Sensory and auditory evoked responses mimic synchronization of cortical oscillations induced by Transcranial Magnetic Stimulation

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Abstract:

Background: Entrainment of cortical oscillations by repetitive Transcranial Magnetic Stimulation (rTMS) is an attractive approach to modulate brain function non-invasively in humans. Here, we applied rTMS in order to modulate oscillatory activity in ventral premotor cortex (PMv), primary motor cortex (M1), and anterior intraparietal sulcus (aIPS). These areas are thought to contribute to recovery after motor stroke and our overarching goal is to enhance their impact by rTMS. To this end, we established a setup with bifocal, neuronavigated rTMS combined with EEG and tested its technical feasibility.

Methods: Bifocal zero-phase lag synchronized rTMS at 11Hz was applied in seven young healthy volunteers to the target pairs (i) PMv and M1 and (ii) aIPS and M1. Adapting to the close vicinity between target areas, we used two small, commercially available coils and applied subthreshold stimuli in order to avoid motor evoked potentials (MEPs). Besides a parieto-occipital sham stimulation, we also included auditory and sensory stimulation in a further control experiment.

Results: First, subthreshold TMS led to a phase synchronization and evoked time-averaged potentials in the EEG. However, the same findings could be elicited by peripheral, somatosensory stimulation combined with auditory stimulation. Second, despite the small coils neuronavigation analysis showed that in most participants aIPS and M1 or PMv and M1 could not precisely be targeted due to their vicinity and restriction in coil positioning. Third, bifocal subthreshold rTMS tended to sum up where the induced fields showed the greatest overlap resulting in overt MEPs and thus raising potential safety issues.

Conclusions: The presented data show refinements for bifocal rTMS studies regarding (i) spurious entrainment or resetting effects on brain oscillations, (ii) precise anatomical targeting of areas in close vicinity, and (iii) summing up of overlapping induced electrical fields.

1. Introduction

Beyond the descriptive analysis and inferences about function and reorganization of large-scale neuronal networks, there are multiple efforts to enhance network function by positively influencing large-scale neuronal networks. For example after a brain lesion due to stroke, there have been many attempts to modulate activity focally in strategic network nodes (Cazzoli et al., 2012; Duque et al., 2005; Y. H. Kim et al., 2006). So far, the reported effect sizes were quite small (for review see (Schulz et al., 2012)). Another, potentially more powerful approach could be to entrain oscillatory coupling between network nodes by stimulation of at least two strategic nodes simultaneously (Plewnia et al., 2008). Conceptually, the latter might be more effective because it targets the signal integration between two areas of interest rather than only modulating one network node. Technically, both repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial alternating current stimulation (tACS) have the potential to exert rhythmic non-invasive brain stimulation and thereby entrain cortical rhythms (Helfrich et al., 2014; Krawinkel et al., 2015; Thut et al., 2011; Vernet et al., 2013; Zaehle et al., 2010). While tACS is easier to apply, rTMS is topographically more specific.

There is converging evidence that successful motor recovery after stroke depends, in part, on enhanced activity of secondary motor areas like the ventral premotor cortex (PMv), supplementary motor area (SMA) or anterior intraparietal sulcus (aIPS) (Bönstrup et al., 2016; Gerloff et al., 2006; Rehme et al., 2011; Rehme and Grefkes, 2013; Schulz et al., 2016; Sharma et al., 2009). Especially when addressing the integration of these areas in the cortical motor network, the analysis of oscillations is of interest because of their close representation of electric neuronal activity at the population level and the high temporal resolution. From recent studies, there is evidence that distinct connectivity signatures of alpha-band oscillations are possibly associated with control of motor function and recovery in stroke patients (Boenstrup et al., 2014; Dubovik et al., 2013). Task-related alpha-band coherence, for example, between aIPS and primary motor cortex (M1) was found to be increased in well recovered chronic stroke patients compared with healthy individuals

(Bönstrup et al., 2018). Within this patient cohort, the parieto-frontal task-induced coupling pattern was significantly and positively related to residual impairment of hand motor function (Bönstrup et al., 2018). One interpretation of this finding is that parieto-frontal functional coupling subserves motor recovery and is more pronounced in patients who exhibit a greater residual deficit, that is, have greater need of further brain reorganisation. Besides the aIPS which has only recently gained more interest in the context of stroke, the influence of the PMv in the motor network has been extensively investigated (Horn et al., 2016; Schulz et al., 2015a). Also for PMv, alpha-band oscillations are likely to have a prominent role in motor coding (Bönstrup et al., 2016).

Hence, we opted to apply rTMS to modulate coupled alpha-band oscillations between aIPS and M1 and between PMv and M1 in a group of healthy, young adults (similar to (Plewnia et al., 2008)). Both aIPS and PMv are located at the hemispheric convexity and have been shown to be accessible to TMS (Koch et al., 2010a, 2010b).

After the first series of experiments, we observed a number of non-specific rTMS effects in this particular setting, which we considered worth reporting. These effects have not been described so far and the information provided here may help avoiding flaws in designing similar experiments in the future.

2. Methods

2.1. Participants and study procedure

Seven young, healthy, female, right-handed participants were included in the study (mean age 26 years, ± 4.1 SD). Contraindications of NIBS were checked using a safety questionnaire (Rossi et al., 2011, 2009). In an initial step, we tested whether it was possible to elicit MEPs in our participants wearing an EEG-cap (easyCAP®, Brain Products GmbH, Gilching, Germany). Two participants were excluded from further testing because it was not possible to elicit reliable motor evoked potentials (MEPs) through the cap. Subsequently, EEG electrode-positions were registered using an ultrasound localization system (CMS20, Zebris, Isny, Germany) and individual resting-motor-threshold (RMT) wearing the EEG-cap

was measured. Afterwards, the EEG-cap was prepared using abrasive gel in order to keep impedances below 10kOhm. In a fourth step neuronavigation for M1, PMv and aIPS was performed ensuring correct target locations of the TMS coils relative to individual brain structure. In general, we stimulated the left, dominant hemisphere. Target positions for PMv, M1 and aIPS were marked on the EEG cap. Then the recording session started. A single-pulse session was followed by a repetitive TMS session. Resting-state EEG was recorded before and after each TMS session.

All participants gave written informed consent according to the declaration of Helsinki. Study procedures were approved by the local Ethical Committee of the Medical Association of Hamburg (PV4931).

2.2. EEG-recordings

EEG was recorded from 60 Ag/AgCl passive electrodes and was referenced to a nose-tip electrode during recordings (BrainAmp MR Plus® amplifier, Brain Products GmbH, Gilching). Positions were arranged in the 10/20 system (easyCAP®, Brain Products GmbH, Gilching, Germany). Recordings were sampled at 5000Hz and amplified in the range of ± 16.384 mV at a resolution of 0.5 µV. To control for MEPs during the experiment, electromyography was measured using a bipolar montage on right first dorsalis interosseous muscle with tendon reference on the index finger (brainAmpExG®, Brain Products GmbH, Gilching, Germany).

2.3. TMS-setup

TMS was performed with a Magstim Super Rapid 2® and Magstim Super Rapid 2 Plus® and two small coils with an inner radius of 25mm (P/N 1165-00, connected via an inline inductor, P/N 3467-00, Magstim, Whitland, UK, Fig. 1). TMS was triggered by a Linux-based, custom-made setup, which marked each TMS pulse in the EEG timeline. MEPs for detection of RMT were recorded, amplified and converted using a CED 1902 and a CED micro 1401 (CED, Cambridge, UK). RMT was detected for each stimulator separately. RMT was defined as the lowest TMS intensity which elicited a motor evoked potential (MEP) amplitude >50µV in at

least five of ten consecutive trials. Neuronavigation was performed with a Brainsight® system (Rogue Research, Montreal, Canada). Individual high-resolution T1-weighted anatomical images were used to perform 3D-reconstructions (3T Magentom Skyra MRI scanner, Siemens, Erlangen, Germany) in each participant. PMv, aIPS and M1 were marked individually on the basis of critical landmarks (see Fig. 6). Since coils overheated due to high intensities especially during application of rTMS, they were cooled between conditions.

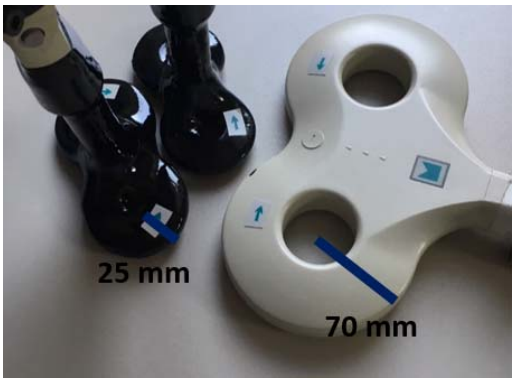

Figure 1. Comparing the Magstim “25mm coils” (left) to a Magstim 70mm coil. TMS with the two “25mm coils” was applied in a shifted fashion to reduce inter-coil-distance.

2.4. TMS-paradigms

The experiment took place in an EEG lab with participants seated in an armchair with the right and left arm comfortably in their lap. Participants were instructed to avoid eye blinks and movements. A full-HD monitor (viewangle ±5°, Monitor 24”, Dell, Texas, USA) presented a fixation cross during all trials.

The initial experiment comprised four conditions with 90% of RMT both for the singe-pulse (4 participants) and the rTMS session (3 participants): (i) bifocal aIPS-M1 stimulation, (ii) bifocal PMv-M1 stimulation and (iii) monofocal M1 stimulation as a control for M1 effects of stimulation. Application of TMS over electrode position PO3 (10-20 system) served as a (iv) sham condition because we did not expect any responses in the motor system to parieto-occipital stimulation. Conditions were randomized across participants.

Single-pulse experiments

A total of 32 trials were recorded for each of the presented 4 conditions during the single-pulse session. Trials had an overall length of 8s, with at least 3s pre-stimulus and 3s post-stimulus interval. A jittered interval (0-2s) was added to the pre-stimulus interval, and the remaining time to 2s was added to the post interval. Thus, in total an interval of 2s was added to each trial. The inter-trial interval was 6s.

Pulse-train experiments

A total of 8 trials were recorded for each of the presented 4 conditions during the rTMS session. RTMS was performed with a frequency of 11Hz resulting in 20 pulses per trial. Trials had a length of 22s, with at least 9s pre-stimulus and 9s post-stimulus interval. RTMS was applied in windows of 2s, the last pulse being the start of the post-stimulus interval. Again, a jittered interval (0-2s) was added to the pre-stimulus interval and the remaining time to 2s was added to the post-stimulus interval. For the rTMS-sessions, the inter-trial intervals were 14s.

The experiment was further adjusted in one participant who was willing to participate in an extended experimental session in which several additional control conditions were added. Due to safety concerns (see section 3.3.) the stimulation intensity was reduced to 70% of RMT in this additional experiment. Next to (i) monofocal M1-stimulation, (ii) bifocal aIPS-M1 stimulation, (iii) bifocal PMv-M1 stimulation and (iv) sham stimulation of PO3, an additional (v) bifocal sham stimulation on PO3 and Fp1 was performed. A further sham condition was implemented. We (vi) inverted a 70mm coil and asked the participant to define the intensity that provoked the same sensation as the TMS-application with the small coils. The participant reported a comparable sensation at 33% stimulator output. Hence we performed a stimulation with the inverted 70mm coil with an intensity of 33% stimulator output. Furthermore, an (vii) auditory stimulation was performed by holding one TMS coil behind the

participant's head (no contact with the skin). The stimulation was applied using the distance from left ear to M1, holding the coil planar and pointing to the participant's left ear with an angle of 45°. Another condition was a (viii) pure sensory stimulation of the left temporal face area being not covered by the EEG cap. For this condition a constant current stimulator (Digitimer, DS7A, Welwyn Garden City, UK, also triggered by the Linux-based-setup) was used, applying two times the intensity of sensory threshold (2x3.7mA, 400V max, pulse width of 50µs). A final control condition (ix) combined somatosensory and auditory stimulation. The trial length of the adjusted setup was analogue to original study setup.

2.5. Data-Analysis

First, single-pulse TMS data were processed into trials from -2 to 2s from the TMS pulse and rTMS data were processed from -4 to 2s from last TMS pulse of each train. Second, the TMS artifacts were removed by interpolating an interval of 15ms following each TMS pulse (Thut et al., 2011). For analysis of TMS-evoked (EEG) potentials (TEPs), the data were subsequently filtered with a bandpass filter (4Hz to 45Hz). Afterwards, the data were down-sampled to 1000Hz, then trials were time-averaged. EMG-data was highpass (4Hz) and bandstop filtered (48-52Hz). For phase analysis, raw data were reverse filtered (9-13Hz) after interpolation. One pass reverse filtering was used to avoid a contamination by filter-ringing in the signal following TMS pulse. After filtering, data was shifted by half the filter order to correct for filter-induced offset. To analyze local phase properties, the filtered data were Hilbert transformed. Due to the small sample size, results are based on visual inspection. We did not perform statistical testing.

In general, the EEG data were analyzed with the FieldTrip package (Oostenveld et al., 2011) on the basis of MATLAB, version 9.2.0.538062 (Mathworks Inc., Massachusetts, USA).

3. Results

All participants tolerated the various forms of single-pulse TMS and rTMS well. No severe adverse effects occurred.

3.1. TMS intensities

As described in section 2.1, initially, RMT was detected in each participant. In one participant, it was not possible to elicit stable MEPs (with the coil placed on top of the cap-mounted electrodes). In another participant, it was not possible to elicit any response in the EMG at all. In all other participants, TMS was applied with 90% RMT which corresponded to 81% stimulator output (±7%) on the Super Rapid 2 and 80% stimulator output (±7%) on the Super Rapid 2 plus, respectively. In the extended experimental session performed in one participant, TMS was applied with 55% (Super Rapid 2) and 57% stimulator output (Super Rapid 2 plus) corresponding to 70% RMT.

3.2. EEG responses to TMS

Since this study focuses on the modulation of ongoing oscillatory activity, TMS-related local phase locking of 11Hz alpha-band was computed as a first step. To comprehend EEG responses to a TMS application with the 25mm coils, EEG during monofocal, single-pulse stimulation of M1 was first examined. Analysis revealed a clear phase-locking to the TMS-stimulus at electrode C3, covering the left sensorimotor cortex. Second, these results were compared with the effects of sham stimulation. Rather unexpectedly, a similar phase-locking pattern at electrode C3 was observed after sham stimulation over position PO3 (Fig. 2A). To further study the effects of sham stimulation, TEPs were computed as time-averaged cortical responses to TMS (Fecchio et al., 2017; Rosanova et al., 2009). Figure 2B shows TEPs to single-pulse TMS. Like in the phase-locking analysis, TEPs were similar with M1- and sham-stimulation.

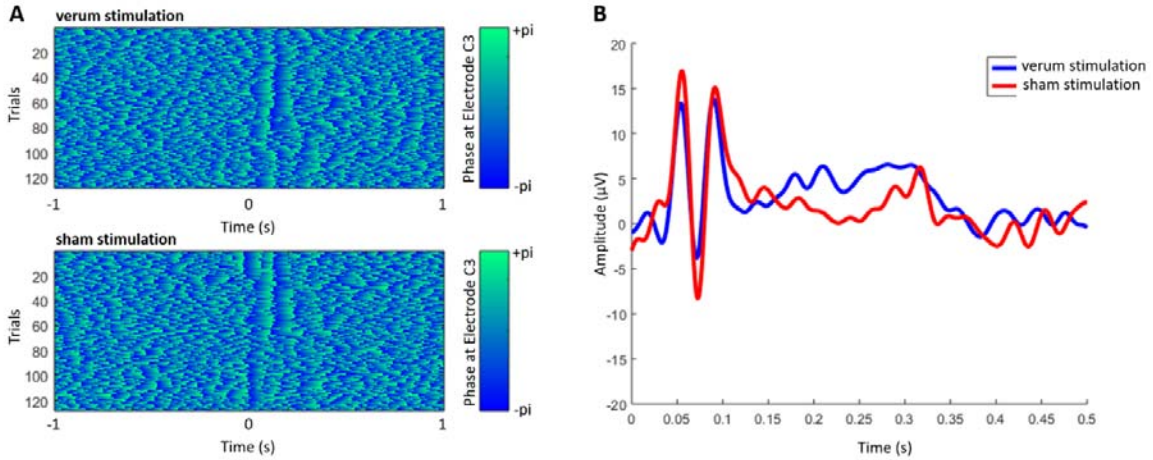

Figure 2. A: Phase properties of 11Hz alpha-band. Figures show responses to monofocal, single-pulse TMS over left M1 (verum) and over parieto-occipital sham stimulation of four participants. Color indicates phase-angles from +pi to –pi at electrode level C3. TMS was applied at time = 0s. **B**: TEPs at central electrodes (mean of C1, C3, FC1, FC3, CP1, CP3) averaged over participants. TMS was applied at time = 0s.

To clarify the influence of somatosensory and auditory input induced by subthreshold TMS, we performed an additional session including somatosensory and auditory stimulation in a single subject. This set of experiments confirmed and extended the key findings of our study: Auditory, somatosensory and combined auditory-somatosensory input led to both an evoked potential as well as a directedness of 11Hz-band phase-angles comparable to a “verum” TMS over M1. Figure 3 shows TEPs, figure 4 shows phase angles of eight conditions including somatosensory, auditory and bifocal stimulations. EEG during the bifocal TMS sham condition in this subject was contaminated by excessive muscle artifacts and was not analyzed further. Results depicted in figure 3A already point to the findings of the specific auditory and sensory stimulation: TEPs of a stimulation with an inverted coil, using an intensity adjusted to the sensation of “verum” stimulation (see section 2.4.) were comparable to TEPs of a stimulation over M1 (Fig. 3B). Also, the effects of sham and verum conditions of the EEG phase angles were similar. Note that in figure 4 bifocal cortical stimulation shows a clear-cut pattern (Fig. 4, “PMv-M1”, “aIPS-M1”) which is less obvious in monofocal cortical

(Fig. 4,"sham", "sham inverted coil", "M1") or unimodal sham (Fig. 4, "somatosensory", "auditory") stimulation. Non-cortical, bimodal sham stimulation (Fig. 4, "somatosensory + auditory"), however, evokes a pattern indistinguishable from that associated with cortical, bifocal stimulation (Fig. 4, "PMv-M1", "aIPS-M1").

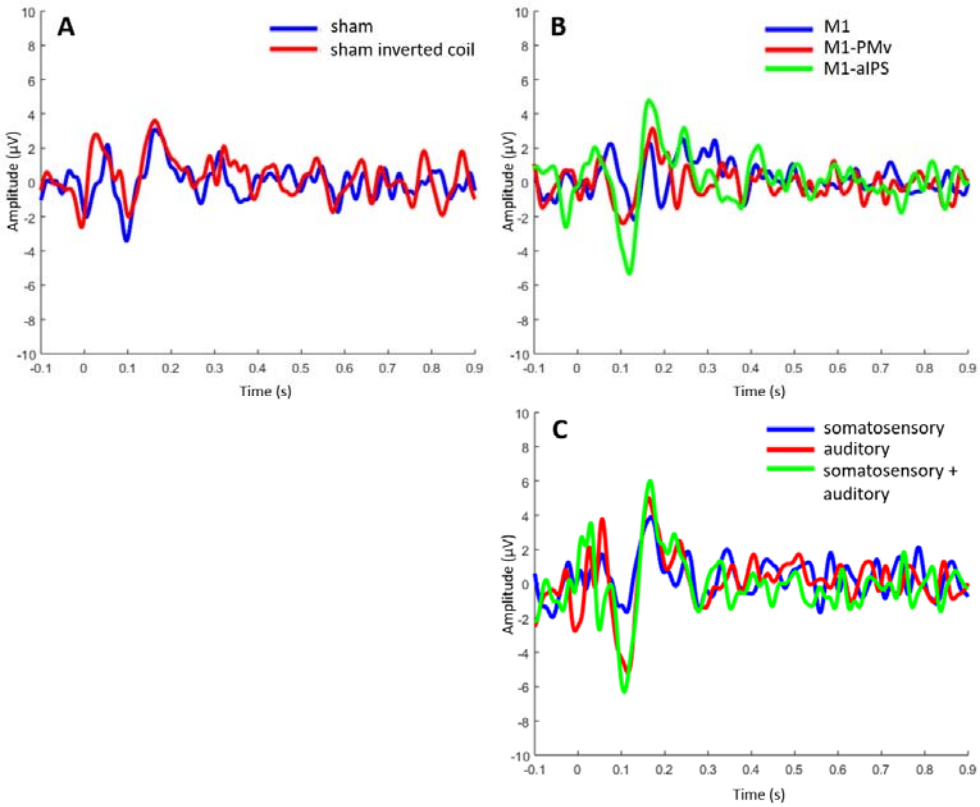

Figure 3. TEPs from -0.1s to 0.9s around the single-pulse TMS at 0s. **A**: Sham indicates monofocal sham stimulation over PO3; sham inverted coil, monofocal sham stimulation with an inverted 70mm coil over M1. **B**: M1 indicates monofocal stimulation of M1; PMv-M1, bifocal stimulation of PMv-M1; aIPS-M1, bifocal stimulation of aIPS-M1. **C**: Somatosensory indicates somatosensory stimulation; auditory, auditory stimulation; somatosensory + auditory, somatosensory combined with auditory stimulation.

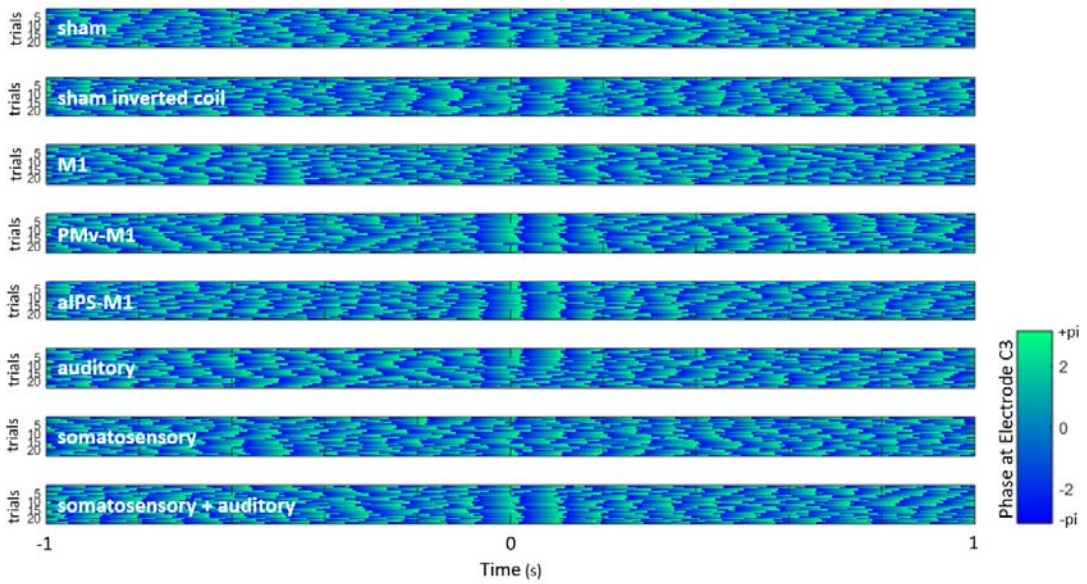

Figure 4. Phase properties (11Hz band) from –pi to +pi at electrode level C3 from -1s to 1s around the single-pulse TMS application at "0s" (single-subject data). Sham indicates monofocal sham stimulation; sham inverted coil, monofocal sham stimulation with an inverted 70mm coil of M1; M1, monofocal stimulation of M1; PMv-M1, bifocal stimulation of PMv-M1; aIPS-M1, bifocal stimulation of aIPS-M1; somatosensory, somatosensory stimulation; auditory, auditory stimulation; somatosensory + auditory, somatosensory combined with auditory stimulation.

3.3. Safety issues regarding bifocal, repetitive TMS

Regarding bifocal, repetitive TMS a potential safety issue arose. In one subject, strong and visually detectable MEPs using bifocal, repetitive stimulation of PMv-M1 were elicited when stimulating with formally 'subthreshold' intensities. As described in section 2.3., RMT was detected for each coil and stimulator respectively. Intensity was adjusted to 90% RMT. In this presented case of non-intended suprathreshold stimulation, PMv-M1 was the first condition of the repetitive part in our randomized design. The experiment was stopped. Figure 5 shows EMG activity in a single participant before terminating the experiment.

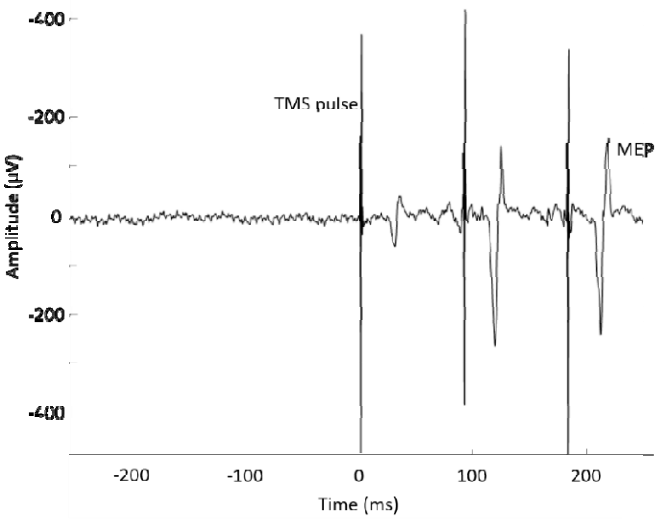

Figure 5. MEPs after subthreshold bifocal rTMS (PMv-M1, 90% RMT) in a single participant. The figure exemplarily shows EMG activity in the first dorsal interosseous (FDI) muscle before and after three stimuli of a train of 20 pulses, starting at time 0s.

Additionally, repetitive bifocal TMS also elicited MEPs in one of the pre-pilot experiments, which were performed to establish RMT-measurements, neuronavigation and the customized code for TMS-triggering. In one of those pre-pilot participants, it was not possible to evoke MEPs with any of the 25mm coils (applied separately) up to a machine-output of 100%. A train of bifocal PMv-M1-Stimulation was run with subthreshold 91% stimulator output, assuming a RMT of at least “101%”. Since visually detectable MEPs were then elicited, the experiment was stopped (data not shown).

3.4. Quality of neuronavigation

Irrespective of neuronavigation and the already very small coil size (Fig. 1), aIPS and M1 or PMv and M1 could be roughly targeted but the deviation from anatomical target was only acceptable in persons with large head circumference. Figure 6 shows individualized target areas of four participants (A-D). As stimulation was primarily adjusted to M1, intended and stimulated locations of the primary motor cortex were closely related. In contrast, intended and stimulated locations of secondary motor areas differed.

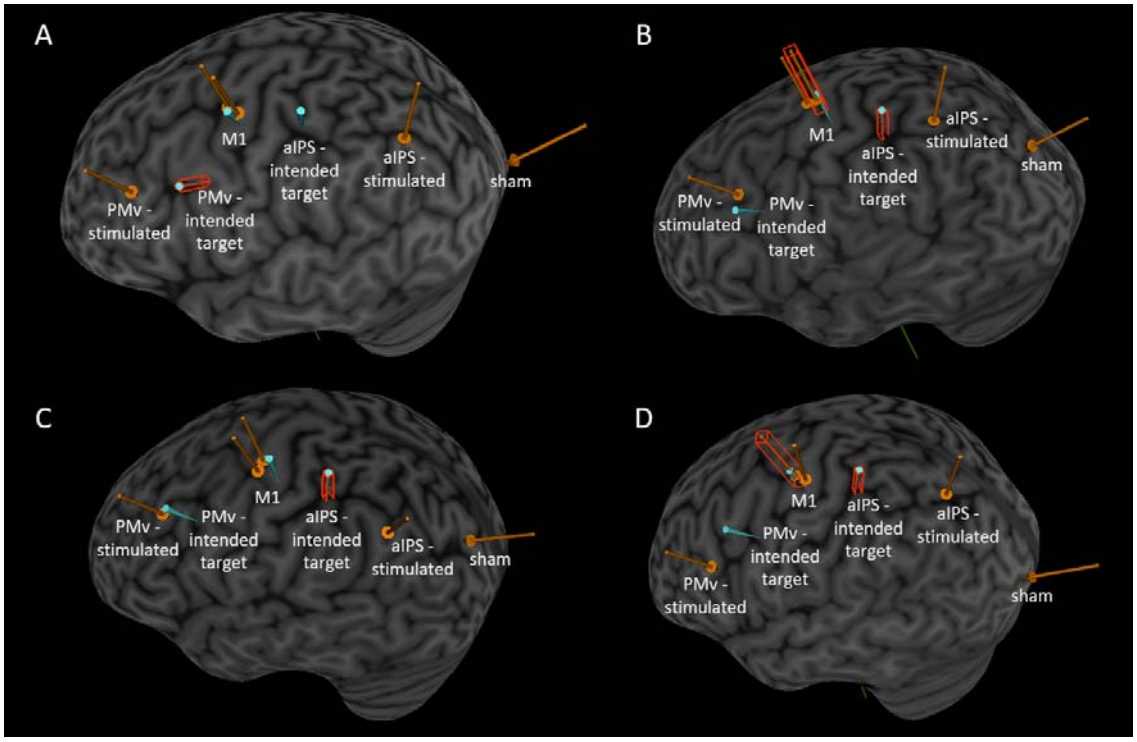

Figure 6. Intended targets (blue) and locations of stimulation (orange) in individual participants (**A-D**). As stimulation was primary adjusted to M1, intended and stimulated locations of the primary motor cortex were closely related. In contrast, intended and stimulated locations of secondary motor areas differed. (Red boxes indicate an active target, topographies were extracted during online navigation-procedure.)

4. Discussion

Inducing phase synchrony by non-invasive brain stimulation is a potentially interesting and powerful technique to study and, ideally, enhance neuronal function (Ahn et al., 2019; Romei et al., 2011; Sauseng et al., 2009; Thut et al., 2011; Zaehle et al., 2010), especially because it is conceptually suited to enhance interregional coupling of oscillatory brain activity (Helfrich et al., 2014; Plewnia et al., 2008; Schwab et al., 2018). Based on these considerations, we aimed at establishing a feasible setting for entraining key cortical areas known to be engaged in the motor recovery process after stroke (Bönstrup et al., 2018, 2016; Rehme et al., 2011; Schulz et al., 2015b). When performing the first series of experiments in healthy control

participants, we observed unexpected technical and physiological effects that finally questioned the application of rTMS in this setting.

There turned out to be three key observations that need to be discussed. First, major components of EEG responses to subthreshold TMS were also found after sham stimulation, and could be attributed to the auditory and somatosensory stimulation related to coil discharge. Second, bifocal TMS, even with small 25mm coils, has substantial refinements as to how closely neighboring target areas can be (i.e., PMv-M1, aIPS-M1). Third, due to the close vicinity of the two 25-mm 8-shaped coils, the field strength was augmented so that we detected some afterdischarges in the EMG despite the formally subthreshold stimuli. This ultimately poses some safety concerns regarding bifocal, repetitive TMS with coils positioned in a very close montage.

(1) Specificity of EEG responses

The motivation for our approach came from previous work indicating that oscillatory coupling signatures are indicative of the cortical reorganization process in stroke patients (Bönstrup et al., 2018, 2016, 2015). Moreover, these EEG findings are well in line with structural and functional connectivity analyses in other modalities like functional MRI or diffusion-tensor imaging (DTI) (Horn et al., 2016; Rehme et al., 2011; Schulz et al., 2016, 2015a, 2015b) and furthermore, so far, attempts to enhance recovery by local up or downregulation of motor areas have suffered from inconsistency and small effect sizes (Cazzoli et al., 2012; Duque et al., 2005; Y. Kim et al., 2006), for review see (Schulz et al., 2012). Given this background, a crucial element of our approach was to detect robust changes of inter-areal coupling metrics (e.g., phase-angles) in EEG (Thut et al., 2011), adjust the stimulation paradigm to optimize these neurophysiological effects, and then enhance the sample size and measure potential effects on motor behavior and recovery after stroke.

First, to contrast responses to bifocal stimulation, control conditions of monofocal M1 and monofocal PO3 stimulation were applied. Both TEP-analysis (Fecchio et al., 2017; Rosanova et al., 2009) and phase analysis of 11Hz band as a marker of TMS effectiveness (Thut et al., 2011) were computed. Analysis of single-pulse TMS data revealed that major components of the EEG responses to TMS were also detectable in the EEG after sham stimulation (Fig. 2). This holds true for both TEPs and phase analysis: the major components were triggered both by M1 targeted stimulation and by PO3 sham stimulation. Likewise, phase resetting of alpha-band oscillations was not only induced by targeted M1 stimulation but also by sham stimulation. From an electrophysiological point of view, analogous results of TEP and phase analysis are possibly owing to the fact that phase synchronization is a causal factor for the presence of time-averaged evoked potentials (Makeig et al., 2002).

The lack of specificity could be related to a non-specific reaction of the cortical neuronal network but also, more trivially, to another property that TMS to M1 and PO3 have in common, that is, auditory or skin sensation. To further evaluate this, additional sham conditions were applied in a single subject. Key finding of this additional experiment was that especially auditory stimulation lead to comparable effects on TEPs (see Fig. 3C, red line). The combination of somatosensory and auditory stimulation was sufficient to cause phase-resetting in the EEG, undistinguishable from the effects of bifocal TMS to PMv-M1 or aIPS-M1 (Fig. 4). In earlier double-pulse TMS experiments, these controls were not uncommon (Ferbert et al., 1992; Gerloff et al., 1998; Ugawa et al., 1994). However, since there is plenty of data proving that TMS can elicit true cortical (trans-synaptic) stimulation of pyramidal cells, somatosensory and auditory control experiments have lost their impact to some extent. Our study suggests that this should be reconsidered in future studies that draw the attention to very sensitive readouts like EEG phase coupling. For this, we must conclude that subthreshold TMS as applied in our protocol did not lead to phase resetting, entrainment, or TEPs over and above what could be seen with sham conditions. This does not rule out that bifocal TMS at 90% RMT has effects on cortical neurons but what we observed was not specific. Our data only allow us to conclude that the observed EEG responses might have

been evoked by the auditory input (“click”) of the coil discharge and the sensory input via the small amount of electrical current that is induced in the skin.

(2) Restrictions by closely adjacent target areas and small TMS coils

Another aspect of this pilot study was the finding that despite having used very small coils, it was not possible to target M1-PMv or M1-aIPS bifocally as planned in most participants (Fig. 6). Only with a very large head circumference these targets can be reasonably reached. As a rule, it was not possible to stimulate anterior parts of the IPS together with M1. PMv stimulation came close to the intended target only in one subject with a large head. Not being able to neuronavigate bifocal TMS on M1 and aIPS simultaneously stands in contrast to some published data (Koch et al., 2010a). Our coils had an inner diameter of 25mm. Already with these coils, finding the hotspot and determining the RMT can be challenging. Out of seven young and healthy participants, MEPs, required for measurements of RMT, could only be elicited in five individuals. In elderly participants and stroke patients, the RMT is expected to be even higher (Cakar et al., 2016). Smaller coils would solve the problem of neuronavigation but probably lack the field strength needed (and heat up on repetitive stimulation). To our knowledge there are, however, no coils commercially available with a smaller diameter than the Magstim® 25mm coils. The problem of low field strength is naturally even greater when TMS is combined with EEG because the electrodes mounted in the cap cause a distance of the coil from the scalp of at least approximately 2mm. The strength of the magnetic field is maximal close to the coil surface and decreases with the square of the distance from there (de Goede et al., 2018). An interesting way out of this problem may be closed-loop stimulation, through which TMS efficacy might be enhanced by better timing relative to the ongoing oscillatory cortical activity (Bergmann et al., 2012; Kraus et al., 2016; Raco et al., 2016).

(3) Safety considerations

Despite the 25mm-coil-related lack of stimulation power, we also observed unexpected suprathreshold effects with bifocal, adjacent stimulation in two participants. In one participant, overt MEPs were elicited in the repetitive, bifocal mode over PMv and M1 with 90% RMT stimulation (Fig. 5). As described in section 3, this phenomenon also occurred in one subject during the preparatory phase for this study. Both experiments were terminated because the observed phenomenon reminded us of excitability spread. For the following control experiment, intensity was reduced to 70% RMT. At this point, we can only speculate that directly adjacent, bifocal application of subthreshold TMS might, in some participants, lead to substantial field overlap with resulting suprathreshold intensity (here, at M1). The two participants had filled out our TMS safety questionnaire and showed no remarkable findings that could have explained the overt responses to subthreshold TMS otherwise.

(4) Limitations

Our group has long-standing experience with complex TMS paradigms and EEG analyses. Nevertheless, our observations reported here are based on a pilot study on a small group of seven healthy volunteers (all women). The additional control experiment of somatosensory, auditory, and combined somatosensory-auditory stimulation was only carried out in one of them. We still consider our conclusions valid because (i) the main effect, i.e., resetting by sham stimulation, was very obvious at group level, (ii) if we can demonstrate spurious resetting by non-TMS somatosensory and auditory stimulation at the level of a single subject, it needs to be considered a potential confounder at the group level. Finding other subjects in whom this effect might be less prominent would not help overcoming this refinement. (iii) We consider it unlikely that the observed effects are specific for women and would not apply to male subjects but formally this cannot be excluded. With respect to technical innovation, there might be future devices that can offer smaller, cooled coils, e.g., in a cap or helmet setup, which could overcome the spatial restrictions demonstrated in this paper but to our knowledge no such device is CE certified and commercially available as of now.

5. Conclusion

Attempting to entrain cortical oscillations and interregional coupling with bifocal rTMS in the alpha-frequency range is subject to relevant technical refinements that may, if not considered, lead to misinterpretations or spurious results. Most importantly, the obligatory acoustic stimulus linked to each TMS pulse, together with the somatosensory (skin) sensation exerted by a magnetic pulse are sufficient to cause clear-cut phase-locking phenomena in EEG recordings. Without proper controls, one might interpret the phase effects as direct consequence of cortical stimulation. Besides, coil size and overlap of induced fields can make accurate targeting of cortical areas difficult and may result in overt motor responses (MEPs) although stimulation intensity was set clearly below RMT.

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