Cerebellar Transcranial Direct Current Stimulation: The Search for the Optimal Montage

Abstract

Previous linguistic processing studies have been successful in using transcranial direct current stimulation (tDCS) to stimulate the right cerebellum, however results from several studies produced contradicting results. A factor that may contribute to the contradiction of these studies could be the limited target region focality of conventionally used electrode montages. In the current study, the electrical field distributions of conventional and alternative montages were examined using the SimNIBS simulation software. Using structural magnetic resonance images, 20 3D head models were created and used to evaluate the effectiveness of conventional and alternative electrode placements of tDCS montages targeting the right cerebellum. Alternative montages were created by (1) moving the active electrode 3 cm anterior to the target region; (2) facing the edges of the electrodes towards each other; (3) placing the electrodes on opposite sides of the target region; (4) moving the reference electrode away from surrounding brain regions to ensure minimal stimulation to non-target areas. The alternative contralateral neck montage showed a significant main effect of montage for both maximum electrical stimulation ($F_{(1,16)} = 54.44$, $p < 0.001$) and average electrical stimulation ($F_{(1,16)} = 10.74$, $p = 0.005$) of the right cerebellum and showed significantly less stimulation in non-target brain regions ($F_{(1,\ 19)} = 6.15$, $p < 0.001$) compared to the conventional ipsilateral buccinator montage. The alternative montage suggested in this study may be applied in future linguistic processing studies using tDCS as this may improve the consistency of results.

Key words: cerebellum; tDCS; buccinator; SimNIBS

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Bachelor Thesis Cognitive and Neurobiological Psychology

Introduction

A large body of research suggests that the cerebellum plays a role in motor, cognitive and behavioral functions. More specifically, the right cerebellum is involved in linguistic processes, such as semantic prediction speeds, speech production and comprehension (D'Mello et al., 2017). Other studies have shown that the right cerebellum contributes to predictive language processing, similar to the predictive properties of the cerebellum regarding motor control (Miall et al., 2016). It has also been found that the cerebellum contributes to speech timing in the perceptual domain (Lametti et al., 2016). These studies utilized cerebellar transcranial direct current stimulation (tDCS) to explore the role of the right cerebellum in linguistic processing. Cerebellar tDCS is a non-invasive technique used to induce long-term functional changes to the cerebellum by delivering a weak electrical current through scalp electrodes for several minutes (Ferrucci et al., 2015). To obtain consistent results, the placement of these electrodes should be consistent across studies utilizing tDCS, as this will result in one less variable to consider when comparing findings from other studies.

Over the last decade tDCS has become a prominent procedure to stimulate the cerebellum, as evidenced by the 55 PubMed search results for the terms 'cerebellum' 'tdcs' and 'direct current stimulation' from 2010 to 2015 and the 158 search results from 2015 to 2020. This increased popularity can be attributed to the effectiveness of tDCS in stimulating the cerebellum and its connected cerebral areas, as well as effecting mood, motor and cognitive abilities and linguistic processing (Ferrucci & Priori, 2014; Oldrati & Schutter, 2018; Palm et al., 2016; van Dun et al., 2016). Due to the proven effectiveness of tDCS and the increased amount of research done with tDCS, it is essential to learn how to use tDCS effectively.

In most cases during tDCS, a weak current (1 - 2mA) is applied to the scalp through an electrode for several minutes (10 - 25 min) (Ferrucci & Priori, 2014; van Dun et al., 2016). This electrode, known as the target electrode, is commonly placed closest to the brain area that is being targeted and a reference electrode is placed elsewhere. However, there is no real consensus on the placement of the reference electrode (Ferrucci & Priori, 2014; Grimaldi & Manto, 2013). Other aspects such as current density and total charge also have influence on the effect of cerebellar excitability. They should be high enough to induce an effect whilst not inducing tissue damage by being too high. Because most studies stay within these thresholds, the only side-effects of tDCS the participants experience are sometimes a tingling sensation and rarely a metallic taste (Ferrucci & Priori, 2014).

Although most studies adhere to these aspects, research on the role of the right cerebellum with tDCS in linguistic processing such as storage of verbal information or verb generation tasks have produced contradicting results. For example, Pope and Miall (2012) used cathodal right cerebellar tDCS to enhance performance on verb generation tasks while in 2012, Spielmann et al. (2017) were unable to reproduce the results (Macher et al., 2014; Pope & Miall, 2012; Spielmann et al., 2017; van Dun et al., 2016). Many factors can contribute to these inconsistencies, such as cerebrospinal fluid distribution, anatomical differences such as skull thickness, the complexity of the gyral folding and the arrangement of cerebellar micro-circuits (Klaus & Schutter, 2018; Thair et al., 2017; van Dun et al., 2016). Age, gender, brain state, hormonal levels, and pre-existing regional excitability may also contribute to the inconsistency of results (van Dun et al., 2016). These factors should be taken into account when selecting data for the simulations and when comparing results. Because the current study utilizes secondary data, only age and gender will be taken into consideration as other aspects cannot be controlled for. The use of different or suboptimal montages may also contribute to the inconsistency of results in these studies and similar studies. A montage where the target region is barely stimulated or surrounding non-target areas are stimulated heavily will result in varying results and the inability to draw conclusions from the stimulation. The present study will therefore focus on the montages employed by linguistic processing studies and how to improve them.

In Figure 1 several montages that have been tried to effectively stimulate the right cerebellum with tDCS are shown. The most common montage is placing the active electrode over the right cerebellum and the reference electrode on the ipsilateral buccinator muscle (Boehringer et al., 2013; Chen et al., 2014; Galea et al., 2009; Hamada et al., 2012, 2012; Hardwick & Celnik, 2014; Herzfeld et al., 2014; Jayaram et al., 2012; Lametti et al., 2016; Macher et al., 2014; Sadnicka et al., 2013; Shah et al., 2013; Zuchowski et al., 2014). Others place the reference electrode on the right shoulder (Miall et al., 2016; Pope & Miall, 2012; Spielmann et al., 2017), or on the contralateral supra-orbital area (Grimaldi et al., 2016; Grimaldi & Manto, 2013). Several meta-studies have concluded that the buccinator montage is the most commonly used (Ferrucci et al., 2015; van Dun et al., 2016). Yet findings also show that this montage is not optimal as even with the use of this montage, studies have produced contradicting results (Ferrucci & Priori, 2014; Klaus & Schutter, 2018; Rampersad et al., 2014; Santos Ferreira et al., 2019; van Dun et al., 2016). Therefore the current study will focus on optimizing tDCS for the right cerebellum by improving upon the buccinator montage.

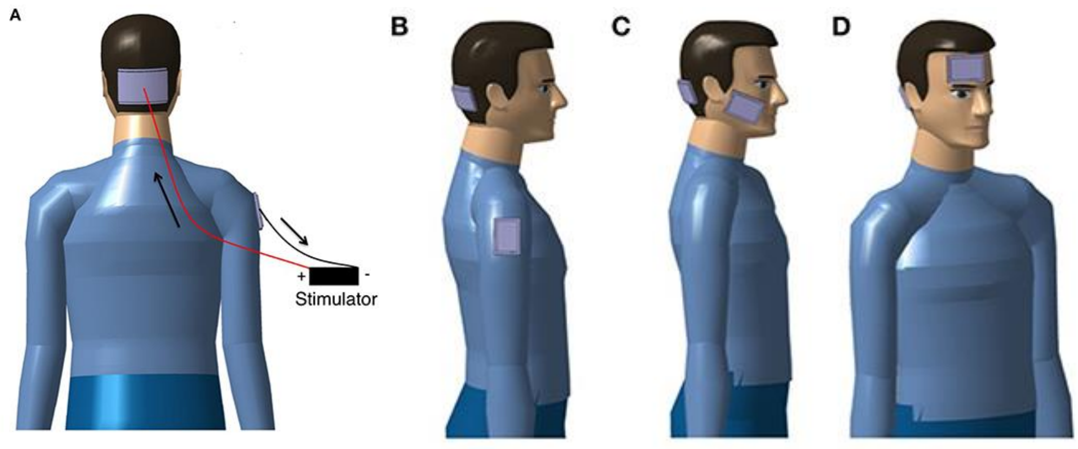

Figure 1. Examples of the most common montages used to apply tDCS to the cerebellum. (A) shows the flow of the current, indicated by the arrows for anodal stimulation of the cerebellum; (B–D) unilateral montages with the reference electrode over (B) the deltoid muscle, (C) the buccinator muscle, and (D) the forehead/supraorbital area. Figure adapted from van Dun et al. (2016).

In order to improve upon the buccinator montage an estimate of electrical field distributions for the conventional electrode placements has to be determined. This electrical field distribution is then compared to the electrical field distributions of an alternative montage in order to determine which montage is superior for right cerebellar stimulation, so future studies can better research the role of the cerebellum in linguistic processes. The alternative montage is created through four modifications (1) moving the active electrode 3 cm anterior to the target region; (2) facing the edges of the electrodes towards each other; (3) placing the electrodes on opposite sides of the target region; (4) moving the reference electrode away from surrounding brain regions to ensure minimal stimulation to non-target areas (Rampersad et al., 2014; van Dun et al., 2016).

The placement of the passive electrode in the alternative montage is on the contralateral neck muscles. There are several reasons for this. First of all, the electrical current will travel from the active electrode to the passive electrode, following the path of least resistance (Ferrucci et al., 2013; Rampersad et al., 2014; Thair et al., 2017). Moving the passive electrode closer to the active electrode will cause the electrical current to travel superficially, avoiding the thick skull and consequently not stimulate the cerebellum optimally (van Dun et al., 2016). Therefore the optimal setup will have the active and passive electrodes on opposite sides of the brain, to force the current to go through the skull and cerebellum. For optimal stimulation the active electrode has to be placed over the target region, the right cerebellum (Ferrucci et al., 2015; van Dun et al., 2016). If this is the case, then the passive electrode has to be placed on the contralateral side, which should ensure the most stimulation of the cerebellum. To ensure minimal stimulation in other non-target brain areas, the passive electrode is moved further down the brain, on the lower end of the left neck. Figure 2 shows the electrode placements on a head model for each montage used in the current study.

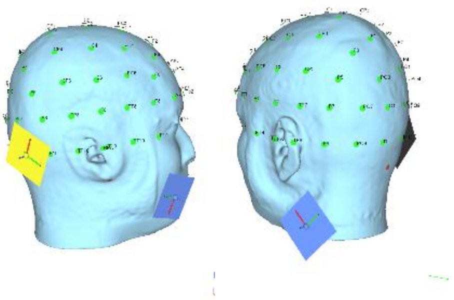

Figure 2. The electrode placements of the two montages, the buccinator montage on the left, the alternative montage on the right, made in SimNIBS.

For the simulations the open source software SimNIBS (Simulation of Non-Invasive Brain Stimulation, version 3.2.1.) was used. SimNIBS allows for realistic calculations of the electrical field induced by transcranial electric stimulation (TES). Head models are created using T1 and T2-weighted structural magnetic resonance images as is recommended (*Creating Head Models — SimNIBS 3.2.2 Documentation*, n.d.; Saturnino et al., 2019). Using the SimNIBS graphical interface, electrodes are placed on areas of these head models, where the size, location, orientation, current intensity, thickness and shape of the electrodes can be altered (see *Setting up and Running Simulations — SimNIBS 3.2.2 Documentation* for a more detailed description of the procedure).

Materials and Methods

Datasets

T1 and T2-weighted resting-state structural magnetic resonance images from 20 participant datasets were used, provided by the publicly available dataset of the Stockholm Sleepy Brain Study (*OpenNeuro*). To account for the differences between gender and age, 5 young males (IDs: 9001, 9007, 9028, 9035, 9044, aged 20-30), 5 young females (IDs: 9018, 9019, 9042, 9053, 9057, aged 20-30), 5 old males (IDs: 9002, 9005, 9008, 9039, 9065, aged 65-75) and 5 old females (IDs: 9032, 9047, 9058, 9064, 9086, aged 65-75) were selected from the dataset.

When the 20 participant datasets were used to create the brain models, three came up with an error. This may be a bug in the SimNIBS algorithm or the images were unclear or incomplete. Three new datasets were selected from their respective categories, from which brain models were successfully constructed on the first try. Consequently the datasets are not selected randomly.

Procedure

Individual tetrahedral head models were created from the participant datasets using the headreco algorithm provided by the SimNIBS pipeline. Electrical field distributions were simulated using anodal 2 mA tDCS with 5x5 cm electrodes, resulting in a current density of 0.08 mA/cm2 and therefore remaining below the recommended limit for both the conventional ipsilateral buccinator setup and the alternative contralateral neck setup (Ferrucci et al., 2015; Thair et al., 2017; van Dun et al., 2016). For all simulations the simple setup was chosen as setup type and an electrode thickness of 5 mm.

Computations

Firstly the electrical field stimulation of the buccinator montage was simulated using the head models, placing the anodal electrode 1 cm below and 3 cm lateral to the inion and the cathodal electrode over the right buccinator muscle as is conventional. For the alternative setup the anodal electrode was also place 1 cm below and 3 cm lateral to the inion. However the cathodal electrode was placed on the left neck muscles to ensure minimal stimulation in other non-target brain areas. In all simulations electrode size, charge and thickness remained the same and the edges of the electrodes faced each other. For both montages the maximum and average electrical field charge in the region of interest (ROI) was taken in addition to the average electrical field charge of the entire brain. The ROI was selected using a 30 mm radius sphere at the center of the right cerebellum (MNI coordinates [26, -67, -40], taken from *MMP 1.0 MNI Projections*).

Data analysis

For the statistical analysis two mixed ANOVAs were employed using SPSS version 26, one for the maximum electrical field strength of the right cerebellum and one for the average electrical field strength over the entire right cerebellum. For the ANOVAs the within-subjects factor was the montage and the between-subjects factors were age and gender. This was done in order to analyze the differences in montage placement per group. Additionally, a paired t-test was utilized to compare the stimulation of the entire brain for each montage to analyze the amount of stimulation in non-target regions. To estimate the amount of stimulation, the average electrical field strength over the entire brain was taken.

Results

Table 1 shows the maximum electrical field strength for each group as well as the average electrical field strength for the ROI for each group broken down by montage (buccinator vs. alternative).

Table 1

Electrical field strength values

	Buccinator			Alternative		
Group	Maximum ROI	Average ROI	Average Total	Maximum ROI	Average ROI	Average Total
Young Males	0.407	0.246	0.106	0.436	0.253	0.100
Young Females	0.481	0.299	0.137	0.521	0.308	0.124
Old Males	0.312	0.200	0.096	0.345	0.209	0.090
Old Females	0.327	0.201	0.097	0.352	0.207	0.089
Average	0.382	0.237	0.109	0.414	0.244	0.101
SD	0.128	0.066	0.022	0.120	0.062	0.018

Note. The average electrical field strength per group, separated by montage (buccinator vs. alternative) and measurement (maximum electrical field of the ROI, average electrical field of the ROI and average electrical field of the entire brain).

A mixed ANOVA was utilized to analyze whether the maximum electrical field strength differed between the two montages, with age and gender as between-subject factors. Figure 3 shows the maximum electrical field strength in the right cerebellum for the two montages for each group. There was a significant main effect of montage, $F_{(1, 16)} = 54.44$, $p < 0.001$ and a significant main effect of age group, $F_{(1, 16)} = 6.62$, $p = 0.020$. There were no interactions between montage, age or gender.

Another mixed ANOVA was used to see if there were significant differences between the average field strength over the region of interest. Figure 4 shows the average electrical field strength of the right cerebellum for the two montages for each group. There was a significant main effect of montage, $F_{(1, 16)} = 10.74$, $p = 0.005$ and a significant main effect for age group, $F_{(1, 16)} = 9.60$, $p = 0.007$. There were no interactions between montage, age or gender.

A paired t-test was utilized to analyze whether the alternative montage resulted in less stimulation of the surrounding non-target areas. Figure 5 shows the average electrical field strength in the entire brain for each group and Figure 6 shows an example of the distribution of the electrical field per montage for each group. There was a significant difference between the two montages in terms of the amount of stimulation over the entire brain, $F_{(1, 19)} = 6.15$, $p < 0.001$.

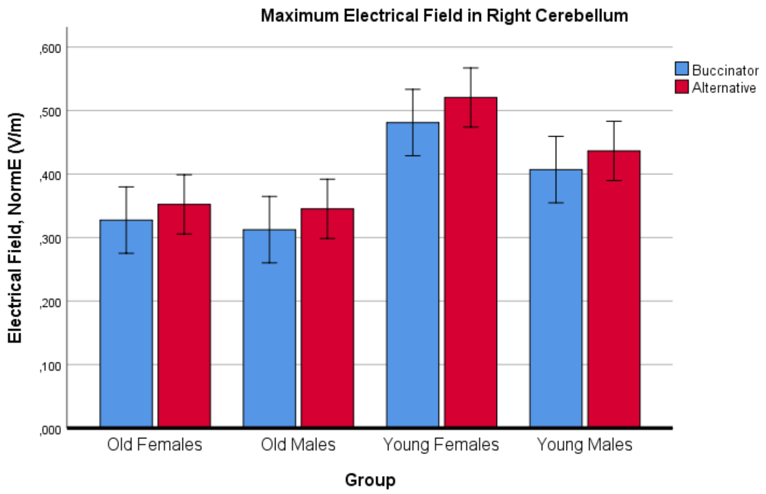

Figure 3. The maximum electrical field strength of each montage in the right cerebellum per group.

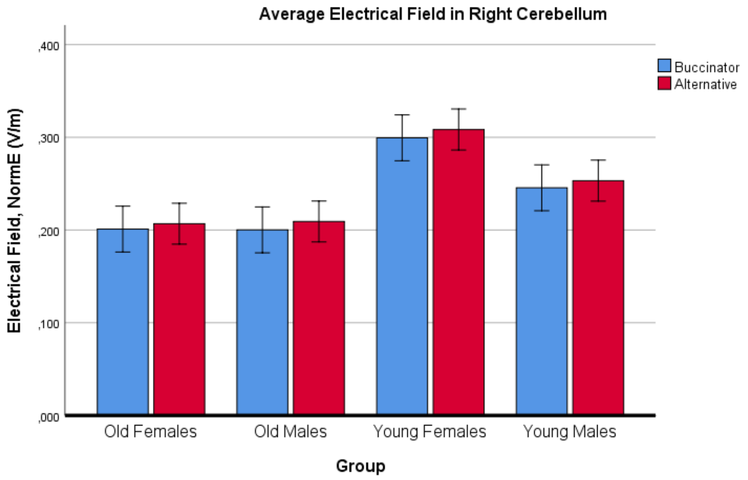

Figure 4. The average electrical field strength of each montage in the right cerebellum per group.

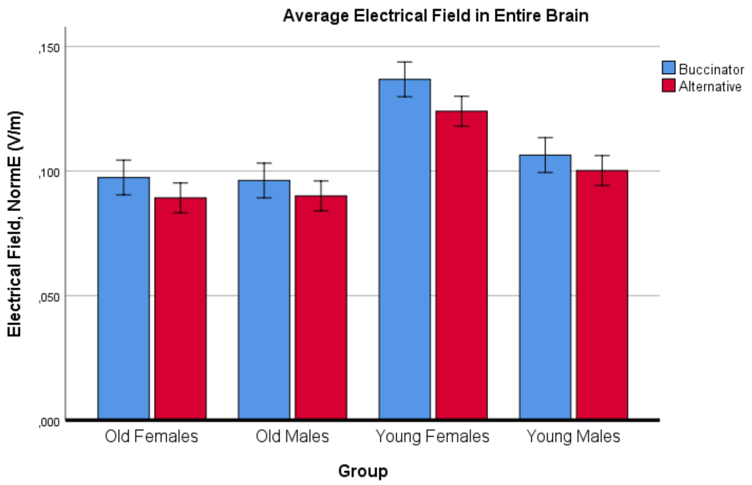

Figure 5. The average electrical field strength of each montage in the entire brain per group.

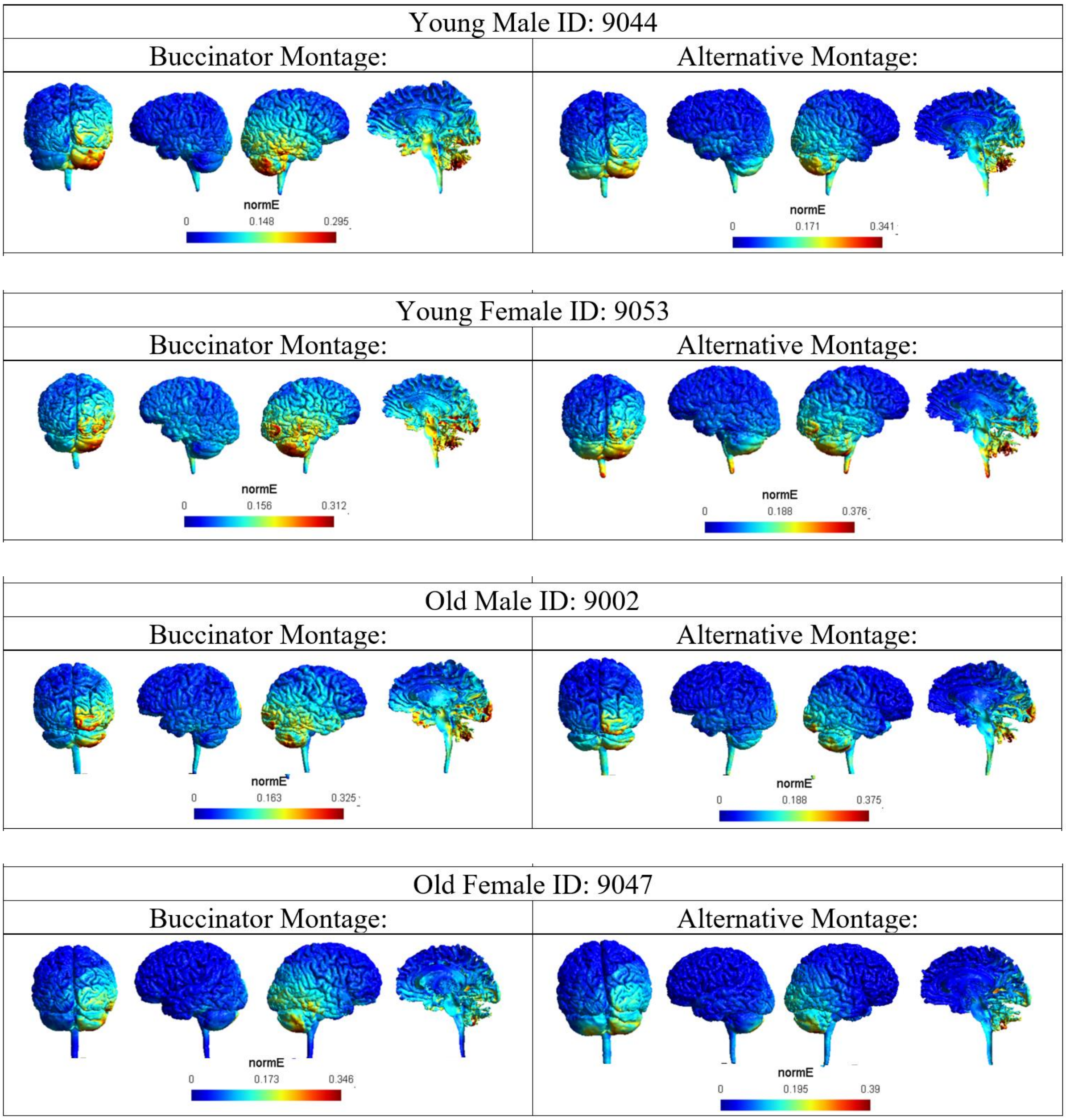

Figure 6. Examples of the amount of stimulation from different perspectives for both montages. From left to right, posterior, left lateral, right lateral and midsagittal view of the brain. Colours indicate the level of electrical field strength, blue indicating low levels and red colours indicating high levels of electrical field strength.

Discussion

In the current study the conventional tDCS montage for the right cerebellum was compared to an alternative montage using computer simulations based on MRI data by comparing their electrical field strength. The results show that the maximum electrical field strength and the average electrical field strength in the right cerebellum are both significantly higher in the alternative montage compared to the conventional montage. Thus right cerebellar tDCS may be improved by employing the alternative contralateral neck montage instead of the conventional ipsilateral buccinator. Using this montage may reduce some variability observed in studies applying tDCS to the right cerebellum. Furthermore, modifying other parameters such as electrode size and thickness may further reduce the stimulation of non-target regions or improve the electrical field strength of the region of interest. Due to the varying result from previous tDCS studies and because the current results are based solely on simulations, it would be preemptive to suggest that the alternative montage will ensure better results (van Dun et al., 2016). Further studies will have to utilize the suggested montage in order to assess its research value in experimental work.

The current results also show less stimulation in the entire brain using the alternative montage compared to the buccinator montage. There is significantly more stimulation in the cerebellum with the alternative montage and significantly less stimulation in the entire brain. From this it can be deduced that the non-target brain areas are significantly less stimulated in the alternative left neck setup compared to the conventional buccinator setup. Less stimulation in non-target brain areas may result in increased target region focality, which may further decrease some variability observed in studies utilizing tDCS on the right cerebellum.

There was also a significant main effect of age for both the average and maximum electrical field strength of the right cerebellum. Therefore there was a significant difference between the two age groups, where the younger group had both a significantly higher average field strength over the right cerebellum and a significantly higher maximum field strength value. This shows the effects of aging on brain connectivity, as has been researched before. Thus the results are in line with the literature that shows there is less within- and between-network connectivity in older adults compared to young adults (Damoiseaux, 2017; Varangis et al., 2019).

It should be noted that the simulations were performed on a small number of brains. Therefore, the generalization of the current results may be limited. Furthermore, the effect of tDCS depends on many individual differences such as skull thickness, cerebrospinal fluid, gyral folding and susceptibility to weak electrical currents (Klaus & Schutter, 2018). These individual differences were also evident in this study, as in both the conventional and the alternative montage there was no uniform distribution of current and high variability in maximum electrical field strength as can be seen in Table 1. Nevertheless, despite these individual differences, most comparisons showed more optimal results with the alternative montage.

While on average the results of the alternative montage showed significantly more stimulation in the cerebellum compared to the buccinator montage, in some simulations the alternative montage resulted in a small decrease compared to the buccinator montage. While electrical modelling is still being explored, a personalized montage could result in more optimal results. Nevertheless, for research labs that do not have access to neuroimaging facilities to individualize tDCS montages, the proposed alternative montage provides a decent substitute.

Considering this study is experimentally focused rather than clinical, the amount of stimulation of non-target brain areas was taken into account. Increased stimulation of surrounding non-target regions causes identifying the role of the right cerebellum in linguistic processing tasks to be problematic. The suggested montage should therefore be optimal for experimental studies. However, tDCS is also being explored to enhance recovery of stroke victims. These studies found that tDCS can facilitate the recovery of cognitive language functions (Marangolo et al., 2018) or motor recovery in balance and gait performance (Zandvliet et al., 2018; Rezaee et al., 2020) in post-stroke rehabilitation. For these instances, the amount of stimulation of surrounding areas may be of less importance than the maximum activation in the region of interest. As such, a different montage which achieves higher activation in the region of interest, independent of the amount of stimulation in non-target areas, may be more suitable in these cases.

Conclusion

The current study shows a significantly higher maximum electrical field strength and a significantly higher average electrical field strength in the right cerebellum for the alternative montage, compared to the conventional buccinator montage. Furthermore, there is less stimulation of non-target areas with the suggested montage compared to the buccinator montage. Nevertheless, because the results are based on a simulation, the application of the alternative montage in tDCS studies researching the right cerebellum still needs to be analyzed. The suggested alternative montage could be utilized by linguistic studies applying tDCS to the right cerebellum as this may improve target region focality, decrease stimulation of non-target areas and thus increasing the consistency of results.

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