic data and the inexperience of the experimenter. The possible hemispheric effects may have been masked because only one hemisphere was stimulated. Lastly, as the experimental setup was not originally intended for sleep research, the slightly

uncomfortable sleeping conditions may have prohibited the occurrence of true natural sleep. Future experiments should overcome the limitations stated above by increasing the number of study subjects and mapping the targeted brain regions with functional MRI. Also, a comfortable NBS navigation system for exact TMS coil positioning should be developed for the use with sleeping subjects. The TMS pulse should be administered with a variable interval and to both hemispheres. And finally, muscle tone recordings could be used for easier assessment of sleep stages.

Conclusion

Non-sensory task-independent TMS stimulation to the occipital cortex in waking and NREM sleep revealed that the state of consciousness had an effect on the TMS pulse propagation, which depended on the area recorded. Although the effort to repeat the results from Stamm et al. (2011) about reduced right-hemispheric slow negative potentials in NREM sleep failed, this could be due to the differences in the experimental plans. The current study used stronger TMS pulses and stimulated only the left hemisphere. We observed that conscious state was associated with more negative potentials in posterior electrodes. Stimulating different visual areas (V1 or LOC) led to different activation patterns while the effect of the state of consciousness was similar in both cases. These data about brain connectivity could be used to develop the diagnostic tools for patients with disorders of consciousness (Boly, 2012; Rosanova, 2012). Overall, the current study and similar future works gradually build up the knowledge to perhaps finally solve the “easy” problems of consciousness.

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Madis Vasser