Neuroscience Research xxx (2019) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Research Paper

Cerebellar transcranial alternating current stimulation modulates human gait rhythm

Satoko Koganemaru[a,*], Yusuke Mikami[b], Masao Matsuhashi[b], Dennis Q. Truong[c], Marom Bikson[c], Kenji Kansaku[a], Tatsuya Mima[d]

[a] Department of Physiology and Biological Information, Dokkyo Medical University, 880 Kitakobayashi, Mibu-machi, Shimotsuga-gun, Tochigi, 321-0293, Japan
[b] Human Brain Research Center, Kyoto University School of Medicine, Sakyo-ku, Kyoto, 606-8507, Japan
[c] Department of Biomedical Engineering, The City College of New York of CUNY, T-403B, 160 Convent Avenue, New York, NY, 10031, USA
[d] The Graduate School of Core Ethics and Frontier Sciences, Ritsumeikan University 56-1, Tojiin, Kitamachi, Kita-ku, Kyoto, 603-8577, Japan

ARTICLE INFO

Article history:
Received 24 November 2019
Accepted 3 December 2019
Available online xxx

Keywords:
Patterned brain stimulation
Transcranial alternating current stimulation
Gait rhythm
Cerebellum
Entrainment
Phase

ABSTRACT

Although specific brain regions are important for regularly patterned limb movements, the rhythm generation system that governs bipedal locomotion in humans is not thoroughly understood. We investigated whether rhythmic transcranial brain stimulation over the cerebellum could alter walking rhythm. Fourteen healthy subjects performed over-ground walking for 10 min during which they were given, in a random order, transcranial alternating current stimulation (tACS) over the left cerebellum at the approximated frequency of their gait cycle, tACS over the skin of the scalp, and during sham stimulation. Cerebellar tACS showed a significant entrainment of gait rhythm compared with the control conditions. When the direction of the tACS currents was symmetrically inverted, some subjects showed entrainment at an approximately 180° inverted phase, suggesting that gait modulation is dependent on current orientation. These findings indicate that tACS over cerebellum can modulate gait generation system in cerebellum and become an innovative approach for the recovery of locomotion in patients with gait disturbances caused by CNS disorders.

1. Introduction

Walking, one of the fundamental transfer movements, requires reciprocal movement of the limbs in a temporally and spatially coordinated pattern (Lacquaniti et al., 2012). Neuronal rhythmicity is important for repetitive patterned movements like walking. In quadrupedal animals, a central rhythm and pattern generator within the spinal system produces walking. Humans have acquired a bipedal walk operated by a newly developed supraspinal system that controls posture and lower limb movements, in addition to the pre-existing spinal system (Lacquaniti et al., 2012). Because brain damage can induce severe walking disturbances in human, it is likely that the supraspinal system is more important in human bipedal walking (Daly et al., 2007; Moore et al., 1993; Moseley et al., 1993).

Brain locomotor regions have been found in the posterior midbrain, subthalamus and cerebellum (Mori et al., 1999; Shik and Orlovsky, 1976; Shik et al., 1969; Takakusaki et al., 2003; Waller, 1940). In animals, the cerebellum influences the spinal locomotor networks through its descending drive and rhythmic bursts, leading to repetitive rhythmic step cycles (Mori, 1987; Mori et al., 1999). In human neuroimaging studies, these locomotor regions including cerebellum were activated during both actual and imaginary walking (Fukuyama et al., 1997; Jahn et al., 2008a, b). It is likely that a similar mechanism might work in human bipedal locomotion and that the supraspinal system might directly control the rhythmical and patterned activities of our bipedal walking.

In recent years, patterned transcranial electrical stimulation (tES), such as transcranial alternating current stimulation (tACS), has been reported to entrain the intrinsic brain rhythms so as to produce a specific behavioural outcome (Antal et al., 2008, 2011; Nitsche and Paulus, 2011; Paulus, 2011). Although exact mechanism remain investigated, patterned tES is hypothesized to enhance the specific neuronal circuits associated with intrinsic rhythmicity, leading to the modification of sensorimotor and cognitive function (Castro-Alamancos et al., 2007; Kanai et al., 2008, 2010; Kirov et al.,

* Corresponding author at: Department of Physiology and Biological Information,Dokkyo Medical University, Shimotsuga-gun, Tochigi, 321-0293, Japan.
E-mail address: kogane@dokkyomed.ac.jp (S. Koganemaru).

https://doi.org/10.1016/j.neures.2019.12.003
0168-0102/

2009; Marshall et al., 2006; Pogosyan et al., 2009; Zaehle et al., 2010). Moreover, it is suggested that the phase lag between the artificial patterned stimulation and the endogenous brain rhythm might be important. For example, the phase-dependence of the tremor-suppressing effects of tACS has been reported in Parkinson disease (PD) tremor when it was given over the motor cortex for the most pronounced tremor muscles (Brittain et al., 2013).

Although bipedal locomotion is the most fundamental rhythmic movement in human life, it is unknown whether this rhythmicity can be modulated by patterned tES. To test this hypothesis, we applied patterned tACS mimicking the walking frequency over the cerebellum during natural walking. Furthermore, the effects of tES depends on the relative angle of the somato-dendritic axis of stimulated neurons to the direction of the electrical field produced by tES (Rahman et al., 2013, 2014). We also investigated whether the tACS effects would be changed or not when the direction of tACS currents were inverted and simulated the electrical field produced by the tACS using finite element models of transcranial electrical stimulation.

2. Methods

2.1. Subjects

The study protocol was approved by the Committee of Medical Ethics of the Graduate School of Medicine, Kyoto University, Japan (C-800) and informed written consent was obtained from all subjects.

We investigated young healthy volunteers that had no history of neurological illness or gait disorders, were all right-handed according to the Edinburgh handedness inventory (Oldfield, 1971), and had right foot preference according to the Chapman test (Chapman et al., 1987). None of the subjects had any contraindications to TMS (Groppa et al., 2012; Rossini et al., 1994; Wassermann, 1998).

2.2. Recording procedures

Subjects were asked to reciprocate a 135 m corridor at a comfortable pace with a regular speed for 10 min while undergoing the tACS conditions described below. Individual gait cycle was assessed by flat foot switches attached to the bilateral heels (PH-450A, FS amplifier, DKH Co., Ltd., Japan). The recording tools were backpacked by the subjects during experiments in order not to interfere with the subjects' gait.

The electrical currents of tACS were delivered through a NeuroConn DC Stimulator (Ilmenau, Germany). The current waveform was a sinusoidal wave produced by the Signal Processing Toolbox™ of Matlab 2014a and Simulink (Mathworks, MA, USA). The current waveform was sent to the stimulator and data were recorded through data acquisition modules equipped with a BNC input/output system (NI USB-6212 BNC, National Instrument Corp., USA). The tACS lasted for 10 min at a peak-to-peak stimulation current of 2 mA (from −1 mA to +1 mA) in addition to 60 s fade-in and fade-out periods along with the walking. Data were sampled (1 kHz) for offline analysis, which was conducted using Matlab 2014a.

2.3. Experiment 1: Effects of cerebellar tACS on gait cycle

We investigated fourteen healthy volunteers (1 women and 13 men) aged 20–23 years (mean ± standard deviation (SD), 21.3 ± 1.1 years).

To administer tACS on the left cerebellum, the electrode (5 × 5 cm) was centred 3 cm left-lateral from the inion, a position that spans the cerebellum (Kikuchi et al., 2012; Ugawa et al., 1997, 1995). The counter electrode (5 × 5 cm) was placed to the right posterior neck. The electrical currents were faded in and out for 60 s with the electrodes placed in the positions used for tACS. To further assess whether the modulation of the gait cycle involved skin sensations of the scalp, we applied tACS to the skin of the scalp. For skin stimulation, the electrode was placed at the same position on the left cerebellum and the centre of the counter electrode was placed 2.5 cm right-lateral from the edge of the electrode with 1 cm of interspace of the edges of both electrodes, so that electrical currents could pass only through the skin surface, not through brain cortical areas (Fig. 1).

Experiments conducted under the following three tACS conditions were performed in a random order at least 30 min apart on the same day: (1) tACS on the left cerebellum (2) tACS on the skin of the scalp (skin sensation similar to that felt during electrical stimulation, except without brain stimulation) and (3) sham stimulation.

The averaged frequency of individual gait cycle was premeasured by a 4-min recording of walking on the corridor at a comfortable pace with a regular speed. Then, tACS was applied at the frequency nearest to that averaged frequency with a 0.01-Hz bin in each condition. The tACS frequency was different in each subject and constant through the 10 min stimulation period.

2.4. Experiment 2: the effects of inverted currents of tACS on gait cycle

To investigate the possible effects of the counter electrode position for the cerebellar stimulation, an additional experiment was performed with the counter electrodes placed at a vertically opposite side to that of Experiment 1 (Experiment 2). We hypothesised that the entrainment phase would be changed since the direction of tACS current flow determines depolarization or hyperpolarization of neurons (Rahman et al., 2013, 2014). In Experiment 2, we investigated the same 14 subjects that participated in Experiment 1. The counter electrode (3 × 3 cm) was centred 2 cm right-lateral from the vertex, with the electrode (5 × 5 cm) over the same portion used for stimulating left cerebellum (Fig. 1). After a 4-min recording to confirm the frequency of the individual gait cycle, tACS was applied at the frequency nearest to the measured gait cycle with a 0.01-Hz bin, as in Experiment 1.

2.5. Simulation of the electrical field produced by tACS

To investigate how the cerebellum was stimulated in Experiment 1 and 2, we simulated the electrical field produced by tACS using MRI-derived finite element models of transcranial electrical stimulation as previously reported (Datta et al., 2009; Truong et al., 2013). We predicted brain current flow using a workflow of commercial simulation packages (COMSOL Multiphysics, Burlington, MA, USA; Simpleware, Synopsys, Mountain View, CA, USA) and customized algorithms (Huang et al., 2013). A high-resolution (1 mm^3 isotropic) T1-weighted MRI of a Japanese adult was segmented into tissues of varying electrical conductivity. Two electrode configurations were modelled as in experiments 1 and 2 (left cerebellum -right neck and left cerebellum -right vertex). Tetrahedral meshes were generated in Simpleware and imported into the finite element package (COMSOL 5.1). The electrical properties of the tissues were assigned representative isotropic average values (in S/m): grey matter: 0.276; white matter: 0.126; CSF: 1.65; skull: 0.01; fat: 0.025; and scalp: 0.465. The muscle, eyes, and blood vessel compartments were assigned the same tissue properties as that of scalp. The sponge electrodes were assigned the electrical conductivity of saline (σ = 1.4 S/m) and the stimulation electrodes were modelled as conductors (σ = 5.8 × 107 S/m). Physics were assumed to be quasi-static ($\nabla \cdot (\sigma \nabla V) = 0$). Boundary conditions were applied as electrically insulated on all external surfaces ($n \cdot J = 0$), excluding ground (V = 0) on the reference electrode and inward current den-

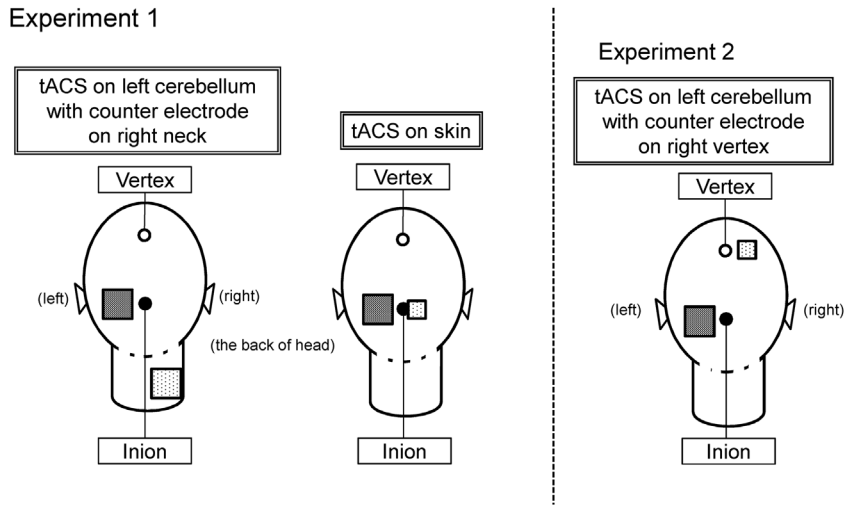

Fig. 1. Electrodes montages. In Experiment 1, the electrode (5 × 5 cm) was centred 3 cm left-lateral from the inion for both tACS on the cerebellum and skin stimulation. The counter electrode (5 × 5 cm) was placed to the right posterior neck for tACS on the cerebellum, and a smaller counter electrode (3 × 3 cm) was placed 2 cm right-lateral from the edge of the electrode for skin stimulation. In Experiment 2, the counter electrode (3 × 3 cm) was centred 2 cm right-lateral from the vertex, with the electrode (5 × 5 cm) placed over the same position used for stimulating the cerebellum.

sity equal to 1 mA total ($\iint(n \cdot J)dS = 1mA$) on the active electrode. We calculated the induced electric field in the brain and spinal cord resulting from the application of 1 mA total current.

2.6. Data analysis

Recorded tACS currents were filtered off-line using a zero-phase bandpass at the cut-off frequencies of 0.5 and 2 Hz. Analytic signals were acquired after applying a Hilbert transform to the bandpass-filtered currents.

The instantaneous phase of the initiation of the gait cycle in the left leg (the timing of the left heel contact recorded by the foot switch) was calculated during a 10-min measurement of the gait. All of the instantaneous phases of the left heel contact were represented by complex numbers and averaged. The absolute value and phase of the average were regarded as the phase synchronisation index (PSI) and the mean phase difference (MPD), respectively. A PSI of 0 represents no entrainment and a PSI of 1 represents complete entrainment of the gait cycle by tACS. During sham stimulation, PSI was calculated offline using an artificially produced sinusoidal waveform. For drawing histograms, phase information from the tACS signals was divided into 36 discrete bins (10° each). Numbers of the left heel contact including each bin were represented.

In Experiment 2, the differences of MPD calculated during tACS with the counter electrode on right vertex (MPD *vertex*) from MPD calculated during tACS with the counter electrode on right posterior neck (MPD *neck*) were calculated (= MPD *neck* − MPD *vertex*) in individual subjects who showed a significant PSI. The differences of the MPDs were represented by complex numbers and averaged. The absolute value and phase of the average was regarded as a PSI for differences between MPD *vertex* and MPD *neck* (PSI_{-diff}) and an MPD differences between MPD *vertex* and MPD *neck* (MPD_{-diff}), respectively.

2.7. Statistical analysis

In Experiment 1, the data for PSI were compared among three conditions ('tACS on cerebellum', 'tACS on skin' and 'sham stimulation') using repeated-measures analysis of variance (ANOVA). The PSIs were subjected to repeated-measures ANOVA with Condition as a within-subject factor. In Experiment 2, individual PSIs and PSI_{-diff} were assessed for statistical significance by non-parametric testing against an empirical null-distribution. The null-distribution was constructed by computing the statistic PSI over randomly oriented unit vectors, repeated 100,000 times. Significance was assessed at a 5% confidence level ($p < 0.05$).

If necessary, the Greenhouse–Geisser correction was used to adjust for the sphericity, changing the degrees of freedom using the correction coefficient epsilon. The Bonferroni correction for multiple comparisons was used for the *post-hoct*-test. Effects were considered significant at $p < 0.05$. All data are given as the mean ± SD.

3. Results

No significant side effects were noted during the experiments, and none of the subjects reported phosphenes or vertigo. Four subjects experienced mild skin irritation for several tens of seconds at the beginning of stimulation, but they did not feel any irritation for the remaining duration of stimulation. None of subjects reported feeling any rhythmicity of the stimulation.

3.1. Experiment 1: Effects of cerebellar tACS on gait cycle

The number of strides of the left leg was 542.6 ± 10.4, 543.1 ± 10.4 and 545.6 ± 11.8; and the frequency of tACS was 0.91 ± 0.06, 0.90 ± 0.06 and 0.91 ± 0.06 Hz during the 10-min walking period under the 'tACS on cerebellum', 'tACS on skin' and 'sham stimulation' conditions, respectively. Under these three conditions, all subjects walked 3 reciprocations of the corridor. The results from a single subject are represented in Fig. 2. Repeated measures ANOVA revealed a significant difference among the PSIs of the three condition (tACS on cerebellum, on skin, and during sham stimulation) ($F_{(2, 26)} = 3.45$, $p = 0.047$). A post hoc *t*-test revealed a significant entrainment in the tACS on cerebellum, compared with the tACS on skin and in the sham stimulation condition (tACS on cerebellum v.s. tACS on skin, $p = 0.035$; tACS on cerebellum v.s. sham stimulation, $p = 0.028$; tACS on skin v.s. sham stimulation, $p = 0.46$; Fig. 3).

3.2. Experiment 2

The number of strides of the left leg was 545.3 ± 8.8 and the frequency of tACS was 0.92 ± 0.06 Hz during the 10-min walking period. Eleven of the 14 subjects showed significant PSIs (0.190 ±

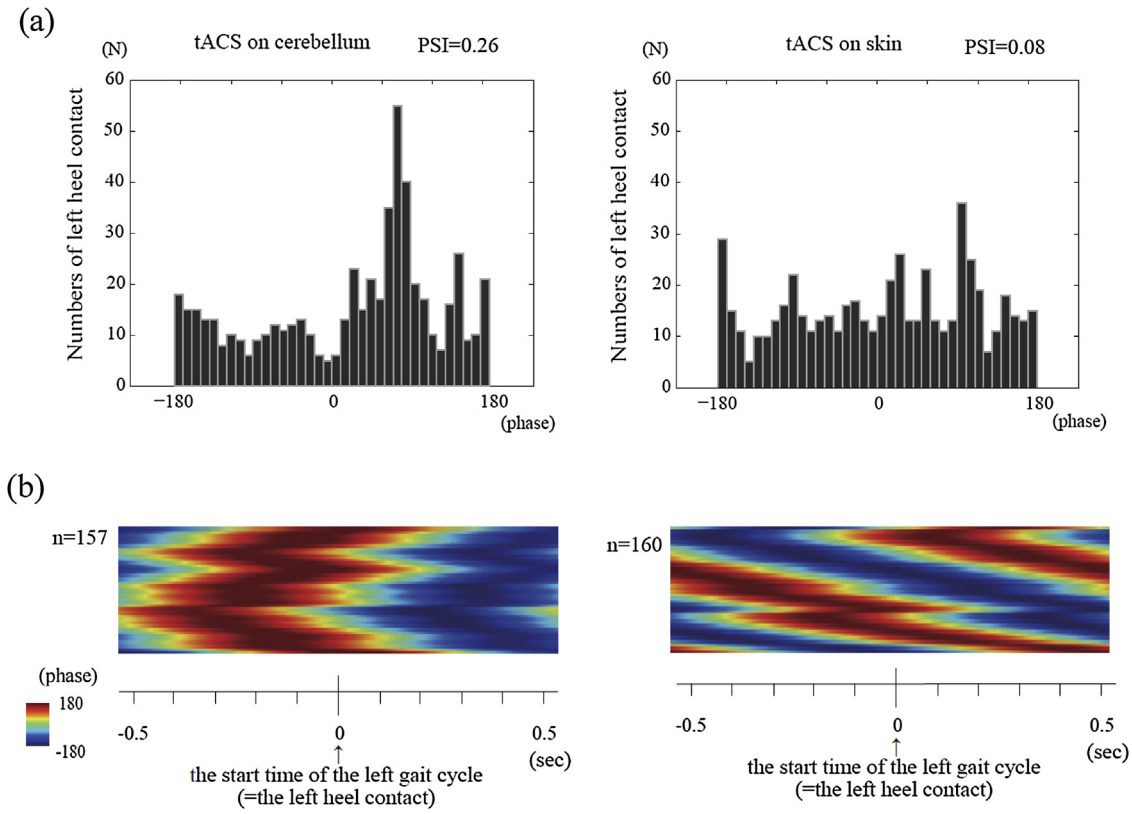

Fig. 2. Representative results from a single subject. The histogram (left) of all the left gait cycles and the stacking of the left gait cycle and phase of tACS (right) are shown for the 3rd reciprocation of walk on the corridor. In the histogram, the x-axis represents the tACS phase and y-axis represents the number of left gait cycles, starting at the phase. In the stacking, the tACS phase ranging from −180 to 180 is coloured. The 0 point on the horizontal axis means the start time of the left gait cycle.

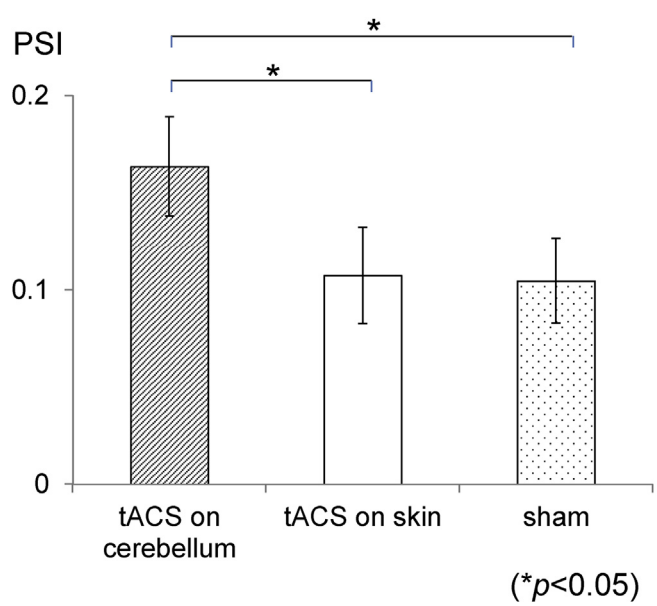

Fig. 3. PSIs of the three conditions (tACS on cerebellum, on skin and sham stimulation). A significant entrainment was seen with tACS on the cerebellum, compared with tACS on the skin and during the sham condition. Error bars represent the SEM.

0.036). The other three subjects showed no significant PSIs (0.029 ± 0.010). The MPDs from the 11 subjects are presented in Table 1. The PSI for the differences between MPD *vertex* and MPD *neck* (PSI_{-diff}) in those 11 subjects was 0.527, a significantly high value ($p < 0.05$). The MPD for the differences between MPD *vertex* and MPD *neck* (MPD_{-diff}) was 168.4°.

Table 1
The MPD (neck) and MPD (vertex) values of the 11 subjects showing significant PSIs in the tACS condition with counter electrodes on the right vertex.

Subject	MPD *neck*	MPD *vertex*
#1	116.9	−41.7
#2	−13.8	173.1
#3	14.6	122.6
#4	125.5	−147.3
#5	−146.3	159.1
#6	−164.2	81.2
#7	−148.6	118.6
#8	−57.0	125.0
#9	97.6	−58.8
#10	89.7	−79.8
#11	−62.2	72.5

3.3. Simulation of the electrical field produced by tACS

Prediction of brain current flow was shown in tACS on left cerebellum with the counter electrode at the right neck and with the counter electrode at the right vertex which was a vertically opposite side to the right neck (Fig. 4). Comparable peak electric field was produced in the left cerebellum for both counter electrode positions. While changing the position of the counter electrodes change with additional brain region were exposed to current flow, the montages were designed to have the left cerebellum as the common stimulated region.

4. Discussion

We found that non-invasive transcranial rhythmic cerebellar stimulation could change and entrain the natural walking rhythm. Because patterned skin stimulation did not show the entrainment

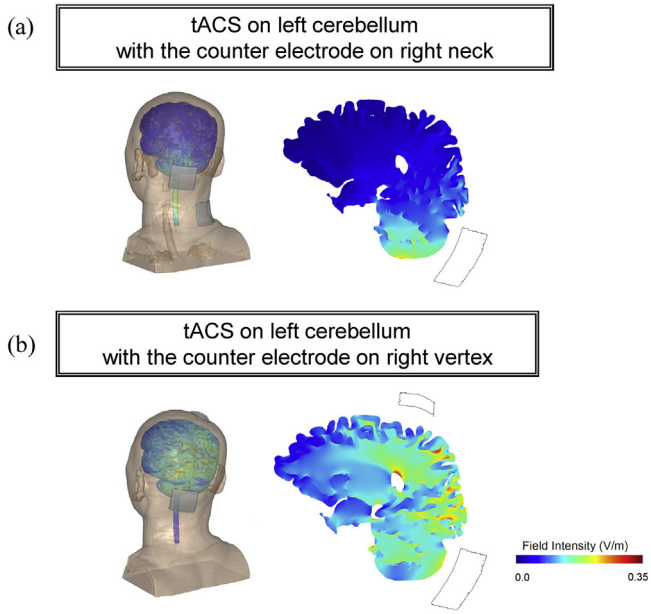

Fig. 4. Simulation of the electrical field produced by tACS. Simulated electrical fields were shown in the two cerebellar tACS conditions with the counter electrodes at the right neck and at the right vertex which was a vertically opposite side (Fig. 3). Both included the left cerebellum.

effects, it is likely that the effect is not mediated by the periodic inputs of sensory afferents but by brain modulation. Furthermore, when the direction of stimulating currents was vertically inverted, a phase inversion between the gait cycle and the exogenous stimulation was observed. Simulated electrical field showed to include the left cerebellum. These results suggest that rhythmic cerebellar stimulation entrains neuronal activities related to gait generation system in the cerebellum dependently on current direction.

Transcranial patterned brain stimulation can modulate the intrinsic brain rhythmicity in a frequency- and phase-specific manner (Brittain et al., 2013; Neuling et al., 2013; Pogosyan et al., 2009; Zaehle et al., 2010). It indicate that extracellular AC fields with weak sinusoidal voltages can increase or decrease the power of oscillatory rhythms in the brain in a frequency- and phase-dependent manner, probably because of synchronising or desynchronising neuronal networks (Fell and Axmacher, 2011; Thut et al., 2017).

Because we intended to match the stimulation pattern with the frequency of the individual gait cycle, a slow oscillatory patterned stimulation (~1 Hz) was given over the cerebellum. In animal studies with computational modelling, the entrainment effects of slow oscillatory AC stimulation on endogenous slow wave oscillations were produced through a network resonance (Ali et al., 2013; Ozen et al., 2010; Reato et al., 2013). The entrainment can be easily produced in the oscillatory network because the small number of neurons directly affected by AC fields can polysynaptically recruit neurons in distant regions (Ozen et al., 2010; Reato et al., 2013). Furthermore, even very low-amplitude stimulation could entrain firing activity but only when the frequency of the endogenous rhythm was matched to that of the stimulation. Polarisation of the membrane in a very small number of neurons can lead to the modulation of the firing rate and timing of the other neurons within the active network (Chan and Nicholson, 1986; Ozen et al., 2010; Reato et al., 2010). Therefore, it is possible that the patterned brain stimulation entrained the rhythmic activities of locomotor network including cerebellum, leading to the modulation of natural human walking.

The cerebellar locomotor region (CLR) in the mid-part of the cerebellar white matter activates the spinal interneuronal networks through projections to the ventromedial medullary reticular formation. Stimulation of the CLR evokes locomotion-like reciprocal patterned activities in the limbs of cats (Mori et al., 1999). Neuroimaging studies in human demonstrated that the middle cerebellum corresponding to the CLR is activated during actual and imagined walking (Fukuyama et al., 1997; Jahn et al., 2008a, b). The present cerebellar stimulation might have affected the CLR activities.

There is also a possibility for the electrical currents to modulate activity of the reticular formation. During the cerebellar tACS, it might have been indirectly activated by the inputs from the neck spinal cord where the electrical field was distributed, especially in the montage with the counter electrode on right neck. Then, the mesencephalic locomotor region in the dorsal reticular formation might have been also influenced and it might have modulated individual gait cycle (Sherman et al., 2015).

Patients with damage in the cerebellum often show ataxic gait with rhythm disturbance and disaggregated limb movements (Ilg et al., 2007; Morton and Bastian, 2003, 2007; Morton et al., 2010). The cerebellar tACS might be a promising method for the treatment of patients with gait disturbance, especially for ataxic gait.

We investigated natural over-ground walking in the present study and the frequency of the gait was sometimes altered in turning around at the end of the corridor. Although treadmill walking has allows better control of the walking parameters, it also has a major drawback that the walking cycle tends to be entrained to a moving floor at a regular speed (Herbin et al., 2007; Pereira et al., 2006; Stolze et al., 1997). Natural over-ground walking might be more appropriate to estimate modulation of gait rhythm by patterned brain stimulation.

In the present study, we have, for the first time, demonstrated that the cerebellar tACS during gait could alter actual gait rhythm in human. This would be an intriguing method for controlling human movements and the neuronal system, and it is a potentially promising approach for the treatment of human movement disorders with gait disturbances.

Funding

This study was partly supported by a Grant-in-Aid for Scientific Research (C) (17K0145307) from the Japan Society for the Promotion of Science(to S.K.), Grant-in-Aid for Scientific Research (A) 19H0109 and Grant-in-Aid for Scientific Research on Innovative Areas 15H05880 from the Japan Society for the Promotion of Science(to T.M.).

Declarations of Competing Interest

The City University of New York has brain stimulation patents with Marom Bikson as inventor. Marom Bikson has equity in Soterix Medical, Inc. and consults for Boston Scientific. GHK, and Mecta.

References

Ali, M.M., Sellers, K.K., Fröhlich, F., 2013. Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. J. Neurosci. 33, 11262–11275.
Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., Paulus, W., 2008. Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. Brain Stimul. 1, 97–105.
Antal, A., Paulus, W., Nitsche, M.A., 2011. Electrical stimulation and visual network plasticity. Restor. Neurol. Neurosci. 29, 365–374.
Brittain, J.S., Probert-Smith, P., Aziz, T.Z., Brown, P., 2013. Tremor suppression by rhythmic transcranial current stimulation. Curr. Biol. 23, 436–440.
Castro-Alamancos, M.A., Rigas, P., Tawara-Hirata, Y., 2007. Resonance (approximately 10 Hz) of excitatory networks in motor cortex: effects of voltage-dependent ion channel blockers. J. Physiol. (Paris) 578, 173–191.

Chan, C.Y., Nicholson, C., 1986. Modulation by applied electric fields of Purkinje and stellate cell activity in the isolated turtle cerebellum. J. Physiol. (Paris) 371, 89–114.
Chapman, J.P., Chapman, L.J., Allen, J.J., 1987. The measurement of foot preference. Neuropsychologia 25, 579–584.
Daly, J.J., Sng, K., Roenigk, K., Fredrickson, E., Dohring, M., 2007. Intra-limb coordination deficit in stroke survivors and response to treatment. Gait Posture 25, 412–418.
Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D., Bikson, M., 2009. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2 (201–207), 207 e201.
Fell, J., Axmacher, N., 2011. The role of phase synchronization in memory processes. Nat. Rev. Neurosci. 12, 105–118.
Fukuyama, H., Ouchi, Y., Matsuzaki, S., Nagahama, Y., Yamauchi, H., Ogawa, M., Kimura, J., Shibasaki, H., 1997. Brain functional activity during gait in normal subjects: a SPECT study. Neurosci. Lett. 228, 183–186.
Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L.G., Mall, V., Kaelin-Lang, A., Mima, T., Rossi, S., Thickbroom, G.W., Rossini, P.M., Ziemann, U., Valls-Sole, J., Siebner, H.R., 2012. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clin. Neurophysiol. 123, 858–882.
Herbin, M., Hackert, R., Gasc, J.P., Renous, S., 2007. Gait parameters of treadmill versus overground locomotion in mouse. Behav. Brain Res. 181, 173–179.
Huang, Y., Dmochowski, J.P., Su, Y., Datta, A., Rorden, C., Parra, L.C., 2013. Automated MRI segmentation for individualized modeling of current flow in the human head. J. Neural Eng. 10, 066004.
Ilg, W., Golla, H., Thier, P., Giese, M.A., 2007. Specific influences of cerebellar dysfunctions on gait. Brain 130, 786–798.
Jahn, K., Deutschlaender, A., Stephan, T., Kalla, R., Huefner, K., Wagner, J., Strupp, M., Brandt, T., Christopher, K., Leigh, R.J., 2008a. Chapter 4.20 - Supraspinal Locomotor Control in Quadrupeds and Humans, Progress in Brain Research. Volume 171 Vol. Elsevier, pp. 353–362.
Jahn, K., Deutschlaender, A., Stephan, T., Kalla, R., Wiesmann, M., Strupp, M., Brandt, T., 2008b. Imaging human supraspinal locomotor centers in brainstem and cerebellum. NeuroImage 39, 786–792.
Kanai, R., Chaieb, L., Antal, A., Walsh, V., Paulus, W., 2008. Frequency-dependent electrical stimulation of the visual cortex. Curr. Biol. 18, 1839–1843.
Kanai, R., Paulus, W., Walsh, V., 2010. Transcranial alternating current stimulation (tACS) modulates cortical excitability as assessed by TMS-induced phosphene thresholds. Clin. Neurophysiol. 121, 1551–1554.
Kikuchi, S., Mochizuki, H., Moriya, A., Nakatani-Enomoto, S., Nakamura, K., Hanajima, R., Ugawa, Y., 2012. Ataxic Hemiparesis: neurophysiological analysis by cerebellar transcranial magnetic stimulation. Cerebellum 11, 259–263.
Kirov, R., Weiss, C., Siebner, H.R., Born, J., Marshall, L., 2009. Slow oscillation electrical brain stimulation during waking promotes EEG theta activity and memory encoding. Proc Natl Acad Sci U S A 106, 15460–15465.
Lacquaniti, F., Ivanenko, Y.P., Zago, M., 2012. Patterned control of human locomotion. J. Physiol. (Paris) 590, 2189–2199.
Marshall, L., Helgadottir, H., Molle, M., Born, J., 2006. Boosting slow oscillations during sleep potentiates memory. Nature 444, 610–613.
Moore, S., Schurr, K., Wales, A., Moseley, A., Herbert, R., 1993. Observation and analysis of hemiplegic gait: swing phase. Aust. J. Physiother. 39, 271–278.
Mori, S., 1987. Integration of posture and locomotion in acute decerebrate cats and in awake, freely moving cats. Prog. Neurobiol. 28, 161–195.
Mori, S., Matsui, T., Kuze, B., Asanome, M., Nakajima, K., Matsuyama, K., 1999. Stimulation of a restricted region in the midline cerebellar white matter evokes coordinated quadrupedal locomotion in the decerebrate cat. J. Neurophysiol. 82, 290–300.
Morton, S.M., Bastian, A.J., 2003. Relative contributions of balance and voluntary leg-coordination deficits to cerebellar gait ataxia. J. Neurophysiol. 89, 1844–1856.
Morton, S.M., Bastian, A.J., 2007. Mechanisms of cerebellar gait ataxia. Cerebellum 6, 79–86.
Morton, S.M., Tseng, Y.W., Zackowski, K.M., Daline, J.R., Bastian, A.J., 2010. Longitudinal tracking of gait and balance impairments in cerebellar disease. Mov. Disord. 25, 1944–1952.
Moseley, A., Wales, A., Herbert, R., Schurr, K., Moore, S., 1993. Observation and analysis of hemiplegic gait: stance phase. Aust. J. Physiother. 39, 259–267.
Neuling, T., Rach, S., Herrmann, C.S., 2013. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. Front. Hum. Neurosci. 7, 161.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Ozen, S., Sirota, A., Belluscio, M.A., Anastassiou, C.A., Stark, E., Koch, C., Buzsaki, G., 2010. Transcranial electric stimulation entrains cortical neuronal populations in rats. J. Neurosci. 30, 11476–11485.
Paulus, W., 2011. Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. Neuropsychol. Rehabil. 21, 602–617.
Pereira, J.E., Cabrita, A.M., Filipe, V.M., Bulas-Cruz, J., Couto, P.A., Melo-Pinto, P., Costa, L.M., Geuna, S., Mauricio, A.C., Varejao, A.S., 2006. A comparison analysis of hindlimb kinematics during overground and treadmill locomotion in rats. Behav. Brain Res. 172, 212–218.
Pogosyan, A., Gaynor, L.D., Eusebio, A., Brown, P., 2009. Boosting cortical activity at Beta-band frequencies slows movement in humans. Curr. Biol. 19, 1637–1641.
Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L.C., Bikson, M., 2013. Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. J. Physiol. (Paris) 591, 2563–2578.
Rahman, A., Toshev, P.K., Bikson, M., 2014. Polarizing cerebellar neurons with transcranial direct current stimulation. Clin. Neurophysiol. 125, 435–438.
Reato, D., Rahman, A., Bikson, M., Parra, L.C., 2010. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J. Neurosci. 30, 15067–15079.
Reato, D., Rahman, A., Bikson, M., Parra, L.C., 2013. Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. Front. Hum. Neurosci. 7, 687.
Rossini, P.M., Barker, A.T., Berardelli, A., Caramia, M.D., Caruso, G., Cracco, R.Q., Dimitrijevic, M.R., Hallett, M., Katayama, Y., Lucking, C.H., et al., 1994. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr. Clin. Neurophysiol. 91, 79–92.
Sherman, D., Fuller, P.M., Marcus, J., Yu, J., Zhang, P., Chamberlin, N.L., Saper, C.B., Lu, J., 2015. Anatomical Location of the Mesencephalic Locomotor Region and Its Possible Role in Locomotion, Posture, Cataplexy, and Parkinsonism. Front. Neurol. 6.
Shik, M.L., Orlovsky, G.N., 1976. Neurophysiology of locomotor automatism. Physiol. Rev. 56, 465–501.
Shik, M.L., Severin, F.V., Orlovsky, G.N., 1969. Control of walking and running by means of electrical stimulation of the mesencephalon. Electroencephalogr. Clin. Neurophysiol. 26, 549.
Stolze, H., Kuhtz-Buschbeck, J.P., Mondwurf, C., Boczek-Funcke, A., Johnk, K., Deuschl, G., Illert, M., 1997. Gait analysis during treadmill and overground locomotion in children and adults. Electroencephalogr. Clin. Neurophysiol. 105, 490–497.
Takakusaki, K., Habaguchi, T., Ohtinata-Sugimoto, J., Saitoh, K., Sakamoto, T., 2003. Basal ganglia efferents to the brainstem centers controlling postural muscle tone and locomotion: a new concept for understanding motor disorders in basal ganglia dysfunction. Neuroscience 119, 293–308.
Thut, G., Bergmann, T.O., Frohlich, F., Soekadar, S.R., Brittain, J.S., Valero-Cabre, A., Sack, A.T., Miniussi, C., Antal, A., Siebner, H.R., Ziemann, U., Herrmann, C.S., 2017. Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper. Clin. Neurophysiol. 128, 843–857.
Truong, D.Q., Magerowski, G., Blackburn, G.L., Bikson, M., Alonso-Alonso, M., 2013. Computational modeling of transcranial direct current stimulation (tDCS) in obesity: impact of head fat and dose guidelines. Neuroimage Clin. 2, 759–766.
Ugawa, Y., Terao, Y., Hanajima, R., Sakai, K., Furubayashi, T., Machii, K., Kanazawa, I., 1997. Magnetic stimulation over the cerebellum in patients with ataxia. Electroencephalogr. Clin. Neurophysiol. 104, 453–458.
Ugawa, Y., Uesaka, Y., Terao, Y., Hanajima, R., Kanazawa, I., 1995. Magnetic stimulation over the cerebellum in humans. Ann. Neurol. 37, 703–713.
Waller, W.H., 1940. Progression movements elicited by subthalamic stimulation. J. Neurophysiol. 3, 300–307.
Wassermann, E.M., 1998. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr. Clin. Neurophysiol. 108, 1–16.
Zaehle, T., Rach, S., Herrmann, C.S., 2010. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PLoS One 5, e13766.

Please cite this article in press as: Koganemaru, S., et al., Cerebellar transcranial alternating current stimulation modulates human gait rhythm. Neurosci. Res. (2019), https://doi.org/10.1016/j.neures.2019.12.003