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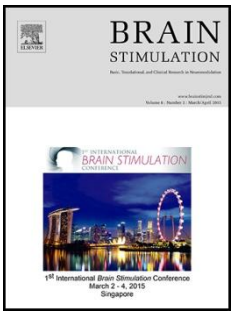

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Evaluation of a modified high-definition electrode montage for transcranial alternating current stimulation (tACS) of pre-central areas

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Abstract

Objective: To evaluate a modified electrode montage with respect to its effect on tACS-dependent modulation of corticospinal excitability and discomfort caused by neurosensory side effects accompanying stimulation.

Methods: In a double-blind cross-over design, the classical electrode montage for primary motor cortex (M1) stimulation (two patch electrodes over M1 and contralateral supraorbital area) was compared with an M1 centre-ring montage. Corticospinal excitability was evaluated before, during, immediately after and 15 minutes after tACS (10 min., 20Hz vs. 30 sec. low-frequency transcranial random noise stimulation).

Results: Corticospinal excitability increased significantly during and immediately after tACS with the centre-ring montage. This was not the case with the classical montage or tRNS stimulation. Level of discomfort was rated on average lower with the centre-ring montage.

Conclusions: In comparison to the classic montage, the M1 centre-ring montage enables a more focal stimulation of the target area and, at the same time, significantly reduces neurosensory side effects, essential for placebo-controlled study designs.

Keywords

Transcranial alternating current stimulation; high-density electrode montage; beta frequency; corticospinal excitability; neurosensory effects

Abbreviations

tACS: transcranial alternating current stimulation

tRNS: transcranial random noise stimulation

TMS: transcranial magnetic stimulation

rMT: resting motor threshold

MEP: motor evoked potential

FDI: first dorsal interosseus muscle

Introduction

Transcranial alternating current stimulation (tACS) currently attracts increasing interest as a method to modulate intrinsic neural oscillations by externally applying weak alternating electrical fields [1] and its potential to analyse causal relationships between neural activity and behaviour [2]. However, it is well known that tACS of central to frontal areas is heavily impacted by neurosensory effects such as visual (phosphenes) or skin sensations (tingling, burning, pain) that are influenced by the stimulation frequency [3-5]. In particular phosphenes are most pronounced at frequencies in the beta range and increase with stimulation intensity [6, 7], most likely due to expansion of the electrical field into the retina [6]. Besides causing discomfort, these side effects are critical since they hamper effective blinding of participants and hence impede placebo-control or crossover study designs. Computational modelling suggests that increasing the number of 'return' electrodes might reduce the occurrence of visual side-effects [6]. In this regard, a 4x1 high-density electrode montage, originally proposed for transcranial direct current stimulation [7] renders a possible solution to these inherent technical problems of tACS [8]. However, exact electrode placement assuring adequate distance between electrodes becomes more difficult, which bears the risk of an uneven distribution of the electrical current or shunting of current over the skin. We therefore evaluated a modification of the high-density montage consisting of one single circular ring electrode surrounding the central electrode overlaying the target area aiming at two main objectives:

Firstly, it was analysed whether an adequate penetration of the motor cortex can be achieved with the ring montage. Previous work has shown an online increase of corticospinal excitability during 20 Hz tACS as evaluated with single-pulse transcranial magnetic stimulation (TMS) at rest [9-12]. This effect has been attributed to the acute modulation of the discharge rate of neural firing [13, 14]. Therefore, we hypothesized a sufficient current flow through the motor cortex with the ring montage in case of significant tACS-induced modulation of corticospinal excitability.

Secondly, it was evaluated whether tolerability of the new montage, i.e. comparably reduced discomfort through accompanying somatosensory and visual side effects, is superior to the classical M1 – contralateral supraorbital area (M1-SO) electrode formation.

Material and methods

Ten (5 female, mean age in years 22.81±2.76, range 20.3-30.2 years, all right-handed) participants volunteered in the experiment. None reported a history of medical, neurological or psychiatric diseases or any contraindications for non-invasive brain stimulation, as probed by a standardized questionnaire based on available safety recommendations [15, 16]. All participants were naïve to the experimental purpose and gave full written informed consent to participate in the experiment in accordance with the medical ethics committee of KU Leuven (protocol number S57359).

The influence of electrode montage on the tACS effect on motor cortical excitability and neurosensory side effects was tested in a double blind crossover design. Participants and study personnel involved in data acquisition and analysis were blind regarding the type of stimulation condition (20Hz tACS versus placebo). 20 Hz tACS with classical montage, 20 Hz tACS with ring montage, and random noise stimulation

as control condition with either of the montages were tested in three separate sessions in pseudo-randomized order. To avoid potential carry-over effects, a minimum interval of one day between sessions was aimed for [17-20]. Within each session, the measurement of corticospinal excitability was performed immediately before (BASELINE), exactly 5 minutes after stimulation was switched on (ONLINE), immediately after (POST) and 15 minutes after stimulation cessation (POST15) (figure 1A). Participants evaluated their subjective level of neurosensory discomfort caused by tACS at the end of each session (Visual Analogue Scale, $VAS_{discomfort}$, extremes constituted of "I perceived nothing" and "I perceived the worst imaginable discomfort/pain") and level of fatigue at the beginning and end of each session ($VAS_{fatigue}$, extremes constituted of "absolutely not tired" and "maximally tired").

Transcranial alternating current stimulation

TACS was applied through conductive patch electrodes (NeuroConn, Ilmenau, Germany) in two different formations: For both, the (A) classical montage (figure 1B) and the (B) ring montage (figure 1C), a round (9 cm^2) 'target' electrode was placed over the left hand knob area centred at the FDI hotspot identified with TMS. For the (A) classical montage the 'return' electrode (35 cm^2) was placed on the contralateral supra-orbital area. For the (B) ring montage the 'return' electrode consisted of a (35 cm^2) ring surrounding the centre electrode with a 2.05 cm distance between electrode borders.

20 Hz tACS lasted for 10 minutes. As a control condition 30 seconds of low frequency random noise stimulation (tRNS low-pass 100 Hz) was selected because this has shown to leave corticospinal excitability unaffected [21]. For both, tACS and tRNS an intensity of 400 µA (peak-to-peak) was chosen yielding an average current density of 0.04 mA/cm^2 at the 'target' electrode and 0.01 mA/cm^2 at the 'return' electrode for both montages (A) and (B). Electrodes were covered with conductive gel to keep impedances below 10 kΩ. The electrode montages (A) and (B) were

randomly chosen for the control condition, counterbalanced across participants. Transcranial alternating current and random noise stimulation were applied using a battery-driven stimulator (NeuroConn, Ilmenau, Germany).

Measurement of corticospinal excitability

A Magstim 200 magnetic stimulator (Magstim Company, Whitland, Dyfed, UK) and one figure-of-eight coil (70 mm inner wing diameter) were used for single pulse application. The coil was placed over the hand motor area, with the handle in antero-medial orientation, 45° to the interhemispheric line. The procedure to establish the motor hotspot for the first dorsal interosseus muscle (FDI) followed established standardized procedures [22]. Resting motor threshold (rMT) [23] and test stimulus intensity to elicit an average motor-evoked potential (MEP) of 1.0 mV peak-to-peak amplitude were adjusted with the tACS electrodes fixed to the head, through the target electrode overlaying the FDI hotspot. MEPs (N=30) were collected at each time point (BASELINE, ONLINE, POST, POST15). EMG signals were recorded with disposable surface Ag/AgCl electrodes from the FDI in a belly-tendon montage, amplified, and digitized (CED MICRO 1401, Cambridge Electronic Design, Cambridge, UK) and electronically stored for off-line analysis.

Computational simulation of the electrical field

The electrical field was simulated for the two electrode montages (A) and (B) for an example participant based on the SimNIBS pipeline (www.simnibs.org) and a finite element head model derived from individual MRI data of the same participant. A detailed description of the methods can be found elsewhere [24, 25]. More specifically, all electrodes were modelled as 1 mm thick rubber layers (conductivity 0.1 S/m) with 1mm thick layers of conductive gel underneath (conductivity of 14 S/m, estimated based on the concentration of sodium in the Onestep Cleargel, as stated by the manufacturer). The positions of the connectors were explicitly modelled, as

depicted in figures 1B and C (see [25] for details on the modelling procedure). A current strength of 200 μA was simulated, corresponding to the 400 μA peak-to-peak amplitude.

Statistical Analysis

Logarithmic transformation (log) assured distribution of MEP data to meet assumptions of the Central Limit Theorem. Linear mixed effects modelling (LME) with a random intercept model [26] was used to estimate the effect of STIMULATION CONDITION (classic M1-SO, ring M1, control condition) on the temporal evolution of corticospinal excitability before during and after stimulation (BASELINE, ONLINE, POST, POST15), fitted as fixed effects. Since MEP amplitude size might influence overall extent of change of cortical excitability, (log transformed) MEP amplitude at baseline was added as a covariate to the model, and random intercept was modelled on SUBJECT level (restricted maximum likelihood criteria, REML). Simultaneous pairwise post hoc comparisons and respective corrections were performed with Tukey contrasts (only significant contrasts are reported). Generalized omega squared statistics (ω^2) was chosen to estimate effect size and post hoc power for the LME design [27, 28] (performed with G*Power version 3.1.9.2 [29]). VAS data (Discomfort, Fatigue) were analysed non-parametrically for dependent (Wilcoxon signed rank test) and independent (Kruskal-Wallis rank sum test) samples comparison. Kendall's τ correlation coefficient (2-sided) was used to examine the potential association between online effects of tACS on MEP amplitude and impedance during tACS or rMT, respectively. The 95% confidence intervals around the mean (bootstrap) correlation coefficient (τ_{boot}) are given as Bias Corrected Accelerated ($95\%CI_{BCA}$) intervals. Data preparation and statistical analyses were performed using the software package R for Statistical Computing, version 3.2.0 (2015-04-16) [30] for Mac OS X x86_64-apple-darwin13.4.0 (64-bit) with using R

packages nlme version 3.1-120 [31], lme4 version 1.1-9 [32], multcomp version 1.4-1 [33], ggplot2 version 1.0.1 [34].

Results and Discussion

Data from all participants was collected for all conditions. The interval between sessions ranged between 43 - 290 hours (mean±SD 102±67 hours). All experimental interventions were well tolerated by all participants and none reported adverse effects during or following the experiments.

Influence of montage on 20Hz tACS modulation of corticospinal excitability

The relationship between STIMULATION CONDITION and change in corticospinal excitability over time showed a significant variance in intercepts across participants SD = 0.20 (95%CI: 0.12-0.32), p<.0001), necessitating the present statistical approach that takes this individual variability into account. LME revealed a main effect of STIMULATION CONDITION ($F_{(2, 3363)}$= 43.67, p<.0001) as well as an effect of MEP amplitude size at baseline ($F_{(1, 3363)}$= 197.15, p<.0001), in the absence of a main effect of TIME ($F_{(1, 3363)}$= 0.90, p>.3). Most important, a significant interaction of STIMULATION CONDITION x TIME ($F_{(2, 3363)}$= 20.18, p<.0001) indicated a different modulation of the tACS effect over time with different montages (figure 2A). While a significant MEP amplitude increase was obtained with the ring montage under tACS (ONLINE vs. BASELINE estimated difference 0.24±0.07, z=3.51, $p_{adjusted}$<.05), and at the end of stimulation (POST vs. BASELINE estimated difference 0.23±0.07, z=3.36, $p_{adjusted}$<.05), no change was observed with the classic montage (all $p_{adjusted}$>.7). In the control condition (30 seconds of tACS), the MEP amplitudes decreased over time (POST vs. BASELINE estimated difference -0.27±0.07, z=-3.94, $p_{adjusted}$<.0001, POST15 vs. BASELINE estimated difference 0.39±0.07, z=-5.54, $p_{adjusted}$<.001). An

effect size of ω^2=0.29 for the whole LME translates into a post hoc power (1-β err prob) of 0.34 with the present design and sample size.

These results imply a stronger focalization of the tACS effect with the ring montage, yielding a more consistent increase of corticospinal excitability in the present sample. The absence of an acute excitability modulation under 20 Hz with the classical montage might be due to a less reliable distribution of the electrical field with two distant patch electrodes and therefore less consistent current flow through motor cortical neurons. As suggested by recent work [11], the individualization of electrode montages with respect to the target area and the aim of the stimulation protocol might be a solution to this problem. In accordance with previous findings [21], we did not observe acute excitability changes with low-frequency tRNS. However, the long-term excitability reduction with tRNS complicates the clear interpretation of these results as placebo condition.

Differences in the electrical field expansion between two montages

The simulation reveals comparable absolute field strengths between 0.06 and 0.12 V/m in M1 and caudal premotor areas for both montages (figure 2C). While the electrical field of the classic montage expands to the right frontal region with a second focus over the right frontopolar cortex, the electrical field of the ring montage is more focalized over the primary motor representation of the hand knob and rostral premotor regions.

The simulation reveals that for the ring montage, the outer ring acts like a curved electrode anterior to the central target electrode with a strong effect of the connector position in guiding the current direction in M1. This means that in both electrode montages, the current flows through the primary motor area in an anterior-posterior axis that has an approximate 45˚ angle to the midline.

Correlation between rMT and amount and direction of tACS ONLINE effect

No correlation was found between rMT (46.80±6.82%, range 34-61% of maximum stimulator output) and online change of MEP amplitude for any of the montages and stimulation condition combinations (all p>.2).

Correlation between impedance and direction tACS ONLINE effect

Impedance of tACS electrodes was checked continuously throughout the experiment (classic montage median= 4.5 kΩ, ring montage median = 9.4 kΩ, tRNS median = 3.5 kΩ). Online change of normalized MEP (%baseline) under tACS was negatively associated with averaged maximum impedance during tACS stimulation for the ring montage (τ_{boot}=-0.51, 95%CI_{BCA}=-1.0-0.35, p<.05), but not for the classic montage (τ_{boot}=0.11, 95%CI_{BCA}=-0.4-0.6, p>.6) or tRNS condition (τ_{boot}=0.31, 95%CI_{BCA}=-0.2-0.8, p>.2). This finding implies better stimulation effects with lower impedance, which stresses the need for close online monitoring of impedance and the integration of this data into the interpretation of the observed stimulation effects.

$VAS_{discomfort}$

Participants reported lower level of discomfort in the ring (median=0.3) than in the classic M1-SO (median=1.4) montage condition (V=98, p<.05, r=-0.67, figure 2B). There was no difference in level of discomfort between tRNS and tACS within the two montage conditions (ring/classic) (p>.4).

The absence of a difference in perceived discomfort between tRNS and tACS for both montages suggests that the chosen low-frequency tRNS serves well to blind participants with respect to the stimulation condition. The discomfort rating for those participants with larger intersession intervals might be less comparable, which constitutes a limiting factor.

$VAS_{fatigue}$

There was an overall difference in level of fatigue between the montage and stimulation conditions (χ^2=17.8, df=3, p<.001), with on average higher levels of fatigue in the classic montage condition (classic/tRNS median=3.4, ring/tRNS median=0.7, classic/20Hz median=2.9, ring/20Hz median=2.05). But change of fatigue over time did not differ among conditions (p>.4).

Conclusions

The present results document a critical influence of the electrode montage on the effectiveness of tACS-induced neuromodulation. We found the M1 ring montage to induce a more focal stimulation of the target area as evidenced by a more consistent online excitability increase. These findings may be explained by a more focalized expansion of the electrical field centred on the target area as evidenced by computational simulation. The marked reduction of neurosensory side effects with the ring montage is an essential feature that facilitates placebo-controlled study designs.

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Figure captions

Figure 1

A) Experimental time flow within in one session. Standard procedures were applied to retrieve the hot spot for the first dorsal interosseus muscle (FDI). TMS intensity was adjusted after tACS electrodes were fixed on the head with

non-conductive elastic bands. 30 MEPs were collected before (BASELINE) tACS/tRNS onset, during, i.e. 5 minutes after tACS/tRNS onset (ONLINE), immediately after (POST) and 15 minutes after tACS cessation (POST15). Participants evaluated their subjective level of neurosensory discomfort caused by tACS at the end of each session (Visual Analogue Scale, $VAS_{discomfort}$) and level of fatigue at the beginning and end of each TMS session ($VAS_{fatigue}$).

B) Schematic of classic montage with target electrode (3.4cm diameter, $9cm^2$) over the primary motor cortex, centred at the FDI hotspot, and the 'return' electrode (5x7cm, $35cm^2$) overlaying the right supraorbital area.

C) Schematic of ring montage with a circular 'return' electrode (7.5 cm inner and 10cm outer diameter, $34.5cm^2$) surrounding the target electrode (same as in the classic montage, 3.4cm diameter, $9cm^2$). The distance between outer borders of the central and the surrounding electrode was 2.05cm.

Figure 2

A) Results for stimulation effect on corticospinal excitability. For illustrative purposes, MEP amplitudes are normalized to baseline. In the ring-montage condition (filled circles), 20Hz tACS led to a significant relative increase in corticospinal excitability during and immediately after 10 minutes of stimulation. No such effect was found in the classic montage condition (filled squares). In the tRNS condition (open triangles), a relative decrease of MEP amplitude was found over time. Error bars indicate SE of the mean. *$p < 0.05$.

B) Overall, participants perceived a higher level of discomfort with the classic montage (left panel) than with the ring montage (right panel). In neither group, participants were able to differentiate between tRNS stimulation (white bars) and 20Hz tACS (grey bars). Whiskers indicate minimum and maximum

values, upper and lower limits of the boxes indicate lower and upper quartiles (25% and 75%), horizontal lines indicate the median. *$p < 0.05$.

C) Electrical field simulation for exemplary participant for the classic montage (left side) and for the ring montage (right side) with 20Hz tACS of 400µA intensity.