No modulatory effects by transcranial static magnetic field stimulation of human motor and somatosensory cortex

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ABSTRACT

Background: Recently, it was reported that the application of a static magnetic field by placing a strong permanent magnet over the scalp for 10 min led to an inhibition of motor cortex excitability for at least 6 min after removing the magnet. When placing the magnet over the somatosensory cortex, a similar inhibitory after effect could be observed as well.

Objective: Our aim was to replicate the inhibitory effects of transcranial static magnetic field stimulation in the motor and somatosensory system.

Methods: The modulatory effect of static magnetic field stimulation was investigated in three experiments. In two experiments motor cortex excitability was measured before and after 10 or 15 min of magnet application, respectively. The second experiment included a sham condition and was designed in a double-blinded manner. In a third experiment, paired-pulse SSEPs were measured pre and four times post positioning the magnet over the somatosensory cortex for 10 min on both hemispheres, respectively. The SSEPs of the non stimulated hemisphere served as control condition.

Results: We did not observe any systematic effect of the static magnetic field neither on motor cortex excitability nor on SSEPs. Moreover, no SSEP paired-pulse suppression was found.

Conclusion: We provide a detailed analysis of possible confounding factors and differences to previous studies on tSMS. After all, our results could not confirm the static magnetic field effect.

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Introduction

Recently, transcranial static magnetic field stimulation (tSMS) was introduced as a novel brain stimulation technique [1]. According to the authors, it offers an easy applicable possibility to modulate the cortical excitability in the motor system by holding a strong permanent magnet over the scalp. They observed an inhibitory effect on the excitability of the human motor cortex following 10 min of tSMS, independent of magnet polarity. The inhibitory effect of tSMS was confirmed in a replication study [2]. Applying 15 min of tSMS. In both studies, the modulatory effect was quantified using motor evoked potentials (MEP) with transcranial magnetic stimulation (TMS). Within 6 min, the inhibitory effect on MEP amplitude vanished and amplitudes returned to baseline levels. Whereas in the first study no modulation of resting motor threshold (RMT) was found [1], in the replication study an inverse correlation between RMT and MEP amplitudes was observed [2]. Another study addressed the effects of 20 min of tSMS on short-latency intracortical inhibition (SICI) in the motor system [3]. SICI was found to reversibly increase after tSMS. In addition, MEP amplitudes were found to be decreased and RMT increased after tSMS and also after exposure to the SMF of an MRI scanner.

The inhibitory effect of tSMS found in the motor system has been shown to be measurable in other cortical regions. For instance, somatosensory evoked potentials (SSEPs) were used to investigate the effect of tSMS on the somatosensory cortex [4]. Applications of a magnet over S1 for 10 and 15 min were investigated. An attenuation of the P14N20 amplitude with the effect turning back to
baseline levels within 10 min was reported. During tSMS no change in the P14N20 amplitude was observed. A recent study of the same authors shows an inhibitory effect of tSMS over M1 on the N33 (P25N30) SSEP amplitude at C3' [5] but no effect on the P14N20 amplitude.

Moreover, findings in the visual cortex were reported. One study demonstrated a significant increase of alpha-wave activity recorded by electroencephalography (EEG) during occipital tSMS application [6]. It was suggested that an increase in alpha-wave activity indicates an inhibition of cortical excitability of the visual cortex. Furthermore, they showed that this effect was accompanied by a slowed performance in a visual search task during and after application of the magnet isolated on the most difficult task conditions.

In another study, it was demonstrated that tSMS of the visual cortex of two monkeys lead to reversible deficits in a visual detection task [7]. Moreover, tSMS led to a reduction of neural activity in two anesthetized cats [7].

Additionally, it was demonstrated that tSMS can be considered safe, as 2 h of tSMS do not increase marker levels of neural and glial lesion markers (Neuron specific enolase and S100) [8].

However, an actual working mechanism of tSMS has not been shown, and the cortical networks being involved in the inhibitory effects upon different cortices are still unknown. In the first study, it was argued that tSMS is unlikely to act on the level of corticospinal axons of pyramidal cells because MEPs evoked by transcranial electrical stimulation remain uninfluenced by tSMS [1]. Thus, it was suggested that the inhibitory effect of tSMS is very likely to act on a cortical level.

Our aim was to evaluate the tSMS induced inhibition by replicating the modulation in the motor and somatosensory system. Therefore, we performed two MEP-experiments in the motor system, with the second experiment being designed as a double-blinded study. Furthermore, we explored the effects of tSMS on the somatosensory cortex to replicate the findings in the somatosensory system.

Material and methods

Subjects

All subjects were screened for any neurological, psychiatric or endocrinologic disorders and regular drug intake. Additionally, all subjects were asked for cranial surgeries in their past and any metal objects implanted in the head region. All subjects of experiment 1 and 2 were right handed according to a modified version of the Edinburgh Inventory Scale [9]. Seventeen subjects participated in experiment 1, of which only 15 (7 male, mean age: 22.7 ± 3.3 years) entered statistical analysis due to exclusion for reasons described below. Twenty subjects (10 male, mean age: 22.4 ± 2.2 years) participated in experiment 2, with two subjects already having participated in experiment 1. In the third experiment, 23 subjects were included. After measurement, three subjects were excluded because of an inconvenient signal-to-noise ratio, providing 20 subjects (10 male, Mean age: 24.1 ± 2.4) for statistical analysis. All subjects gave their written informed consent and were paid for their participation. The study followed the declaration of Helsinki and all experiments were approved by the Ethics Committee of the University of Ulm.

Measurement of excitability

MEPs in the resting muscle were evoked by single pulses of TMS and delivered using a Magpro X100 stimulator (Mag Venture a/S, Farum, Denmark), connected to a figure-of-eight coil (MC-B70).

First of all, the motor “hotspot” generating the highest amplitudes in the right first dorsal interosseous muscle (FDI) with suprathreshold TMS pulses, was identified and marked on the subject’s scalp. The coil position was kept tangentially to the scalp with the handle pointing backwards in an angle of 45° to the sagittal plain [10]. Coil position at the hotspot was maintained using a neuronavigation system (BrainView2, Fraunhofer IPA, Stuttgart). TMS intensity for monitoring excitability was calibrated individually to elicit a mean MEP amplitude of about 1 mV. Single TMS pulses for MEP monitoring were applied continuously with a frequency randomly jittering within 0.125 Hz and 0.5 Hz (interstimulus interval: 5–8 sec) with the intention to decrease anticipation and habituation.

MEPs of the right FDI were recorded using surface electrodes in a belly-tendon montage. Signals were bandpassed (10–2000 Hz) and amplified using a Toennies universal amplifier (Erich Jaeger GmbH, Hochberg, Germany), sampled with 5000 Hz and online presented, analyzed, and stored on a PC for offline-analysis using DasyLab 13.0 (measX GmbH und Co. KG, Mönchengladbach, Germany).

Relaxation of the FDI was controlled online by an acoustic feedback signal and recordings with muscle activity were excluded offline. Two subjects in experiment 1 had to be excluded due to continuous pre-innervation of their FDL. SSEPs in experiment 3 were recorded from C3’ (left S1) and C4’ (right S1) with a reference at FZ (according to the EEG 10–20 system). C3’ was defined as 4.5 cm occipital to the motor hotspot found over the left motor cortex by TMS. C4’ was marked after performing the same procedure on the right side. The median nerves were stimulated on both sides at the wrist with paired-pulses. The interstimulus interval was set to 30 ms to produce reliable paired-pulse suppression [11]. Stimulation intensity was set to 2.5 times sensory-threshold, thus subjects reported a noticeable prickling in the thumb, index- or middle finger.

On each side, 240 paired-pulses were administered, with a stimulation frequency of 2 Hz, first on the right wrist and after 30 s pause on the left one. Thus one block of both sided measurements lasted 4 min and 30 s.

As in the former experiments, bandpassing (10–2000 Hz) and amplification were realized using a Toennies universal amplifier. Signals were sampled with 5000 Hz and presented online using DasyLab 13.0. A time frame of 45 ms before the first stimulation pulse and 105 ms after the second pulse was recorded and stored for offline analysis of latency and peak to peak amplitudes.

Static magnetic field stimulation

For tSMS, a cylindrical neodymium magnet (NdFeB) of 30 mm height and 45 mm diameter (model 5–45–30-N, Supermagnete, Gottmadingen, Germany) was used. The maximum energy density of the magnet was 358 kJ/m3 (45MGOe) with a nominal strength of 628 N (64 kg) and a weight of 360 g. The surrounding magnetic field density perpendicular to the magnets pole surface was measured with a digital Teslameter (FM 210, „MagMess“, Bochum, effective sensor area = 2.065 mm²), yielding values in concordance with recently reported measurements on the same magnet class from the same manufacturer [12]. It was shown that field density remains comparable to studies using a slightly different magnet class with a diameter of 50 mm [5]. Assuming a scalp thickness of 2 cm, a maximum magnetic field density of about 160 mT is present at the cortical level perpendicular beneath the magnets south pole surface.

The magnet was held manually over the predetermined motor hotspot (experiments 1 and 2). In experiment 1, tSMS was applied for 15 min with the north pole pointing to the scalp, in experiment
2 the south pole was directed to the subject’s scalp for 10 min. In addition, a stainless steel cylinder of weight and appearance identical to the real magnet was used for sham stimulation in experiment 2. Subjects were not able to differentiate between the real and the sham magnet: 11 of 20 subjects identified the correct sequence when asked for.

In experiment 3, the south pole was placed 2.25 cm occipital to the motor hotspot just in front of the recording electrode C3’, applying the magnetic field over the central sulcus and the post-central gyrus (S1; see Fig. 1). Thus, the recording electrode remained on its position during tSMS. The tSMS lasted for 10 min.

**Experimental design**

For all experiments, subjects took a seat in a comfortable chair. To control for the subject’s cognitive activity during tSMS, an acoustic oddball task was performed [13]. During MEP recording (experiment 1 and 2) subjects were asked to keep their eyes open and refrain from talking. Moreover, in experiment 3 subjects were asked to close their eyes while SSEPs were measured.

In experiment 1, a biphasic TMS pulse form was used. Baseline MEP excitability was measured with 100 single pulses lasting about 12 min. Then, tSMS was applied for 15 min. After a fixed time interval of 2 min, recording of 100 MEPs (post-stimulation) was started, again lasting about 12 min.

Experiment 2 was sham controlled and double-blinded. A monophasic TMS pulse form was used. The subjects participated in two sessions receiving either real or sham tSMS. The order of the stimulation-mode (real vs. sham) between the two sessions was counterbalanced. Sessions were separated by at least one week. Compared to experiment 1, the pre-MEP-measurement of experiment 2 was shortened to 4 min and the post-measurement lasted for 10 min. Duration of tSMS was 10 min. An additional experimenter, who entered the room only for tSMS, applied real or sham stimulation. Subjects had to log their fatigue in a visual analogue scale (VAS) three times: before the baseline measurements, during tSMS and after every session.

In experiment 3, four blocks of SSEP measurements using wrist paired-pulse stimuli were performed: One before tSMS (baseline) and three times after 10 min of tSMS (immediately, 5 min and 10 min). A fifth block was performed 15 min after tSMS and used a single-pulse protocol. The amplitude of the single-pulse protocol was used for linear subtraction from the second response of the same subject’s paired-pulse data of the former points of time (Fig. 2). Thus, the interference by superposition of the first paired-pulse SSEP (A1) and the second paired-pulse SSEP (A2) is excluded and the second N20P25 amplitude can be viewed isolated [11].

**Data analysis**

Firstly, all MEP data were visually inspected for spontaneous motor activity 800 ms before and after every MEP. In experiment 1 two subjects had to be excluded due to pre-innervation. Mean peak-to-peak amplitudes of MEPs were calculated over 2 min intervals (including 16–19 pulses per 2 min interval). This procedure led to 6 points of time pre and post stimulation, respectively. In experiment 2, the pre-measurement was aggregated to two values, and the post-measurement to five values.

MEP data were normalised for every subject with respect to the mean amplitude averaged over all individual baseline measurements.

For experiment 3, the subtracted SSEP data can be used to express the paired-pulse suppression as an amplitude ratio. The second N20P25 amplitude after subtraction (A2s) was divided by the first N20P25 amplitude (A1) within one paired-pulse. The ratio (A2s/A1, subtracted SSEP2/SSEP1) shows the amount of paired-pulse suppression [11,14].

Inference statistics was calculated using Statistica (V 10, StatSoft GmbH, Hamburg, Germany). Violation of sphericity, if applicable, was tested using Mauchly’s test. In case of violation, ε and corrected p-values are reported applying Greenhouse-Geisser correction.

**Results**

**Experiment 1**

Mean stimulation intensity for the 1 mV MEPs was 46.2 ± 9.7% of maximum stimulator output (MSO). Mean MEP amplitude averaged over all baseline (pre) measurements was 1.22 ± 0.28 mV.

Normalised MEPs were subjected to an rMANOVA with the within-factors STIMULATION (pre, post) and TIME (1–6). There was no main effect of the factor STIMULATION ($F_{(1,14)} = 0.002$, $p = 0.97$) and no effect of TIME ($F_{(5,70)} = 2.72$, $\epsilon = 0.57$, $p = 0.06$). Visual inspection reveals a continuous increase of MEP amplitude during baseline measurement as well as after tSMS (time range about 12 min each). The interaction did not yield significant results ($F_{(5,70)} = 1.29$, $p = 0.28$). The results of experiment 1 are depicted in Fig. 3.

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**Fig. 1.** Electrode position of experiment 3. FZ, C3’, and C4’ represent the electrodes for SSEP recording. Electodes were placed 45 mm (diameter of magnet) occipital to the particular motor-hotspot. The reference electrode was placed over FZ and the grounding electrode on the right earlobe.

**Fig. 2.** SSEP curve subtraction procedure. The curves show an example of the subtraction procedure for one subject. The SSEP of the paired-pulse (upper curve) was subtracted by the single-pulse SSEP (middle curve), thus yielding a new SSEP (bottom curve) where the N20P25 is not influenced by the SSEP of the first pulse. A decrease in the N20P25 amplitude of the second pulse (grey bar) after subtraction (bottom curve) can be seen.
Experiment 2

Mean intensity for the 1 mV MEPs was 60.3 ± 11.0% MSO. Mean MEP amplitude in the baseline measurements was 1.15 ± 0.43 mV in the tSMS session (real) and 1.24 ± 0.37 mV in the sham session.

Normalised MEP values (2 min intervals) were analyzed by an rmANOVA with the within-factors MODE (real, sham) and TIME (1–7). Neither factor MODE ($F_{(1,19)} = 0.15, p = 0.71$) nor TIME ($F_{(6,114)} = 1.49, p = 0.19$) reached statistical significance, neither did the interaction ($F_{(6,114)} = 0.15, p = 0.99$). The results of experiment 2 are depicted in Fig. 4. Individual data is shown for the real and sham condition in Fig. 5.

Additionally, a sub analysis restricted to the points of time immediately before and after tSMS and sham-stimulation was performed. An rmANOVA with the within-factors MODE (real, sham) and TIME (pre, post) did not yield significant results for any factor and no interaction (MODE: $F_{(1,19)} = 0.39, p = 0.54$; TIME: $F_{(1,19)} = 1.89, p = 0.19$; MODE*TIME: $F_{(1,19)} = 0.06, p = 0.81$).

On a visual analogue scale between 0 = 'very tired' to 10 = 'wide awake' subjects started the experiment with a mean activation level of 7.6 ± 1.6. The majority of subjects got tired during the experiment, yielding a mean activation level of 5.1 ± 2.3. There was no correlation between tiredness and MEP amplitudes at any point of time (before measurement and first baseline MEP 2 min interval: $r = 0.09, p = 0.58$; during tSMS and first 2 min interval after tSMS: $r = 0.01, p = 0.94$; after measurement and last 2 min interval: $r = 0.24, p = 0.13$).

Experiment 3

In experiment 3, a decreasing effect on the P14N20 amplitude at points of time 0 min and 5 min after tSMS was reported by former studies [4]. In our analysis P14N20 amplitudes before and four times after tSMS were included yielding 5 points of time. As we performed a paired pulse wrist stimulation protocol, two SSEPs were generated (A1 and A2) of which only P14N20 amplitudes of the first one (A1) are comparable to Kirimoto et al. [4] and thus entered analysis. An rmANOVA with the factor SIDE (left, right) and TIME (1–5) did not show an effect of tSMS on the P14N20 amplitude of the first pulse: Factor TIME did not enter the significance level ($F_{(4,76)} = 1.40, p = 0.24$), neither did factor SIDE ($F_{(1,19)} = 4.11, p = 0.06$) or the interaction of both ($F_{(4,76)} = 1.29, p = 0.28$). The P14N20 amplitudes of both hemispheres before and after tSMS are shown in Fig. 6a.

An additional rmANOVA of the N20P25 amplitude of the SSEP of the first pulse with factors SIDE (left, right) and TIME (1–5) did not show an effect of tSMS on the P14N20 amplitude of the first pulse: Factor TIME did not enter the significance level ($F_{(4,76)} = 1.40, p = 0.24$), neither did factor SIDE ($F_{(1,19)} = 4.11, p = 0.06$) or the interaction of both ($F_{(4,76)} = 1.29, p = 0.28$). The N20P25 amplitudes of both hemispheres before and after tSMS are shown in Fig. 6b.

For all paired-pulse data, the N20P25 amplitude of the second pulse (after subtraction, A2s) was divided by the first N20P25 amplitude (A1), thus generating a paired-pulse suppression quotient (A2s/A1, subtracted SSEP2/SSEP1). The analysis of the paired-pulse using the suppression quotient lacked any significant effect: An analysis with the within-factors SIDE (left, right) and TIME (1–4)
was performed. The factors TIME ($F_{(3,57)} = 1.15, p = 0.34$) and SIDE ($F_{(1,19)} = 0.005, p = 0.94$) and also the interaction ($F_{(3,57)} = 0.01, p = 0.99$) did not reach significance levels. The paired-pulse suppression quotients of both hemispheres are shown in Fig. 6c.

Discussion

We investigated the effect of tSMS on two different systems. In two experiments in the motor system applying suprathreshold TMS pulses, no systematic modulation of MEPs following tSMS could be observed. The third experiment investigated the somatosensory cortex. No modulatory effect of tSMS on paired-pulse SSEPs was found. Thus, we were not able to replicate the results published previously.

First of all, the question arises whether there are any substantial methodological differences between the former reports of tSMS modulatory effects\[1,2,4\] and our attempt to replicate the effects.

Differences in the stimulation magnet might account for the discordant data. We used the same type of magnet (model S-45-30-N, Supermagnete, Gottmadingen, Germany) as Oliviero et al. [1] and Silbert et al. [2]. Kirimoto et al. [4] used a magnet from another company with a little difference in the magnets diameter (50 mm instead of 45 mm, manuafacturer NeoMag, Ichikawa, Japan). As shown previously, magnets of that size yield comparable magnetic field strengths[5,12].

Compared to our experiments, stimulation duration was also in the same range between 10 min[1,4] and 15 min[2,4] in all previous studies. Oliviero et al. [1] reported inhibitory effects independent of magnet polarity, whereas the effect was stronger when pointing the south pole to the subject’s scalp. Silbert et al.[2] and Kirimoto et al. [4] used south polarity for tSMS as well. As we used north polarity for tSMS in our experiment 1, this could have contributed to the discrepancies between the results. Therefore, in experiment 2 and 3 south polarity was used, but our observation was still not in line with previous studies. Taken together, neither magnet type, magnet polarity nor application duration seem to explain the contradictory results, since those parameters were comparable to that used in the former studies.

An alternative explanation for the differences observed in the results could be a variation of the measurement conditions: We applied MEP pulses with a jittered interstimulus interval [cf.15] to lower an expectation bias. Additionally, in contrast to former studies [1,2] we used a Neuronavigation system with the ability to save the hot-spot location between two sessions of the double-blinded design study. This method was shown to offer better measurement conditions and more robust effects[16–18]. In our view the differences in measurement conditions mentioned above strengthen the reliability of our measurements.

Concerning the measurements in the somatosensory system and in difference to Kirimoto et al. [4] we used a paired-pulse protocol with an interstimulus interval of 30 ms [11]. Moreover, we recorded SSEPs on both hemispheres, whereas the measurements in the former study were limited to the left hemisphere [4]. However, the points of time of the left hemisphere measurement in our experiment remained comparable to those of Kirimoto et al. [4] (baseline, immediately after, 5 min and 10 min after tSMS).

Looking for further explanations of the contradictory results, the design of the experiments has carefully to be compared. Differences between our experimental study design and that of Oliviero et al. [1] remain limited to the design of the baseline measurement. We

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**Fig. 6. Results of experiment 3.** In this experiment tSMS was applied to the left hemisphere only, the right hemisphere served as control. The grey bars represent the tSMS application of 10 min. Error bars show 95% confidence-interval. a) The P14N20 amplitudes of the first SSEP pulse pre and post tSMS for both hemispheres are shown. b) The N20P25 amplitudes of the first SSEP pulse pre and post tSMS for both hemispheres are shown. c) The paired-pulse suppression quotients A2s/A1 pre and post tSMS for both hemispheres are shown.
used 100 MEP pulses lasting about 10 min in experiment 1 and shortened our baseline measurement in experiment 2 to about 36 pulses (0.125–0.2 Hz; lasting about 4 min) in order to align our design with that of Oliviero et al. [1]. Nevertheless, it still provides a more extensive baseline measurement than experiment 2 of Oliviero et al. (20 MEP pulses; 0.15 Hz; about 2 min 13 s) [1] and slightly more than the study of Silbert et al. (30 MEP pulses; 0.2 Hz; about 2 min 30 s) [2]. By the use of 2 min intervals for MEP analysis about 17 MEPs constitute every points of time in our study and thus are comparable to the points of time of the former studies. It has been shown that 30 pulses seem to be the less possible number of stimuli to make a determination of a given corticospinal excitability level reliable [19]. A limitation of our and all former tSMS studies is that, by the use of 2 min intervals, this rule is violated. We chose the use of 2 min intervals, however, to keep our results comparable to former studies.

It is conceivable, that the broad baseline measurement in experiment 1 could occlude any plasticity changes induced by tSMS [20]. For this reason the baseline measurement of experiment 2 was shortened to a minimum of MEP pulses necessary to establish a reliable excitability level.

Moreover, the use of several points of time in the baseline measurement has the advantage of showing that MEP baseline levels are not stable. A physiological inner system fluctuation was indicated by a nearly significant factor TIME in experiment 1. This inner system changes could possibly mask a modulatory effect. Nevertheless, the same fluctuations should be present in the former studies in the motor system although not shown before tSMS by their baseline measurements. Thus, it seems unlikely that these fluctuations caused the observed differences in the results.

None of the differences listed above between our and preceding studies give a satisfactory explanation for the contrast in the results. The majority of differences like the use of a neuronavigation system, longer baseline measurement or jittered interstimulus intervals rather serve to improve than impair measurement conditions in our opinion.

However, further effects of static magnetic fields (SMFs) on neuronal systems under in-vivo conditions were observed. A different stimulation protocol applying SMFs has been reported by McLean et al. [21]. They demonstrated the gradient of the magnetic field to be more crucial for the formation of neural effects than the actual field strength. They were able to show a prolongation of the seizure latency of audiogenic seizures in mice pretreated by a 1 h SMF of 100–220 mT strength and a gradient component of 15–40 T/m. For comparison: The gradient component perpendicular to the south pole surface center of the Neodymium magnet used in our study (and presumably most of the other studies using NdFeB-magnets of that size) was around 10 T/m in 2 cm distance to the magnets surface.

Moreover, studies of the SMF effects in a Magnetic Resonance Imaging (MRI) scanner are of high interest due to the daily use of MRI in medical practice. An MRI imaging sequence includes time varying magnetic fields on top of the static magnetic field, so the investigation of SMF effects requires a silent magnet, i.e. no imaging sequence. Although such effects of the SMF of an MRI scanner on MEP amplitude and RMT have been reported [3], several studies on cortical excitability in the SMF of a MRI scanner were not able to show any effect on silent period and RMT [22], nor on somatosensory or acoustic evoked potentials [23–25] (but see Ref. [26]).

Nojima et al. [3] argued that former non findings in the motor system might be explained by differences in TMS coil geometry.

Certainly, the field of an MRI scanner varies from that of a Neodymium-magnet in several factors like geometry, strength and gradient of the magnetic field. Especially in the middle of an MRI scanner bore a homogenous SMF is present with barely no gradient.

Whether the direct comparison between studies performed in the SMF of an MRI scanner and the ones using a permanent magnet is possible remains doubtful as long as the mechanism of excitability changes exerted by a SMF is unclear. But taking into account reported effects in the MRI scanner, this mechanism should act in a weak SMF with strong gradient [21] as well as in a strong SMF with quasi no gradient [3].

One of the mechanisms of action proposed by the first study on tSMS [1] is a change in the activation time constant caused by molecular reorientation of membrane canal proteins [27]. They suggested that the molecular reorientation affecting the membrane bound canal proteins is based on magnetic torque forces of a homogenous SMF on diamagnetic anisotropic membrane molecules. By this effect, the canal protein would be influenced by the SMF in an inhibitory way and the effect would be dependent on magnetic flux density, but not on the field gradient [27] (in contrast to McLean et al. [21]). Findings which point in a similar direction have been reported by other research groups [28–30].

However, it was argued [31] that most of the in-vitro processes related to torque forces caused by anisotropic susceptibility are negligible under in-vivo conditions. Whether this statement is valid for electrophysiological activities on the neuronal level remains unclear.

It seems mentionable that in the first patch clamp experiments the Calcium channel dynamics were mainly affected during exposure to the SMF and the effect only showed a short overhang of around 2 min [32]. Also effects of occipital tSMS seem to be restricted to the exposure of a SMF and do not show after effects: EEG recordings show an increase in alpha oscillation power isolated to the SMF exposure time [6]. Also inhibitory effects on a visual search task were clearly present during SMF exposure and only weak afterwards [6]. Moreover, 2 h of occipital tSMS do not induce any effect on reaction time in easy visuomotor behavioral tasks [8]. Contradictory to the presence of SMF effects during exposure, no effects of tSMS have been present in SSEP measurements under SMF exposure conditions [4]. Mainly tSMS on the motor and somatosensory system seems to evoke the inhibitory effect 6–10 min after SMF exposure [1, 4]. Further investigations should clarify the contradictory picture of SMF effects and their time course.

At this point we can sum up that keeping records of the magnetic field used in an experimental research on SMF seems important to allow repeatability and comparison. It was shown that lots of experimental studies on the therapeutic use of SMF do not offer enough information about their experimental circumstances [33, 34]. Many studies on the therapeutic use of SMF lack a convenient description of the field parameters that exist in the region of interest. Target tissue, magnet data, stimulation length, field strength and field gradient components at the target tissue should be reported in such experiments to enable replication.

Finally, our findings leave many open ended questions as they do not resemble with any former findings of SMF effects. Nevertheless, this constellation is not unknown especially in neurosciences like brain stimulation research [35]. Although established brain stimulation techniques like transcranial direct current stimulation and repetitive TMS are grounded on experimental results, they sometimes fail to replicate the propagated effect [13, 15, 36, 37], especially if the effects are small like the reported inhibition by tSMS ($\frac{\pi^2}{2} < 0.4$ for tSMS in the motor cortex [3]). One restriction for detecting the actual nature of small effects is the high physiological variability of excitability measurement techniques like MEPs. Even under constant measurement conditions, variability and physiological instability remains high [38–41]. The same observation could be made in our experiments, witnessed best during the long baseline measurement of experiment 1, where constant measurement conditions were maintained. During SSEP baseline
measurement a high instability in the amplitudes of the non-stimulated area could be observed as well. Studies addressing the variability of these techniques propose some possible factors influencing the baseline activity of excitability measurements like MEPs [10,42–44], but the establishment of a use of such variables as predicting factors of baseline variance is just at the beginning [15].

Indeed, high variability does not give a satisfactory explanation of the contradictory results in tSMA research - but it leads to the question, whether the neurophysiological parameters used are feasible to examine potential SMF effects.

Conclusions

Although lots of experimental findings on effects of moderate SMF on living tissue exists, up to now many of them have never been replicated. From the present point of view, most reliable findings are limited to strong SMFs in the MRI [31,45,46]. We conclude that effects exerted by a permanent magnet in the motor and somatosensory system measured by MEPs and SSEPs have not been observable in our study. Thus, an unsatisfactory picture remains concerning this new stimulation technique and the discussion about further evaluation of its relevancy as brain stimulation method has to be continued.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2017.03.001.

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