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Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability

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Abstract. *Purpose*: External transcranial electric and magnetic stimulation techniques allow for the fast induction of sustained and measurable changes in cortical excitability. Here we aim to develop a paradigm using transcranial alternating current (tACS) in a frequency range higher than 1 kHz, which potentially interferes with membrane excitation, to shape neuroplastic processes in the human primary motor cortex (M1).
Methods: Transcranial alternating current stimulation was applied at 1, 2 and 5 kHz over the left primary motor cortex with a reference electrode over the contralateral orbit in 11 healthy volunteers for a duration of 10 min at an intensity of 1 mA. Monophasic single- pulse transcranial magnetic stimulation (TMS) was used to measure changes in corticospinal excitability, both during and after tACS in the low kHz range, in the right hand muscle. As a control inactive sham stimulation was performed.
Results: All frequencies of tACS increased the amplitudes of motor- evoked potentials (MEPs) up to 30–60 min post stimulation, compared to the baseline. Two and 5 kHz stimulations were more efficacious in inducing sustained changes in cortical excitability than 1 kHz stimulation, compared to sham stimulation.
Conclusions: Since tACS in the low kHz range appears too fast to interfere with network oscillations, this technique opens a new possibility to directly interfere with cortical excitability, probably via neuronal membrane activation. It may also potentially replace more conventional repetitive transcranial magnetic stimulation (rTMS) techniques for some applications in a clinical setting.

Keywords: Primary motor cortex (M1), transcranial magnetic stimulation (TMS), neuroplasticity, transcranial alternating stimulation (tACS), high frequency stimulation (HFS)

1. Introduction

The last decades have established repetitive transcranial magnetic stimulation (rTMS) as an effective tool for modulating and interrupting cortical processing, in addition to treating neurological disturbances like major depression (O'Reardon et al., 2007). Alternative methods such as transcranial direct current stimulation (tDCS) (Nitsche and Paulus, 2000) have also emerged as an indispensable tool to modify cortical plasticity in the human cortex by shifting the resting potential of neuronal membranes (for an overview see Nitsche et al, 2008). When compared with rTMS (Ziemann, 2004) electrical stimulation methods and paradigms have the advantage of being more cost effective, although so far less well investigated.

The emergence of applying oscillating currents to the cerebral cortex not only showed the possibility to interfere with high frequency cortical oscillations within the ripple range (Moliadze et al., 2010) or to interfere with motor performance (Pogosyan et al.,

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2009); it also allowed the transient induction of plastic aftereffects (Antal et al., 2008). At present, electrical stimulation methods using alternating currents are currently being explored for a variety of conditions. An attenuation in the proliferation of tumor cells in cell lines, mouse models and patient groups was documented, after being exposed to an electric field of 200 kHz alternating current for 18 hours/day, in both mice models and within a clinical trial (Kirson et al., 2007). A recent study has reported evidence of a reversal of cognitive impairment in the mouse model of Alzheimer's disease after exposure to a 918 MHz electromagnetic field (Arendash et al., 2009).

Here we investigate the effects of tACS in a low kHz range, clearly outside the range of physiological network oscillations. We have already found that similar neuroplastic aftereffects as seen here are more likely to occur with frequencies between 100 Hz and 640 Hz when compared with frequencies below 100 Hz, by using transcranial random noise stimulation (tRNS) (Terney et al., 2008). In the present study we demonstrate that application of tACS in the range of 1–5 kHz over the primary motor cortex (M1) can induce significant changes in cortical excitability which outlasts the duration of stimulation.

2. Materials and methods

2.1. Subjects

11 healthy participants volunteered for the study (5 male, mean age 26.08 ± 5.2 years). All participants were informed as to all aspects of the experimental procedure and all gave written consent. None of the subjects suffered from any neurological disorders, had implanted electrical devices/metallic implants, nor took any relevant medication. One subject was left handed, while all other participants were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). All departmental procedures conform to the Declaration of Helsinki, and all experimental protocols were approved by the Ethics Committee of the University of Göttingen.

2.2. tACS in the low kHz range

tACS was applied over the M1, using a DS5 isolated bipolar constant current stimulator (Digitimer, Welwyn Garden City, UK) connected via a chinch cable to the input of a wave form generator (Peak Tech, Ahrensburg, Germany). Stimulation was delivered via rubber electrodes; one attached to the scalp over the motor cortical representation of the M1, while the other was placed over the contralateral orbit of the right eye. Both electrodes were kept in place with adhesive paste (10/20 conductive EEG paste, Kappamedical, USA). Stimulation electrodes were 6×8 cm (48 cm^2). Participants were required to keep both the EMG and rubber stimulation electrodes attached to the hand and head montage throughout the experiment. tACS was applied at 1, 2 and 5 KHz for a duration of 10 min over the left M1, at an intensity of 1 mA. For placebo stimulation, no current was applied.

2.3. Transcranial magnetic stimulation: measuring corticospinal excitability

To detect current-driven changes of excitability, motor evoked potentials (MEPs) of the right first dorsal interosseous (FDI) were recorded following stimulation of its motor-cortical representation field by single-pulse TMS. These were induced using a Magstim 200 magnetic stimulator (Magstim Company, Whiteland, Wales, UK), with a figure-of-eight standard double magnetic coil (diameter of one winding, 70 mm; peak magnetic field, 2.2 T; average inductance, 16.35 μH). Surface electromyogram (EMG) was recorded from the right FDI through a pair of Ag-AgCl surface electrodes in a belly-tendon montage. Raw signals were amplified, band-pass filtered (2 Hz–3 kHz; sampling rate, 5 kHz), digitized with a micro 1401 AD converter (Cambridge Electronic Design, Cambridge, UK) controlled by Signal Software (Cambridge Electronic Design, version 2.13), and stored on a personal computer for offline analysis. Complete relaxation was controlled through auditory and visual feedback of EMG activity and whenever it was necessary, the subject was instructed to relax. The coil was held tangentially to the skull, with the handle pointing backwards and laterally at 45° from the midline, resulting in a posterior–anterior direction of current flow in the brain. This orientation of the induced electrical field is thought to be optimal for predominantly transsynaptic mode of activation of pyramidal tract neurons synapsing onto the corticospinal system. The optimum position was defined as the site where TMS resulted consistently in the largest MEP in the resting muscle. The site was marked with

a skin marker to ensure that the coil was held in the correct position throughout the experiment.

2.4. Experimental design

Subjects were seated in a comfortable reclining chair with a mounted headrest throughout the experiments. The measurements were always performed by the same investigator. Coil position, angle and proximity to the subjects' scalp were carefully controlled for. Every effort was made to ensure that laboratory conditions for every session were kept the same. They participated in four experimental sessions, on separate days, at least 5 days apart. They received 1, 2 and 5 kHz tACS and sham stimulation in a randomised order. Resting motor threshold (RMT), active motor threshold (AMT), the intensity to evoke MEP of ~1 mV peak-to-peak amplitude (SI1mV) and a baseline of TMS-evoked MEPs (30 stimuli) were recorded at 0.25 Hz prior to stimulation. Stimulus intensities (in percentage of maximal stimulator output) of TMS were determined at the beginning of each experiment. RMT was defined as the minimal output of the stimulator that induced a reliable MEP (50 μV in amplitude) in at least three of six consecutive trials when the FDI muscle was completely relaxed. AMT was defined as the lowest stimulus intensity at which three of six consecutive stimuli elicited reliable MEP (200 μV in amplitude) in the tonically contracting FDI muscle (Rothwell et al., 1999). During stimulation 150 single-pulses were recorded from the left M1 during tACS (and through the stimulating electrode), and then immediately following stimulation, 30 single test-pulse MEPs were recorded at 0.25 Hz, i.e. approximately every 5 min for half an hour post-stimulation and then at 60 and 90 min post stimulation. These parameters and experimental procedures were measured at every session for both active tACS and sham stimulation.

2.5. Calculations and statistics

MEP amplitude (peak-to-peak SI1mV) was automatically calculated by the NuCursor programme (IoN, UCL, London, UK) and the mean value was determined for each timepoint after data had been visually analysed offline, and any MEPs with EMG artefacts were rejected. As we aimed to determine the effectiveness of a given verum stimulation compared to sham stimulation a comparison among different experiments, with regard to the raw MEP data, was performed using repeated measures ANOVA (TYPE (1 or 2 or 5 kHz versus sham) × TIME of MEP recordings). Student's *t*-test (paired samples, two tailed) was used to compare MEPs at single time points before and after stimulation between and within groups. A p-value <0.05 was considered statistically significant.

3. Results

All of the subjects tolerated the stimulation; none of the experimental sessions were interrupted due to side effects of the stimulation. The subjects reported no side effects during or after the stimulation. Subjects were asked to give informal feedback as to the stimulation sensation, and all subjects reported that they were unable to discern whether they had received active or sham stimulation during the experimental sessions.

RMT, AMT and SI1mV baseline values were compared between tACS and sham conditions using Student's-test. There was no significant difference between tACS and sham stimulation in any of the measurements ($p > 0.05$).

When tACS was applied over the M1 the induced excitability increases rose up to 40–80%, as revealed by single pulse TMS. They lasted for 60–90 min post-stimulation (Fig. 1). According to the Student's *t*-test there was a significant increase in MEPs amplitudes during 1 kHz stimulation at the time points 2–8 min ($p = 0.002$–0.007, $t = 2.39$–3.9) and after stimulation at the time points 20 and 60 min ($p = 0.03$, $t = 2.4$–2.47).

There was a significant increase in MEPs amplitudes during and after 2 kHz stimulation at all of the time points until 90 min post stimulation ($p = 0.0000$–0.03, $t = 2.5$–9.2). With regard to 5 kHz stimulation there was a significant increase in MEPs amplitudes during and after stimulation at all of the time points until 90 min post stimulation ($p = 0.002$–0.05, $t = 2.3$–4.6). Interestingly, there was a significant amplitude increase during sham stimulation at 4 and 6 min ($p = 0.01$) and after stimulation at 20 min ($p = 0.03$).

When 1 kHz and sham stimulation was compared repeated measurements ANOVA revealed no significant main effect of TYPE of stimulation ($F(1,10) = 4.4$, $p = 0.06$), however the factor TIME was significant ($F(13,130) = 2.2$, $p = 0.01$). The interaction between TYPE of stimulation and TIME was not significant ($F(13,130) = 1.3$, $p = 0.2$). According to the post-hoc

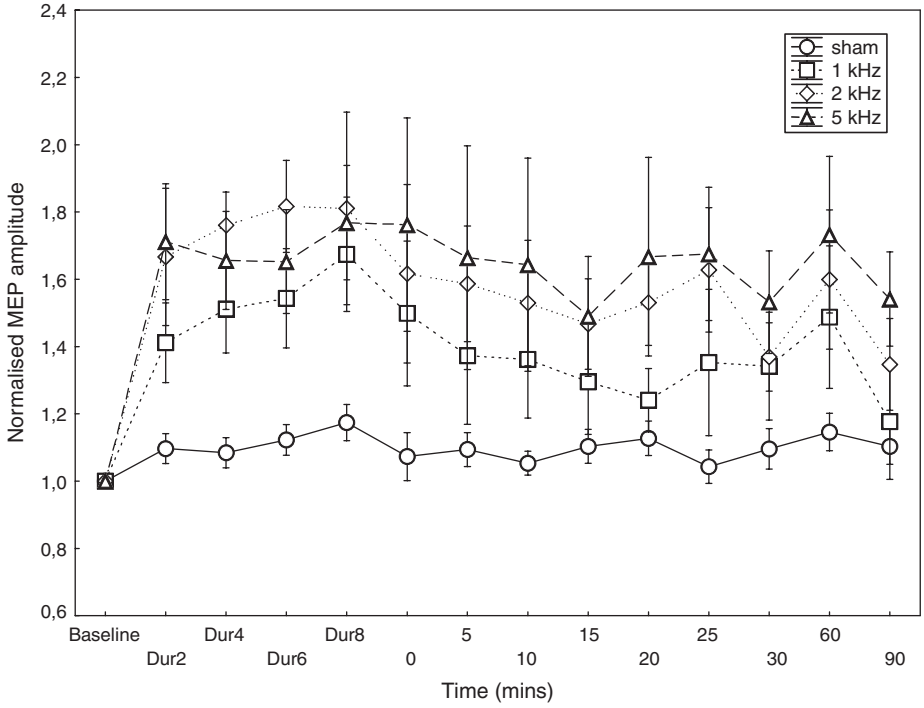

Fig. 1. Effect of 10 min application of tACS on the M1, during stimulation and time course poststimulation. Effects of 1, 2 and 5 kHz on cortical excitability of M1, as measured by mean MEP amplitude. MEP values are normalised to baseline. Timecourse over 90 min is shown. ±error bars indicate SEM.

analysis, significantly increased MEPs were observed during stimulation at 2–8 min time points compared to sham stimulation ($p < 0.05$).

When 2 kHz and sham stimulation was compared repeated measurements ANOVA revealed significant main effect of TYPE of stimulation ($F(1,10) = 15.5$, $p = 0.003$) and TIME ($F(13,130) = 2.3$, $p = 0.009$). The interaction between TYPE of stimulation and TIME was not significant ($F(13,130) = 1.6$, $p = 0.09$). According to the post-hoc analysis, significantly increased MEPs were observed during stimulation at 2–8 min time points ($p < 0.05$) and at 5–15 and 20 min compared to sham stimulation ($p < 0.05$).

Concerning 5 kHz stimulation repeated measurements ANOVA revealed significant main effect of TYPE of stimulation ($F(1,10) = 10.7$, $p = 0.01$) and TIME ($F(13,130) = 1.8$, $p = 0.04$). The interaction between TYPE of stimulation and TIME was not significant ($F(13,130) = 1.21$, $p = 0.2$). According to the post-hoc analysis, significantly increased MEPs were observed during stimulation at 2–10 min time points ($p < 0.05$) and after stimulation at 25, 30 and 90 ($p < 0.05$) compared to sham stimulation. Figures 2A–D show intraindividual responses to tACS in the low kHz range on M1 excitability.

4. Discussion

We report here that a 10 min application of low kHz tACS over the M1 is able to induce sustained elevations in cortical excitability that outlast the duration of stimulation, compared to sham control. 2 and 5 kHz stimulation was significantly more effective than 1 kHz stimulation (2 kHz: $p = 0.0000$–0.03; 5 kHz: $p = 0.002$–0.05, across time course) compared to the baseline values and to the sham stimulation condition. Single- pulse TMS used during the stimulation to measure changes in cortical excitability has also shown that elevations in the amplitudes of elicited MEPs are clearly evident during stimulation, and so may indicate an entrainment of the targeted neuronal population to the external application of oscillating currents.

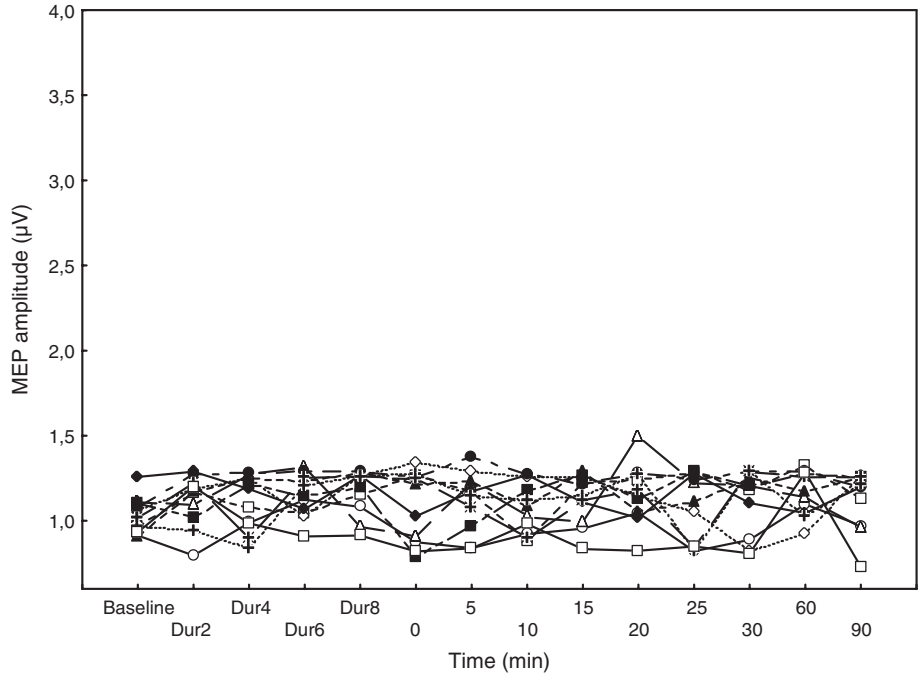

Fig. 2A. Intraindividual responses to Sham tACS on M1 excitability poststimulation. Intraindividual responses to tACS on M1 excitability as measured by mean MEP amplitude. Timecourse over 90 min is shown.

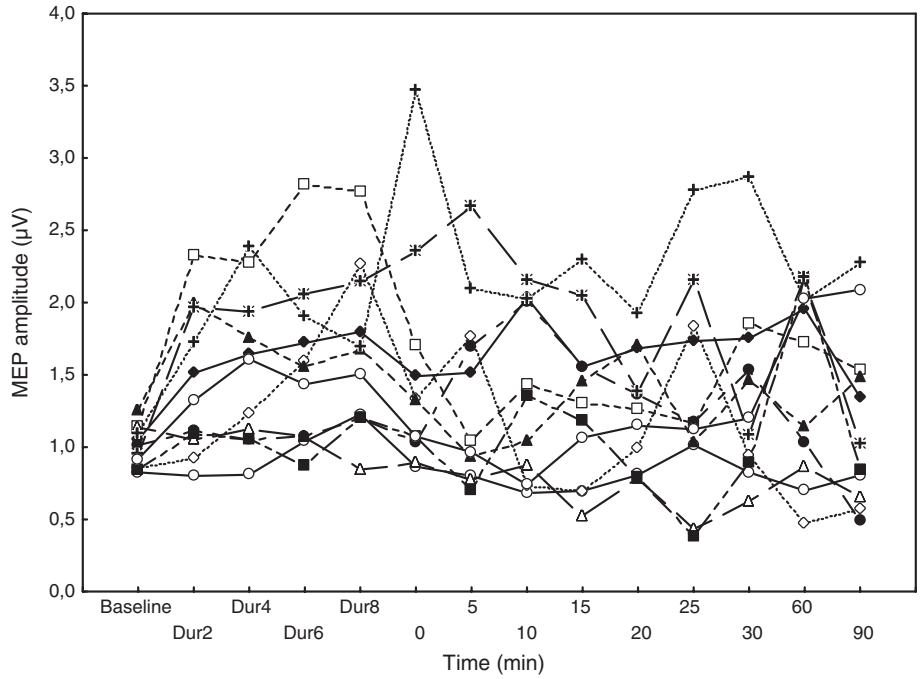

Fig. 2B. Intraindividual responses to 1 kHz tACS on M1 excitability postimulation. Intraindividual responses to tACS on M1 excitability as measured by mean MEP amplitude. Timecourse over 90 min is shown.

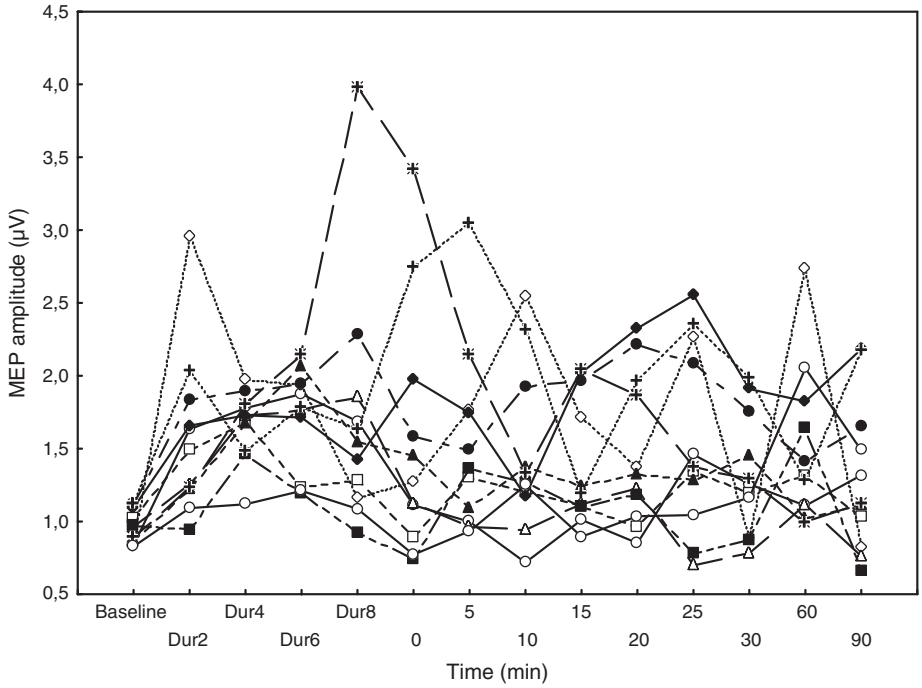

Fig. 2C. Intraindividual responses to 2 kHz tACS on M1 excitability postimulation. Intraindividual responses to tACS on M1 excitability as measured by mean MEP amplitude. Timecourse over 90 min is shown.

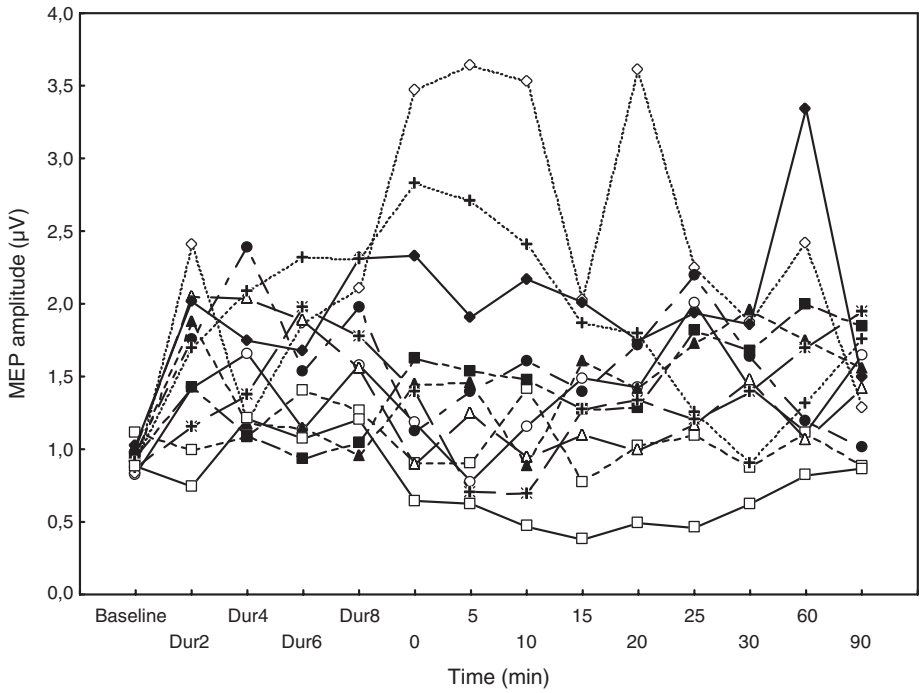

Fig. 2D. Intraindividual responses to 5 kHz tACS on M1 excitability postimulation. Intraindividual responses to tACS on M1 excitability as measured by mean MEP amplitude. Timecourse over 90 min is shown.

It appears that transcranial techniques using higher frequencies aim to amplify and emulate recent studies reporting that the application of high frequency oscillating currents to cell cultures *in vitro* and animal studies *in vivo* are effective in entraining neuronal rhythmicity and propagating synchronicity in neuronal networks (Jinno et al., 2007; Radman et al., 2007a). The application of a 'blanket' electric field over populations of neurons is able to entrain and modulate neuronal output, which in human subjects may manifest as measurable alterations in cortical excitability (Radman et al., 2007b). Many recent studies have sought to investigate whether neuronal networks can be entrained, synchronized or desynchronized by the application of such currents, and whether high frequency oscillations are much more effective in generating synchronization patterns in neuronal assemblies, than those of low frequency oscillations. A recent study has reported that applications of 140 Hz tACS over the M1 increased levels of cortical excitability, lasting up to 1 hour poststimulation, with 250 Hz having a lesser effect on sustained levels of excitability (Moliadze et al., 2010). Application of oscillating currents outside of the physiological range, aiming to interfere with ongoing cortical rhythmicity, however may also be subject to harmonics and/or subharmonics within physiological ranges due to the nature of their alternating cycle. Nevertheless studies suggest that oscillations in a range of several 100 Hz may still interfere with interneuronal rhythms (Ylinen et al., 1995) whereas frequencies in the kHz range are much more likely to interfere with membrane excitability. The underlying mechanisms resulting in such marked increases in cortical excitability are not yet fully understood but may be related to the jamming of neural transmission and/or the production and release of low molecular weight proteic neurotransmitters; studies conducted on patients receiving HF deep brain stimulation have also postulated similar mechanisms along with the direct inhibition of spike initiation at the membrane due to activation of inhibitory terminals and retrograde activation of upstream neuronal structures (for a review see Benabid et al., 2005). However, frequencies applied during HF deep brain stimulation are much lower (around 130 Hz) than those used in the current study, and so this may also indicate a differing mechanism of action (Benabid et al., 1996). Applications of external currents which cause membrane activation are also accompanied by changes in neurotransmitter release and ion channel potentiation, which in turn lead to changes in protein synthesis (Gartside, 1968; Islam et al., 1995). It may well be that the temporary modification of the synapse once exposed to a rapidly alternating electrical field, alters the associated biochemical mechanisms, such as accumulation of calcium in the presynaptic nerve terminals, and leads to short-term synaptic plasticity effects (Citri and Malenka, 2008).

Another study by Kirson et al., reports that exposure of cell lines to tACS at higher frequencies such as 100 kHz (for mouse melanoma), 200 kHz (for rat glioma) and 150 kHz (for human breast carcinoma) decreased the rate of cell proliferation in targeted tumours; an effect that is associated with two distinct mechanisms: the disruption of mitotic spindle microtubule formation, and the elimination of dividing cells during cleavage. Both of these events are determined by the orientation of the mitosis axis and the AC field vector (Kirson et al., 2004, 2007). A more recent study has reported evidence of the regression of amyloid-β deposition in models of transgenic Alzheimer's disease mice, leading to a reversal in cognitive impairment as measured by a cognitive interference task also after exposure to a 918 MHz electromagnetic field (EMF) (Arendash et al., 2009). Studies investigating the effect of mobile phone emissions on cortical excitability and cerebral blood flow have contrasting findings. Haarala et al., 2003 reported that exposure to an active mobile phone produced an immediate decrease in cerebral blood flow bilaterally in the auditory cortex relative to an unexposed area in a study using PET. Subjects were required to perform a visual working memory task during sham and active scanning sessions. No significant results were attributed to the EMF emitted by the active mobile phone. However, Ferreri et al., 2006 demonstrated that the EMF of an active mobile phone modified intracortical excitability during exposure, with short intracortical inhibition (SICI) being reduced and intracortical facilitation (ICF) enhanced in the hemisphere directly exposed, compared to the contralateral non-exposed hemisphere, or to the sham condition.

The advantages in utilizing oscillating currents, especially those of a high frequency, is that potentially neuronal populations can no longer be entrained to the rhythm of an external electric field; with higher frequencies above 1 kHz, membranes can be targeted more selectively. Even though this has so far been observed preferentially *in vitro* at much lower alternating current frequencies and with a uniform field, there

is growing evidence that external transcranial techniques may also be able to achieve such pronounced effects (Bikson et al., 2006). Furthermore, compared to tDCS, tACS in general, has the advantage of not being affected by polarity constraints (Antal et al., 2008; Terney et al., 2008). However, transfer of current flow or impact of closely associated brain regions with afferents into the M1 on the aftereffects of stimulation primary somatosensory cortex or supplementary motor area for example, cannot be ruled out. Other studies examining this effect using tDCS or tRNS have also reported this as a factor in aiming to understand how transcranial stimulation techniques have divergent effects in remote areas of the cortex (Lang et al., 2005; Chaieb et al., 2009). Use of paired-pulse TMS measures to investigate the acute intracortical effects of tACS within this kHz range would enable us to better understand the ways in which tACS differs from better characterized transcranial stimulation methods like tDCS. As tACS in the low kHz range does not influence measures of global corticospinal excitability, like RMT or AMT, this suggests that the mechanism of tACS may be to modulate synaptic activity, as motor thresholds reflect neuronal membrane excitability and are modulated by voltage-gated sodium channel blockers (Ziemann et al., 1996). Within a clinical perspective, external stimulation techniques like tRNS and tACS that are often applied with no noticeable skin sensations (Ambrus et al., 2010), offer the possibility for controlled blinding studies within patient groups, targeting neurological and psychiatric disorders such as depression and stroke (Nitsche et al., 2009; Nowak et al., 2009), disorders currently often targeted by more conventional stimulation techniques like rTMS (Ridding and Rothwell, 2007). tACS aftereffects also compare favorably with those observed poststimulation with tDCS; increases in M1 excitability are able to endure longer after a short stimulation duration. This could potentially provide a preferential therapeutic option, particularly when seeking to target symptoms of neurological disorders or aiding in rehabilitation post trauma. However, the effects of continuous application and long-term use of high frequency transcranial techniques like tACS and tDCS still have yet to be investigated with regards to safety. Animal studies along with recent consensus reports suggest that techniques like TMS are safe and therapeutically relevant but more research is required, especially with regard to use as treatment for neurological and neuropsychiatric disorders (Liebetanz, 2009; Rossi et al., 2009).

5. Conclusion

In summary, our preliminary study has sought to evaluate the durable aftereffects of relatively short-duration low kHz tACS over the M1. Stimulation in the low kHz range allows for the generation of similar sustained cortical excitability increases, as previously seen with rTMS or tDCS paradigms. However, they possess a different physiological mode of action. rTMS and tDCS will remain the method of choice for inducing inhibitory effects. But for the induction of enduring excitatory aftereffects low kHz tACS offers a new possibility for transcranial electrical stimulation techniques.

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