The impact of cerebellar transcranial alternating current stimulation (tACS) and simultaneous motor network activation via motor sequence learning (MSL) on movements and muscle strength

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ABSTRACT

The cerebellum and its connections to the cerebrum can be modulated by noninvasive brain stimulation (NIBS) techniques, especially transcranial alternating current stimulation (tACS). This modulation may affect movements and muscle strength by increasing the cortical excitability. Moreover, the effect depends on the state of the neurons involved in these executions. Therefore, it is important to gain further insight into how cerebellar tACS with and without simultaneously activation of the motor network via motor sequence learning (MSL) affects movements and muscle strength. Using inertial measurement units (IMU) and electromyography (EMG), we were able to record and evaluate movements of 20 participants regarding this issue. We were able to demonstrate that simultaneous activation of the motor network partly led to longer task durations because it is suspected to interfere with the tACS effect. Concerning the muscle strength, a strength enhancing effect occurred, due to the irritation of the motor system by tACS and particularly the simultaneous MSL. These findings are of importance for future therapeutic approaches using tACS.

KEYWORDS

cerebellum, transcranial alternating current stimulation, tACS, motor sequence learning, MSL, alterations in movement, inertial measurement units, IMU, electromyography, EMG

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1 INTRODUCTION

The cerebellum is substantial for motor function, including error-free target motor control and diadochokinesis [1]. It is also involved in learning new motor sequences (Motor Sequence Learning) [2, 3]. It is suspected that pathologies of the cerebellar structures lead to the development and maintenance of certain neurological movement disorders such as myoclonus dystonia or ataxias [4]. Noninvasive brain stimulation (NIBS) techniques are able to target cerebellar

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structures, gain insights in their communication with each other and are considered effective methods to modulate cerebello-cortical connections [5, 6]. This cerebellar modulation may result in new therapeutic approaches [7, 8]. To achieve this, it is imperative to further investigate the modes of action of NIBS. A previous study of our group found transcranial alternating current stimulation (tACS) of the cerebellum to be the most effective method to modulate cerebellar output and thereby increase cortical excitability compared to transcranial direct current stimulation (tDCS), transcranial random noise stimulation (tRNS) and a control stimulation (sham) [9]. The aim of the present study was to further investigate the mechanisms of cerebellar tACS regarding behavioral changes. tACS effects on movement acceleration and increased grip strength have already been demonstrated by Naro et al. [2017] following 1-minute 50 Hz cerebellar tACS [10]. Continuing, this study examines the effect of 20-minute (l-tACS) compared with 40-second 50 Hz tACS (s-tACS) on the speed of movements and grip strength. For a precise record of changes, behavior was assessed using inertial measurement units (IMU) and electromyography (EMG) while performing Wolf Motor Function Test (WMFT) movement tasks.

It is postulated that the magnitude of the effect of tACS depends on the initial state of the targeted neurons involved [11, 12]. Therefore, we further evaluated how simultaneous activation of the motor network using a motor sequence learning (MSL) task during the intervention affects subsequently executed movements and modulates the effect of stimulation. To the best of our knowledge, this has not been investigated previously.

2 EXPERIMENTAL DETAILS

2.1 Participants

Twenty neurologically and psychiatrically healthy, right-handed subjects with a mean age of 26.5 years (SD: 8.22) participated in the study. Of these, 7 participants were male and 13 participants were female. Exclusion criteria were neurotropic medications, playing an instrument or video games regularly and contraindications to magnetic resonance imaging and transcranial electrical stimulation (tES). Written informed consent was obtained.

2.2 Experimental design

All participants received T1-weighted MRI to locate the right cerebellar lobus VIIIa for later stimulation in a neuronavigated manner using Brainsight (Rogue Research, Montreal, Canada).

Each subject participated in four appointments that differed only in the intervention: 20 minutes tACS without MSL (l-$\text{tACS}_{\text{REST}}$), 20 minutes tACS with MSL (l-tACS_{MSL}), 40 seconds tACS without MSL (s-$\text{tACS}_{\text{REST}}$), 40 seconds tACS with MSL (s-tACS_{MSL}). There was at least one week between each measurement day to rule out persistent neuroplasticity changes due to tACS. Each appointment started with the fitting of the electromyography (EMG) and IMU montage. This was followed by a practice run of the WMFT. Thereafter, the pre-plasticity baseline measurement of the WMFT (t0) followed. Thereafter one of four interventions was applied randomized and double-blinded. This was followed by two additional post-plasticity runs (t1 and t2) of the WMFT.

2.3 WMFT

The WMFT is a motor assessment of the upper limb, initially developed for treatment outcomes of stroke patients and patients after trauma [13]. We extracted five exercises from the WMFT that resulted in significantly better performance after 60 seconds of tACS in Naro et al. [2017] [10]. Increases in speed and increases in muscle strength were considered. We performed: (1) Pick up a pencil and lift it up to a mark, (2) Pick up a paper clip and lift it up to a mark, (3) Stack two checkers on a checker lying in the middle, (4) Turn over three cards in a fixed order and (5) Turn a key in a lock ten times each 90 degrees to the left and to the right. Subjects were seated on a chair and had both hands on the left and right of the items at fixed positions on the table. This hand position was to be resumed before and after each task. The distance between chair and table was chosen that the key task could be performed at a comfortable angle. Exercises (1)-(5) were performed alternately first with the right and after that with the left hand. Exercises (1)-(4) were repeated two times for each hand and the mean values were calculated, exercise (5) for each hand was performed only once.

2.4 EMG and IMU

We used the IMU and EMG systems from Myon (Cometa GmbH, Bareggio, Italy). For recording muscle strength, we used Myon EMG sensors. A surface EMG belly-tendon montage was placed. One electrode was added to each of the left and right pollicis breves muscles. The reference electrode was placed on the radial styloid process of both wrists. The IMU (Myon Aktos-t sensors) enabled us to record movements in three axes with accelerometer, gyroscope and magnetometer. IMU placement was done in the middle of the biceps brachii muscle on both arms, also on the distal parts of the forearms and with the help of gloves on the back of the hands.

2.5 Cerebellar alternating current stimulation

Cerebellar stimulation was ensured by the DC electrostimulator (neuroConn GmbH, Ilmenau, Germany) and two 3x3 cm electrodes. Alternating current with a current intensity of 1 mA, a frequency of 50 Hz, a fade in and fade out phase of the current of 2 seconds each was delivered. The resistance was always less than 6 kOhm. The position of the cerebellar electrode was determined based on neuronavigation and corresponded to the right lobus VIIIa. The reference electrode was placed on the right masseter muscle. Subjects sat relaxed, without speaking, with eyes open in a chair for the stimulation period of 20 minutes or performed a MSL task for the entire period.

2.6 MSL

We used a Serial Reaction Time Task (SRTT) for implicit motor sequence learning [14, 15]. Given sequences had to be imitated on a laptop by keystrokes as quickly and accurately as possible. Here, a distinction was made between 5 random blocks (RND) and 5 sequence blocks (SEQ). The RND consisted of 80 keystrokes of pseudorandomized sequence. The SEQ consisted of recurrent sequences of 8 keystrokes repeated 15 times per block. These blocks appeared alternately on the screen.

2.7 Statistics

The preprocessing of WMFT exercises were done using R (version 2022.07.1) and time was provided using accelerometry data from exercises (1)-(4). For exercise (5), the gyroscope data were used to provide time from 7 complete key rotations. The root mean square was determined from the EMG data of exercise (5) to evaluate muscle strength. All statistics were performed using Jamovi (version 2.3.21.0). The statistics for speed and muscle strength refer to the relative changes, thus we were able to eliminate the interindividual time differences and the variations between days. Training effects over all four days were examined using absolute times. The significance level was set at $p<0.05$.

3 RESULTS AND DISCUSSION

3.1 Results

3.1.1 *Sensitivity of the IMU.* Multifactorial ANOVA for the factor HAND (left and right) in the pre-plasticity run (t0) revealed that the right-handed subjects completed tasks (1), (3), and (4) faster with right than with left hand ($F_{1,19}=8.908$, $p=0.008$, $\eta^2_p=0.319$; $F_{1,19}=16.184$, $p<0.001$, $\eta^2_p=0.46$; $F_{1,1.0}=5.813$, $p=0.026$, , $\eta^2_p=0.234$, respectively). Thus, the IMU montage was sensitive enough to show even slight differences in speed.

3.1.2 *Alterations in speed.* Task (4) and (5) showed a significant shorter duration over time (Task (4) left: $F_{2,1.43}=9.442$, $p=0.002$, $\eta^2_p=0.332$; right: $F_{2,1.59}=4.66$, $p=0.015$, $\eta^2_p=0.197$; Task (5) left: $F_{2,1.37}=14.994$, $p<0.001$, $\eta^2_p=0.097$; right: $F_{2,1.88}=20.96$, $p<0.001$, $\eta^2_p=0.165$). The ANOVA revealed no effects for the factor INTERVENTION (s-tACS$_{\text{REST}}$, l-tACS$_{\text{REST}}$, s-tACS$_{\text{MSL}}$, l-tACS$_{\text{MSL}}$), for the interaction between TIME (t0, t1, t2) x INTERVENTION and after splitting interventions by MSL/REST. Thus, the faster execution was independent of the intervention.

Outcomes of task (1), (2) and (3) showed intervention-dependent effects. For task (1), there was a trend to significance ($F_{3,2.07}=2.668$, $p=0.08$, $\eta^2_p=0.123$) in the multifactorial ANOVA for the main factor INTERVENTION with right hand. It was mainly based on the slower performance of the task after l-tACS$_{\text{MSL}}$. The following comparison of MSL/REST showed a deceleration for the runs with MSL ($F_{1,1.0}=6.426$, $p=0.02$, $\eta^2_p=0.253$).

Task (2) supported this, revealing a trend to significance ($F_{1,18}=3.296$, $p=0.086$, $\eta^2_p=0.155$) for both hands for the main effect of MSL/REST. The analyses for task (2) were performed under exclusion of one subject who was the only one using a different technique to perform the task. Including this outlier in the analysis yielded $F_{1,19}=1.555$, $p=0.228$ and $\eta^2_p=0.076$. For task (3), the multifactorial ANOVA resulted in a trend to significance for the factor INTERVENTION (separate for the left and right hand) (left: $F_{1,1.0}=3.232$, $p=0.088$, $\eta^2_p=0.145$; right: $F_{1,19}=3.226$, $p=0.088$, $\eta^2_p=0.145$). When comparing l-tACS to s-tACS, the performance of the task was faster after s-tACS. The ANOVA for both hands showed a trend to significance ($F_{3,2.14}=2.748$, $p=0.073$, $\eta^2_p=0.126$), where slower task performance occurred after l-tACS$_{\text{REST}}$ and l-tACS$_{\text{MSL}}$. The fastest performance occurred after s-tACS$_{\text{REST}}$. The comparison of s-tACS and l-tACS for both hands revealed to be significant ($F_{1,1.0}=5.025$, $p=0.037$, $\eta^2_p=0.209$).

3.1.3 *Alterations in grip strength.* Grip strength during task (5) showed a significant increase for the main factor TIME with left and right respectively independent from the intervention; for the left hand, time points t0 to t1($t_{16}=-3.786$, $p=0.006$) and t0 to t2 ($t_{16}=-3.054$, $p=0.016$) and for the right hand from t0 to t2 ($t_{18}=-2.83$, $p=0.033$).

Looking at each intervention separately, s-tACS$_{\text{MSL}}$ for the right hand ($F_{2,36}=7.9$, $p=0.001$, $\eta^2_p=0.305$) and l-tACS$_{\text{MSL}}$ for the right hand were significant for the increase of strength across time points ($F_{2,38}=3.55$, $p=0.039$, $\eta^2_p=0.091$). Comparison of MSL and REST for the left hand yielded a statistical trend ($F_{1,1.0}=3.608$, $p=0.076$, $\eta^2_p=0.184$) for the main factor. The multifactorial ANOVA of the left hand with the factors TIME, INTERVENTION and MSL/REST showed a three-way interaction with a trend to significance ($F_{2,1.44}=3.281$, $p=0.070$, $\eta^2_p=0.170$).

3.1.4 *Training effect.* To evaluate a training effect, we performed analyses of absolute data pre-plasticity across days. For task (1), there was significantly faster performance from day 1 to 3 and 4 for the left and right hand in the multifactorial ANOVA for DAY (day 1, day 2, day 3 and day 4) (left: $F_{3,57}=5.73$, $p=0.002$, $\eta^2_p=0.232$; right: $F_{3,2.04}=7.74$, $p=0.001$, $\eta^2_p=0.290$). For task (2), there was a trend to significance (left: $F_{3,1.76}=2.58$, $p=0.097$, $\eta^2_p=0.120$; right: $F_{3,57}=2.34$, $p=0.083$, $\eta^2_p=0.11$) for the main effect DAY with both hands respectively. Tasks (3), (4) and (5) showed faster performance with the right hand (and left hand for task (4) and (5)) for the comparison of day 1 with days 2, 3 and 4 (Task (3): $F_{3,57}=5.22$, $p=0.003$, $\eta^2_p=0.216$; Task (4): left: $F_{3,1.53}=11.7$, $p<0.001$, $\eta^2_p=0.382$; right: $F_{3,1.81}=21.8$, $p<0.001$, $\eta^2_p=0.535$; Task (5): left: $F_{3,57}=34$, $p<0.001$, $\eta^2_p=0.268$; right: $F_{3,1.4}=39.7$, $p<0.001$, $\eta^2_p=0.26$). A training effect across days was not detected for the increase in muscle strength (left: $F_{3,2.57}=0.711$, $p=0.550$, $\eta^2_p=0.043$; right: $F=_{3,2.81}=1.370$, $p=0.262$, $\eta^2_p=0.071$).

3.1.5 *Summary.* In summary, during task (1), the simultaneous MSL during l-tACS lead to a slower performance. Overall, the task is not performed significantly faster after any of the interventions and there is no significant difference between the interventions. Task (2) affirmed that participants performed slower after tACS with MSL than participants after Rest during the intervention. Here, task performance was particularly fast after s-tACS. Also, for task (3), participants performed faster after s-tACS, this was significantly faster compared to l-tACS and independent of MSL. For tasks (4) and (5), subjects achieved faster execution across the two time points regardless of intervention and MSL. Grip strength at task (5) improved, especially with the left hand after MSL. A training effect across days was shown for every task (1)-(5) for time, but not for muscle strength.

3.2 Discussion

This project investigated the influence of cerebellar s-tACS and l-tACS on speed and strength of movements and how additional activation of the motor network by MSL during stimulation modulates the tACS effects.

3.2.1 Alterations in movement speed and muscle strength. The IMU montage was able to detect differences in performance as shown by comparing pre-plasticity times of the left and right hand.

Shorter stimulation duration of 40 seconds without MSL showed faster execution of task (2) and (3), for task (4) and (5) the performance improved independent from the kind of intervention. The grip strength for task (5) improved after tACS in general.

One reason for the behavioral improvements after s-tACS may be the influence of stimulation on Purkinje cells and their surrounding neural circuits. One explanation could be the disinhibition of the dentato-thalamo-cortical pathway on which the Purkinje cells have inhibitory influence. The 50 Hz tACS may interfere directly with these cells, eliciting a long-term depression (LTD) like effect over time and thus attenuating their effect on the nucleus dentatus, leading to the increased excitability of the cortex. [9] Another possibility is that granule cells, which are acting excitatory on Purkinje cells, are attenuated by the stimulation. This in turn would result in a lower output of Purkinje cells. [9] Regarding l-tACS, longer interventions are also thought to induce plasticity in the longer term through LTD [16, 17]. However, we were unable to demonstrate this specifically for the 20-minute stimulation. 40 seconds or 60 seconds, following Naro et al. [2017], seem to be a more appropriate duration to induce increased excitability, measured in the achievement of faster execution of the tasks [10].

It was also noticeable that subjects slowed down in task (1) and (2) after tACS applied simultaneously with MSL. This could be due to the fact that for both tACS and MSL, the expected effect is LTD [10, 15, 18]. The co-occurrence of both plasticity effects of tACS and MSL, may attenuate each other due to so-called "homeostatic plasticity" [19].

There was a gain of grip strength throughout all interventions. The greatest improvements occurred after the interventions with simultaneous MSL, opposite to the speed effects. In general, individuals with cerebellar pathologies, especially with damage to the dentate nucleus and Purkinje cells, show an overshooting force [20]. This is interpreted as the need to ensure a stable grip even in situations where the motor system is working inadequately [21], which here is affected by tACS and especially additionally MSL.

There have been effects in speed and grip strength affecting both hands. This suggests that the stimulation may have global rather than focal effects in the cerebellar cortex. This is further supported by the fact that the training effect is more pronounced with the left hand than with the right. With the dominant right hand, a plateau is reached earlier, after which performance does not improve further (usually day 3). However, movement changes with the left hand may remain measurable longer. This could cause masking of the stimulation effect for the right hand while the effect is still visible for the left hand.

Overall, we could not reproduce the motor improvement after tACS of Naro et al. [2017] to the same extent [10]. Methodological differences such as the different intervention of 60 seconds versus 40 seconds or 20 minutes may be responsible for this. The smaller number of participants of 15 versus 20 may also be a reason. They measured time using a stopwatch, which is less accurate than our survey using IMUs and EMGs. Our montage was able to measure time to the hundred thousandth of a second. Another finding of our study is that there is a training effect across days for probably all tasks, which was not observed in their project. It is likely that the improvement over time during a measurement day may also be partly due to training effects. In particular we assume this to be the case for tasks (4) and (5), where no intervention-specific effects occurred.

3.2.2 Limitations. Limitations of our study are the small number of subjects studied and, therefore, the high relevance and weighting of errors made during the tasks. Furthermore, it is difficult to distinguish between true plasticity effects and the training effect. Therefore, it would be advisable to choose other exercises that are not affected by training. It would be possible to interpret the grip strength as a parameter for all exercises since it is not affected by the training effect. In addition, it makes sense to use a suitable, low-effect control stimulation but which is not recognized as such by the subjects. The control stimulation must be combined with MSL to survey the sole effect of MSL on behavior.

4 CONCLUSIONS

In summary, 50 Hz tACS likely has the ability to influence human behavior and can be modified by MSL. Simultaneous MSL seems to attenuate the time effect of stimulation but improves grip strength.

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