

Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation

Aliénor Richard, Angèle Van Hamme, Xavier Drevelle, Jean-Louis Golmard,
Sabine Meunier, Marie-Laure Welter

► **To cite this version:**

Aliénor Richard, Angèle Van Hamme, Xavier Drevelle, Jean-Louis Golmard, Sabine Meunier, et al.. Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation. *Neuroscience*, Elsevier - International Brain Research Organization, 2017, <10.1016/j.neuroscience.2017.06.047>. <hal-01558251>

HAL Id: hal-01558251

<http://hal.upmc.fr/hal-01558251>

Submitted on 11 Jul 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation.

Aliénor Richard,^{1,2,3} Angèle Van Hamme,⁴ Xavier Drevelle,⁴ Jean-Louis Golmard,⁵ Sabine Meunier,^{1,2,3} Marie-Laure Welter.^{1,2,3,4,6,7}

Author Affiliations

1 Université Pierre et Marie Curie-Paris 6, Institut du Cerveau et de la Moelle épinière (ICM), UMR-S975, Paris, France; 2 Inserm, U975, Paris, France; 3 CNRS, UMR 7225, Paris, France; 4 Plateforme d'Analyse du Mouvement (PANAM-CENIR), Institut du Cerveau et de la Moelle Epinière, Paris, France; 5 Département de Biostatistiques et Information Médicale, Hôpitaux Universitaires Pitié-Salpêtrière/Charles Foix, Assistance Publique-Hôpitaux de Paris, ER4 (ex EA3974) Modélisation en Recherche Clinique, Paris, France; 6 Centre d'Investigation Clinique, Hôpitaux Universitaires Pitié-Salpêtrière/Charles Foix, Assistance Publique-Hôpitaux de Paris, Paris, France; 7 Département de Neurologie, Hôpitaux Universitaires Pitié-Salpêtrière/Charles Foix, Assistance Publique-Hôpitaux de Paris, Paris, France.

Corresponding author: ML Welter,

Département de Neurologie, Bâtiment Paul Castaigne, Groupe Hospitalier Pitié-Salpêtrière, 47-83 bd de l'Hôpital, 75013 Paris, France.

Tel: +33142162461, Fax: +33142161958

E-mail address: marie-laure.welter@aphp.fr.

Statistics: *Title*: 149 characters including spaces, *Running head*: 35 characters including spaces, *Abstract*: 233 words, *Text*: 3234, 2 Figures, 4 Tables, 59 References

Abstract

Several brain structures including the brainstem, the cerebellum and the frontal cortico-basal ganglia network, with the primary and premotor areas have been shown to participate in the functional organisation of gait initiation and postural control in humans, but their respective roles remain poorly understood. The aim of this study was to better understand the role of the supplementary motor area (SMA) and posterior cerebellum in the gait initiation process. Gait initiation parameters were recorded in 22 controls both before and after continuous theta burst transcranial stimulation (cTBS) of the SMA and cerebellum, and were compared to sham stimulation, using a randomized double-blind design study. The two phases of gait initiation process were analysed: anticipatory postural adjustments (APAs) and execution, with recordings of soleus and tibialis anterior muscles. Functional inhibition of the SMA led to a shortened APA phase duration with advanced and increased muscle activity; during execution, it also advanced muscle co-activation and decreased the duration of stance soleus activity. Cerebellar functional inhibition did not influence the APA phase duration and amplitude but increased muscle co-activation, it decreased execution duration and showed a trend to increase velocity, with increased swing soleus muscle duration and activity. The results suggest that the SMA contributes to both the timing and amplitude of the APAs with no influence on step execution and the posterior cerebellum in the coupling between the APAs and execution phases and leg muscle activity pattern during gait initiation.

Highlights

- Using transcranial magnetic stimulation, we investigate the role of the SMA and posterior cerebellum in the gait initiation
- SMA contributes to both the timing and amplitude of the APAs
- The posterior cerebellum participates to the coupling between the APAs and execution phases
- The posterior cerebellum also contributes to intra- and inter-limb muscle activity pattern

Key words: Gait initiation, Anticipatory postural adjustments, Supplementary motor area, Cerebellum, Transcranial magnetic stimulation

Abbreviations

APAs = anticipatory postural adjustment; CoG = Centre of gravity; CoP = Centre of foot pressure; EC = Eyes closed; EO = eyes opened; FC = foot contact; FO = Foot off; rTMS = repetitive transcranial magnetic stimulation; SMA = Supplementary motor area; SOL = Soleus muscle; TA = tibialis anterior muscle; TBS = theta burst stimulation.

Acknowledgements

We thank the Centre for Clinical Investigations (CIC) of the Pitié-Salpêtrière Hospital for administrative support.

Funding source

This work was supported in part by a grant from the Association AMADYS and the Fondation Areva (to A. Richard).

Disclosures

ML Welter reports having received research funding from the Brain and Spine Institute (ICM) and Agence Nationale de la Recherche (ANR) and consulting fees from Medtronic.

A Richard, A Van Hamme, X Drevelle, JL Golmard and S Meunier report no financial disclosure.

Authors' contributions:

A.R, X.D, A.V.H and M.-L.W. performed experiments; A.R, X.D, A.V.H, J.-L.G and M.-L.W analyzed data; A.R, A.V.H, S.M. and M.-L.W interpreted results of experiments; A.R; A.V.H. and M.L.W prepared figures; A.R., A.V.H., S.M and M.-L.W. drafted, edited and revised manuscript; S.M. and M.L.W. conception and design of research.

Introduction

In humans, gait initiation is particularly challenging for motor and postural control as the subject has to simultaneously perform a whole body forward movement and pass from a stable (double leg stance) to an unstable position (single leg stance). It is associated with anticipatory postural adjustments (APAs) with a backward and lateral shift of the centre of foot pressure (CoP) towards the swing leg, in relation with activation of both tibialis anterior (TA) muscles, allowing the swing leg to lift. The neural substrates for APAs generation and step execution are not fully known. In animals, locomotion can be initiated by electrical or chemical activation of the supplementary motor area at the cortical level, and the subthalamic, the mesencephalic locomotor and cerebellar midline regions at the subcortical level (Mori et al. 1989; Takakusaki et al. 2004). In humans, few studies have examined the role of these brain regions in the gait initiation process. However, repetitive transcranial magnetic stimulation applied above the SMA provokes a shortening of the APA duration of the first step after stimulation with no change in APA amplitude (Jacobs et al. 2009a). Startle stimuli, thought to modulate pontomesencephalic reticular formation activity, shorten APAs with no change in the step execution characteristics (Queralt et al. 2010). Acoustic stimuli can also elicit APAs without being followed by step execution (Delval et al. 2012), but only when the subject is expecting to initiate a step, suggesting that the brainstem releases APAs depending on the cognitive context (to walk or not) (MacKinnon et al. 2007). Lastly, transcranial direct current stimulation applied over the cerebellum affects spatial characteristics of walking during locomotor adaptation (Jayaram et al. 2012), but the effects of cerebellar stimulation on APAs generation and gait initiation have not been studied. In patients with lesions and/or dysfunction of these different brain regions, various gait initiation deficits have also been reported. In patients with premotor cortical areas involving the SMA, a lack of gait initiation (or freezing of gait-FOG phenomenon) has been reported with an inability to lift the feet from the ground and execute the first step (Bartels and Leenders 2008; Nadeau 2007; Nutt et al. 1993). Such a FOG phenomenon is also observed in patients with mesencephalic locomotor region (MLR) lesions (Masdeu et al. 1994) and people with Parkinson's disease (PD) (Giladi et al. 1997) and has been linked to altered APAs prior to gait initiation (Jacobs et al. 2009b) with reduced SMA-MLR connectivity (Gallea et al. 2017; Halliday et al. 1998; Okada et al. 2011). Patients with cerebellar lesions or dysfunction show increased stride

width and shorter stride length with longer duration and increased lower leg muscle activity and co-activation (Timmann et al. 2000); with abnormal temporal organisation of the muscular pattern (Bruttini et al. 2015; Martino et al. 2014).

Recently, distorted APAs prior to step execution and altered postural control during walking with shorter and irregular steps (Fernandez et al. 2013; Morton and Bastian 2007) have been reported in patients suffering from essential tremor (ET), these patients presented with posterior cerebellar atrophy (Gallea et al. 2015). Taken together these data support the involvement of the cortico (SMA)-pontine-cerebello-thalamo-cortical pathway in APAs generation and the gait initiation process.

In order to provide a more detailed understanding of how the cortico (SMA)-pontine-cerebello-thalamo-cortical pathway contributes to the preparation and the execution of the first step in humans, we selectively disrupted the SMA and the cerebellum with continuous theta burst repetitive transcranial magnetic stimulation (cTBS) and evaluated the effects of the stimulation on the APAs and execution phases of gait initiation. Consistent with previous studies, we hypothesised that the SMA would be mainly involved in generating the APAs to lift the leg from the ground while the cerebellum would adjust the postural balance and foot placement during walking.

Experimental procedures

Participants

Twenty-two healthy volunteers (14M/8F, mean age \pm SD = 29.5 \pm 7.3 years) were included in this study which received approval from the local ethics committee (Paris VI University) and was promoted by the INSERM (C12-05, N° ID RCB 2012-A00796-37, ClinicalTrials.gov Registration NCT02976298). All the participants gave written informed consent to participate. Exclusion criteria were any history of peripheral neurological or orthopaedic disease, and of central nervous systems or psychotropic drug use or contraindication to rTMS (Rossi et al. 2009).

Gait initiation protocol

Subjects, barefoot, and standing upright and motionless on a force plate (0.9 x 1.8 m, Advanced Mechanical Technology Inc. LG6-4-1, USA) were instructed to commence walking for 5 m (5-7 steps per trial) following an auditory cue. The outlines of the participants' feet were recorded to ensure that stance width remained consistent throughout the experiments. In each trial, the first two steps were captured for analysis. The subjects were instructed to walk at their usual self-paced speed. Each subject walked a total of 10 trials before and after rTMS. The subjects performed separate sessions in a randomised order for rTMS over the SMA, cerebellum and sham stimulation (to either SMA or cerebellum). The sessions were separated by at least 7 days.

rTMS protocol

The intensity of stimulation applied to SMA or cerebellum was chosen relative to the active motor thresholds (aMT) of the right tibialis anterior (TA) or right abductor pollicis brevis (APB) muscles respectively, as previously reported (Gerloff et al. 1997)(Popa et al. 2013). The rationale for using TA muscle representation as hotspots for adjusting SMA stimulation intensity was that leg representations in the SMA and the primary motor cortex are located in adjacent positions and at a similar depth in the interhemispheric fissure (Gerloff et al. 1997). Accordingly stimulation sessions started by identifying the motor 'hot spot' of either the right TA or right APB muscles according to the session and calculating their aMT using standard procedures (Rossini et al. 1994; Rothwell 1997). To that end TMS pulses were applied by using a 70-mm figure-of-eight coil connected to a Rapid2 magnetic stimulator (Magstim Company).

Induced currents were biphasic and directed posterior to anterior (Arai et al. 2012). For the TA muscle, the coil was held on or close to the midline with the handle pointing backwards. For the APB muscle, the coil was held at $\sim 45^\circ$ from the midline for optimal trans-synaptic activation of the motor cortex (Kaneko et al. 1996; Werhahn et al. 1994).

The SMA and cerebellum targets were marked on the individual brain MRIs by the use of an MRI-based neuro-navigation system (eXimia 2.2.0, Nextstim Ltd). For the SMA, the target was the SMA proper and marked on the MRI relative to a vertical line from the anterior commissure perpendicular to the antero-posterior commissure line in the sagittal plane, which is a standardized separator for the SMA proper and the pre-SMA (Picard and Strick 1996; Vorobiev et al. 1998; Zilles et al. 1996). The centre of the coil was positioned over the target, with the coil handle pointing backwards so that the induced current had a posterior-anterior orientation. For the cerebellum, stimulation was applied consecutively to each side targeting lobule VIII of the cerebellum (Popa et al. 2010; Popa et al. 2013), with the coil handle pointing upwards so that the induced current had a caudal to rostral orientation.

Continuous theta-burst stimulation (cTBS) protocol (Huang et al. 2005) was used with 600 stimuli delivered at 80% TA aMT (for SMA) or 80% APB aMT (for cerebellum) in three-pulse bursts at 50 Hz, repeated every 200 ms continuously for 40 s (5 Hz). For sham stimulation (delivered with a cTBS pattern), we used a 'sham' coil that delivered only 10% of the intensity. The stimulation intensities used in this study are well below the maximum limit recommended by current rTMS safety guidelines (Rossi et al. 2009).

Data collection and analysis

The investigators analysing kinematic, dynamic and EMG data were blinded to the stimulation conditions.

Kinetic and dynamic data

The spatial and temporal kinetics parameters, i.e. acceleration and velocity of the centre of gravity (CoG) and displacements of centre of foot pressure (CoP), were extracted from the force platform data in real time and displayed in a custom-built MATLAB interface (Chastan et al. 2010). The force platform analogue signals were sampled at 1000 Hz.

The onset of the APAs was defined as the moment of the first biomechanical event (t_0) with posterior and lateral CoP displacement (Figure 1), and its end as the moment of the foot-off of the swing leg (FO1). The APAs phase was divided in 2 distinct phases (Hass et al. 2004): the S1 phase starting at t_0 and ending at the time of the maximum posterior and lateral CoP shift, and the S2 phase starting at the onset of the lateral shift of the CoP in the opposite direction towards the stance limb and ending when the CoP is in its most lateral and posterior position under the stance limb (Figure 1). The APAs duration and maximum posterior and lateral CoP displacements were measured.

The step execution phase was defined as the period between FO1 and the foot-off of the stance leg (FO2). The step length, step width, execution velocity and duration of the swing (time between FO1 and the foot-contact of the stance leg – FC1) and double stance (period between the foot contact of the swing leg – FC1 and FO2) phases were calculated (Figure 1). Two values were extracted from the vertical CoG velocity: the peak negative value during the swing phase (V1) and its value at the time of foot contact (V2), allowing us to calculate the braking index $((V1-V2)/V1*100)$, which reflects active postural control (Welter et al. 2007).

EMG data

Electromyographic (EMG) activity of the Soleus (SOL) and Tibialis anterior (TA) muscles were recorded with surface bipolar electrodes according to SENIAM procedure (Hermens et al. 2000) (WAVE Plus, Ref. WP180, Cometa srl, Italy). The EMG signals were band-pass filtered at 30–300 Hz (6th order Butterworth filter), and rectification and low-pass filtering at 50 Hz (2nd order Butterworth, zero- phase forward and reverse filter) were applied. Muscular bursts were detected by the Teager-Kaiser energy operator method by calculating the energy of the signal (Solnik et al. 2010). The linear envelopes of each muscular burst were measured, normalised to the maximum peak amplitude in each gait condition and the root mean square (RMS) calculated (Barzilay and Wolf 2011). The onset, duration of each SOL and TA muscles burst and co-contraction (simultaneous SOL and TA muscles activity) were calculated. We calculated a ratio of co-contraction by dividing the linear envelope of SOL or TA muscle activity with the sum of the SOL and TA linear envelopes (Hesse et al. 2000).

Statistical Analysis

For each stimulation condition, we employed a linear mixed effects model with two fixed effects: stimulation (before stimulation, sham-cTBS and cerebellar-cTBS or SMA-cTBS) and day (chronological order of sessions), adding a random effect on subjects to take into account the inter-subject variability. When a significant main effect was seen, the Tukey-Kramer test was used for multiple comparisons. Statistical analyses were performed using R (version 3.2.2). The significance level was taken as $p < 0.05$ with Bonferroni correction. We considered as significant the changes induced by the cTBS only if there was a significant difference between the values obtained before and after the stimulation and a difference between the values obtained during real and sham cTBS. We considered as a trend the changes induced by cTBS if there was a significant difference between the values obtained before *versus* after the stimulation or after active cTBS *versus* sham stimulation, but no difference between the values obtained at baseline and after sham stimulation.

Results

Effects of functional inactivation of the SMA or cerebellum on the APAs phase

With SMA-cTBS, the APAs phase duration significantly decreased, the swing SOL muscle activity started significantly earlier and the stance TA muscle RMS activity significantly increased (Figure 2). In comparison to baseline, after SMA-cTBS, the S2 phase duration tended to decrease and the stance SOL muscle activity to start earlier. Lastly, with SMA-cTBS in comparison to sham stimulation, the lateral CoP displacement tended to increase and the swing SOL muscle activity tended to be activated longer and with increased RMS amplitude (Table 1).

With cerebellar-cTBS, the amplitude and timing of APAs were not significantly modified, but the duration of the TA and SOL muscle co-activation of the stance leg significantly increased (Table 1). After cerebellar-cTBS, the stance TA muscle activity tended to start later in comparison to baseline, and the duration of the swing and stance SOL muscle activity tended to increase. Lastly, with cerebellar -cTBS the lateral CoP shift tended to decrease in comparison to sham stimulation, (Table 1).

Effect of functional inhibition of the SMA or cerebellum on step execution

With SMA-cTBS, the execution and double-stance durations, step length, execution velocity (Figure 2) and braking index (not shown) were not significantly modified. The stance SOL muscle activity duration significantly decreased (Table 2). In comparison to baseline, the swing TA muscle activity duration tended to decrease and the swing SOL-TA muscle co-activation to start earlier (Table 2).

With cerebellar-cTBS, the execution duration was significantly lower with no significant change in the double-stance duration, step length, execution velocity (Figure 2) or braking index (not shown). The swing SOL muscle activity duration was significantly increased (Figure 2). With cerebellar-cTBS, the swing SOL muscle activity RMS amplitude tended to increase in comparison to baseline, with reduced swing TA muscle RMS amplitude. Lastly, with cerebellar-cTBS the swing TA muscle activity duration tended to decrease in comparison to sham stimulation (Figure 2, Table 2).

Discussion

In the present study, we investigated how the APAs and step execution could be modified by cTBS over the SMA and the cerebellum in healthy subjects. Shorter APAs were produced by cTBS over the SMA with earlier activation of swing SOL muscle, with no significant changes in the step execution parameters, except for a shorter stance SOL muscle activation. Conversely, no significant change in the APAs timings and amplitudes were induced by cTBS over the cerebellum but an increased stance SOL-TA muscle co-activation duration during APAs and a shorter step execution duration with longer swing SOL muscle activation. Neither SMA nor cerebellar-cTBS provoked significant changes in the step length and velocity or postural control during gait execution (i.e. double stance duration and braking index).

In this study, we used the classical parameters used for cTBS, i.e. 0.8 aMT, 600 pulses, thought to induce a transient decrease in synaptic efficacy in the targeted area lasting approximately 30 minutes after stimulation (Huang et al. 2005), through a combination of long-term depression and long-term potentiation mechanisms (Huang et al. 2005; Stagg et al. 2009), with, however, a significant inter-subject variability. In our study, cTBS of the SMA led probably to a reduction in its output signal that provoked increased APAs performance with changes both in the timing (shortening) and amplitude (tendency to increase CoP displacements) of the APAs, related to an earlier and greater activation of TA muscles (Mann et al. 1979). Our results are in line with reports of reduced APAs durations prior to step initiation with 1 Hz rTMS of the SMA (Jacobs et al. 2009a). This effect could result from disruption of sensory perception of self-generated actions (Haggard and Whitford 2004), in addition to changes in perception threshold (Legon et al. 2013), leading to decreased effort perception (Zenon et al. 2015) with, in consequence, an increased force production and increased muscle activity (our results). Another explanation would be that SMA disruption interferes with the automatic inhibitory control of motor responses (Albares et al. 2014). The finding that SMA disruption significantly improves akinesia (Eggers et al. 2015) and decreases abnormally prolonged APAs phase durations prior to gait initiation (Jacobs et al. 2009a) in PD patients, is also in line with our results. In contrast, anodal transcranial direct current stimulation (tDCS) of the SMA (thought to induce an excitation) provokes an increase in the APAs developing in the biceps and the triceps brachii during brisk index-finger flexions, without changes in prime mover muscle recruitment and index-finger kinematics (Bolzoni et al. 2015). Lastly, we

observed no significant change in balance control during gait after functional inhibition of the SMA suggesting that the SMA is not specifically involved in dynamic postural control while walking, *per se*, but more in internal representation of sensory information regarding postural status (Jacobs and Horak, 2007).

cTBS of the cerebellum produced no marked effects on the spatiotemporal APAs parameters but altered the leg muscle pattern and increased intra-limb muscle co-activation. Our present findings are in line with the fact that anodal tDCS applied to the lateral cerebellum does not modify locomotor patterns, except in the case of adaptive learning (Jayaram et al. 2011; Jayaram et al. 2012), whereas posterior cerebellar disruption provokes maladjustment of sensorimotor calibration with a decoupling between the motor component of the movement (execution) and the afferent sensory information (postural adjustment) (Hubsch et al. 2013) with an alteration of muscle activation pattern with increased co-activation of agonist and antagonist muscles during movement (Mari et al. 2014). The changes in muscle activation pattern during the APAs or the first step execution induced by cerebellar TBS were probably mediated through the cerebello-thalamo-projections to the motor areas as we targeted lobule VIII of the cerebellum (Popa et al. 2010), this lobule being activated during sensori-motor tasks (Stoodley et al. 2012) in connection with the premotor and motor cortical regions (O'Reilly et al. 2010). The fact that, in our experiment, cTBS of the cerebellum has little or no effect on postural control suggests that we did not significantly modified vermis or vestibular cerebellum activity (Inukai et al. 2016).

We took several precautions to ensure reliable findings. Subjects were randomly assigned to begin with sham, or cerebellar or SMA stimulation to minimise any possible order effects. By having the sessions scheduled at least one week apart we excluded a 'take over' effect. We used a within-subject design and a sham condition to limit the influence of the known large inter-subject variability in susceptibility to develop TBS-induced plasticity (Lopez-Alonso et al. 2014; Vallence et al. 2015) and stimulation of SMA and the lobule VIII of the cerebellum were both performed under neuro-navigation control. Despite this precaution, we observed changes in gait initiation parameters after sham stimulation. This could have led to underpowered results. An unsolved issue is how to assess the efficacy of the cerebellum or SMA theta-burst stimulation in individuals and consequently, how to determine the sample size needed for such experiments. Stimulation intensity was

adjusted according to the individual's motor cortex excitability yet it is unclear to what extent M1 excitability reflects cerebellar or SMA excitability. Lastly, we could not exclude the possibility that stimulation-induced effects on EMG pattern and amplitude occurred by influencing the tonic descending drive exerted on the spinal motoneurons through the descending cerebellar vestibular and reticulospinal tracts. The fact that cerebellar stimulation with single TMS pulses facilitates the ipsilateral soleus H reflex without increasing the soleus electromyographic activity goes against this hypothesis, however (Matsugi et al. 2014).

Conclusion

In summary, the results support distinct roles for the SMA and the lateral posterior cerebellum in human gait initiation, with the SMA coding for the timing, and probably amplitude, of the preparatory phase of the gait initiation, and the posterior cerebellum contributing to the inter- and intra-limb muscle coordination, and probably coupling between the APAs and the execution phases. Further studies are needed to examine the potential therapeutic effect of such non-invasive cerebral stimulation in patients suffering from SMA or cerebellar dysfunction.

Captions

Figure 1. Biomechanical parameters and leg muscle activity during gait initiation

in a control subject. Curves represent the smoothed mean of ten trials and standard deviation. The rectified electromyographic activity of the tibialis anterior (TA) and soleus (SOL) muscles of the swing and the stance legs is shown in the four lower panels. AP: antero-posterior; CoG: centre of gravity; CoP centre of pressure; t0: time of the first biomechanical event; FO1: foot-off of the swing leg; FC1: foot contact of the swing leg; ML: medio-lateral CoP displacement; L: length of the first step; Vm: peak antero-posterior velocity of the centre of gravity; V1: peak negative value of CoG velocity; V2: value of CoG velocity at the time of FC1

Figure 2. Effects of SMA and cerebellar stimulation on gait initiation in healthy

subjects. Biomechanical parameters and electromyographic activity during gait initiation before (baseline; black), after SMA (red) or cerebellar (green) theta burst stimulation and after sham stimulation (blue). Upper panel: anticipatory postural adjustments phase; lower panel: execution phase.

References

- Albares M, Lio G, Criaud M, Anton JL, Desmurget M, and Boulinguez P. The dorsal medial frontal cortex mediates automatic motor inhibition in uncertain contexts: evidence from combined fMRI and EEG studies. *Hum Brain Mapp* 35: 5517-5531, 2014.
- Arai N, Lu MK, Ugawa Y, and Ziemann U. Effective connectivity between human supplementary motor area and primary motor cortex: a paired-coil TMS study. *Exp Brain Res* 220: 79-87, 2012.
- Bartels AL, and Leenders KL. Brain imaging in patients with freezing of gait. *Mov Disord* 23 Suppl 2: S461-467, 2008.
- Barzilay O, and Wolf A. A fast implementation for EMG signal linear envelope computation. *J Electromyogr Kinesiol* 21: 678-682, 2011.
- Bolzoni F, Bruttini C, Esposti R, Castellani C, and Cavallari P. Transcranial direct current stimulation of SMA modulates anticipatory postural adjustments without affecting the primary movement. *Behav Brain Res* 291: 407-413, 2015.
- Bruttini C, Esposti R, Bolzoni F, Vanotti A, Mariotti C, and Cavallari P. Temporal disruption of upper-limb anticipatory postural adjustments in cerebellar ataxic patients. *Exp Brain Res* 233: 197-203, 2015.
- Chastan N, Westby GW, du Montcel ST, Do MC, Chong RK, Agid Y, and Welter ML. Influence of sensory inputs and motor demands on the control of the centre of mass velocity during gait initiation in humans. *Neurosci Lett* 469: 400-404, 2010.
- Delval A, Dujardin K, Tard C, Devanne H, Willart S, Bourriez JL, Derambure P, and Defebvre L. Anticipatory postural adjustments during step initiation: elicitation by auditory stimulation of differing intensities. *Neuroscience* 219: 166-174, 2012.
- Eggers C, Gunther M, Rothwell J, Timmermann L, and Ruge D. Theta burst stimulation over the supplementary motor area in Parkinson's disease. *J Neurol* 262: 357-364, 2015.
- Fernandez KM, Roemmich RT, Stegemoller EL, Amano S, Thompson A, Okun MS, and Hass CJ. Gait initiation impairments in both Essential Tremor and Parkinson's disease. *Gait Posture* 38: 956-961, 2013.
- Gallea C, Ewenczyk C, Degos B, Welter ML, Grabli D, Leu-Semenescu S, Valabregue R, Berroir P, Yahia-Cherif L, Bertasi E, Fernandez-Vidal S, Bardinet E, Roze E, Benali H, Poupon C, Francois C, Arnulf I, Lehericy S, and Vidailhet M.

- Pedunculopontine network dysfunction in Parkinson's disease with postural control and sleep disorders. *Mov Disord* 2017.
- Gallea C, Popa T, Garcia-Lorenzo D, Valabregue R, Legrand AP, Marais L, Degos B, Hubsch C, Fernandez-Vidal S, Bardinet E, Roze E, Lehericy S, Vidailhet M, and Meunier S. Intrinsic signature of essential tremor in the cerebello-frontal network. *Brain* 138: 2920-2933, 2015.
- Gerloff C, Corwell B, Chen R, Hallett M, and Cohen LG. Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. *Brain* 120 (Pt 9): 1587-1602, 1997.
- Giladi N, Kao R, and Fahn S. Freezing phenomenon in patients with parkinsonian syndromes. *Mov Disord* 12: 302-305, 1997.
- Haggard P, and Whitford B. Supplementary motor area provides an efferent signal for sensory suppression. *Brain Res Cogn Brain Res* 19: 52-58, 2004.
- Halliday SE, Winter DA, Frank JS, Patla AE, and Prince F. The initiation of gait in young, elderly, and Parkinson's disease subjects. *Gait Posture* 8: 8-14., 1998.
- Hass CJ, Gregor RJ, Waddell DE, Oliver A, Smith DW, Fleming RP, and Wolf SL. The influence of Tai Chi training on the center of pressure trajectory during gait initiation in older adults. *Arch Phys Med Rehabil* 85: 1593-1598, 2004.
- Hermens HJ, Freriks B, Disselhorst-Klug C, and Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. *J Electromyogr Kinesiol* 10: 361-374, 2000.
- Hesse S, Brandl-Hesse B, Seidel U, Doll B, and Gregoric M. Lower limb muscle activity in ambulatory children with cerebral palsy before and after the treatment with Botulinum toxin A. *Restorative neurology and neuroscience* 17: 1-8, 2000.
- Huang YZ, Edwards MJ, Rounis E, Bhatia KP, and Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron* 45: 201-206, 2005.
- Hubsch C, Roze E, Popa T, Russo M, Balachandran A, Pradeep S, Mueller F, Brochard V, Quartarone A, Degos B, Vidailhet M, Kishore A, and Meunier S. Defective cerebellar control of cortical plasticity in writer's cramp. *Brain* 136: 2050-2062, 2013.
- Inukai Y, Saito K, Sasaki R, Kotan S, Nakagawa M, and Onishi H. Influence of Transcranial Direct Current Stimulation to the Cerebellum on Standing Posture Control. *Front Hum Neurosci* 10: 325, 2016.

Jacobs JV, Lou JS, Kraakevik JA, and Horak FB. The supplementary motor area contributes to the timing of the anticipatory postural adjustment during step initiation in participants with and without Parkinson's disease. *Neuroscience* 164: 877-885, 2009a.

Jacobs JV, Nutt JG, Carlson-Kuhta P, Stephens M, and Horak FB. Knee trembling during freezing of gait represents multiple anticipatory postural adjustments. *Exp Neurol* 215: 334-341, 2009b.

Jayaram G, Galea JM, Bastian AJ, and Celnik P. Human locomotor adaptive learning is proportional to depression of cerebellar excitability. *Cereb Cortex* 21: 1901-1909, 2011.

Jayaram G, Tang B, Pallegadda R, Vasudevan EV, Celnik P, and Bastian A. Modulating locomotor adaptation with cerebellar stimulation. *J Neurophysiol* 107: 2950-2957, 2012.

Kaneko K, Kawai S, Fuchigami Y, Morita H, and Ofuji A. The effect of current direction induced by transcranial magnetic stimulation on the corticospinal excitability in human brain. *Electroencephalogr Clin Neurophysiol* 101: 478-482, 1996.

Legon W, Dionne JK, and Staines WR. Continuous theta burst stimulation of the supplementary motor area: effect upon perception and somatosensory and motor evoked potentials. *Brain Stimul* 6: 877-883, 2013.

Lopez-Alonso V, Cheeran B, Rio-Rodriguez D, and Fernandez-Del-Olmo M. Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimul* 7: 372-380, 2014.

MacKinnon CD, Bissig D, Chiusano J, Miller E, Rudnick L, Jager C, Zhang Y, Mille ML, and Rogers MW. Preparation of anticipatory postural adjustments prior to stepping. *J Neurophysiol* 97: 4368-4379, 2007.

Mann RA, Hagey JL, White V, and Liddell D. The initiation of gait. *J Bone Joint Surg* 61: 232-239, 1979.

Mari S, Serrao M, Casali C, Conte C, Martino G, Ranavolo A, Coppola G, Draicchio F, Padua L, Sandrini G, and Pierelli F. Lower limb antagonist muscle co-activation and its relationship with gait parameters in cerebellar ataxia. *Cerebellum* 13: 226-236, 2014.

- Martino G, Ivanenko YP, Serrao M, Ranavolo A, d'Avella A, Draicchio F, Conte C, Casali C, and Lacquaniti F. Locomotor patterns in cerebellar ataxia. *J Neurophysiol* 112: 2810-2821, 2014.
- Masdeu JC, Alampur U, Cavaliere R, and Tavoulareas G. Astasia and gait failure with damage of the pontomesencephalic locomotor region. *Ann Neurol* 35: 619-621, 1994.
- Matsugi A, Mori N, Uehara S, Kamata N, Oku K, Mukai K, and Nagano K. Task dependency of the long-latency facilitatory effect on the soleus H-reflex by cerebellar transcranial magnetic stimulation. *Neuroreport* 25: 1375-1380, 2014.
- Mori S, Sakamoto T, Ohta Y, Takakusaki K, and Matsuyama K. Site-specific postural and locomotor changes evoked in awake, freely moving intact cats by stimulating the brainstem. *Brain Res* 505: 66-74, 1989.
- Morton SM, and Bastian AJ. Mechanisms of cerebellar gait ataxia. *Cerebellum* 6: 79-86, 2007.
- Nadeau SE. Gait apraxia: further clues to localization. *Eur Neurol* 58: 142-145, 2007.
- Nutt JG, Marsden CD, and Thompson MD. Human walking and higher-level gait disorders, particularly in the elderly. *Neurology* 43: 268-279, 1993.
- O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, and Johansen-Berg H. Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. *Cereb Cortex* 20: 953-965, 2010.
- Okada Y, Fukumoto T, Takatori K, Nagino K, and Hiraoka K. Variable initial swing side and prolonged double limb support represent abnormalities of the first three steps of gait initiation in patients with Parkinson's disease with freezing of gait. *Front Neurol* 2: 85, 2011.
- Picard N, and Strick PL. Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* 6: 342-353, 1996.
- Popa T, Russo M, and Meunier S. Long-lasting inhibition of cerebellar output. *Brain Stimul* 3: 161-169, 2010.
- Popa T, Russo M, Vidailhet M, Roze E, Lehericy S, Bonnet C, Apartis E, Legrand AP, Marais L, Meunier S, and Gallea C. Cerebellar rTMS stimulation may induce prolonged clinical benefits in essential tremor, and subjacent changes in functional connectivity: an open label trial. *Brain Stimul* 6: 175-179, 2013.
- Queralt A, Valls-Sole J, and Castellote JM. Speeding up gait initiation and gait-pattern with a startling stimulus. *Gait Posture* 31: 185-190, 2010.

Rossi S, Hallett M, Rossini PM, and Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 120: 2008-2039, 2009.

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH, and et al. 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, 1994.

Rothwell JC. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *J Neurosci Methods* 74: 113-122, 1997.

Solnik S, Rider P, Steinweg K, DeVita P, and Hortobagyi T. Teager-Kaiser energy operator signal conditioning improves EMG onset detection. *Eur J Appl Physiol* 110: 489-498, 2010.

Stagg CJ, Wylezinska M, Matthews PM, Johansen-Berg H, Jezzard P, Rothwell JC, and Bestmann S. Neurochemical effects of theta burst stimulation as assessed by magnetic resonance spectroscopy. *J Neurophysiol* 101: 2872-2877, 2009.

Stoodley CJ, Valera EM, and Schmahmann JD. Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. *Neuroimage* 59: 1560-1570, 2012.

Takakusaki K, Oohinata-Sugimoto J, Saitoh K, and Habaguchi T. Role of basal ganglia-brainstem systems in the control of postural muscle tone and locomotion. *Prog Brain Res* 143: 231-237, 2004.

Timmann D, Baier PC, Diener HC, and Kolb FP. Classically conditioned withdrawal reflex in cerebellar patients. 1. Impaired conditioned responses. *Exp Brain Res* 130: 453-470, 2000.

Vallence AM, Goldsworthy MR, Hodyl NA, Semmler JG, Pitcher JB, and Ridding MC. Inter- and intra-subject variability of motor cortex plasticity following continuous theta-burst stimulation. *Neuroscience* 304: 266-278, 2015.

Vorobiev V, Govoni P, Rizzolatti G, Matelli M, and Luppino G. Parcellation of human mesial area 6: cytoarchitectonic evidence for three separate areas. *Eur J Neurosci* 10: 2199-2203, 1998.

Welter ML, Do MC, Chastan N, Tornay F, Bloch F, du Montcel ST, and Agid Y. Control of vertical components of gait during initiation of walking in normal adults and patients with progressive supranuclear palsy. *Gait Posture* 26: 393-399, 2007.

Werhahn KJ, Fong JK, Meyer BU, Priori A, Rothwell JC, Day BL, and Thompson PD. The effect of magnetic coil orientation on the latency of surface EMG and single motor unit responses in the first dorsal interosseous muscle. *Electroencephalogr Clin Neurophysiol* 93: 138-146, 1994.

Zenon A, Sidibe M, and Olivier E. Disrupting the supplementary motor area makes physical effort appear less effortful. *J Neurosci* 35: 8737-8744, 2015.

Zilles K, Schlaug G, Geyer S, Luppino G, Matelli M, Qu M, Schleicher A, and Schormann T. Anatomy and transmitter receptors of the supplementary motor areas in the human and nonhuman primate brain. *Adv Neurol* 70: 29-43, 1996.

ACCEPTED MANUSCRIPT

Table 1. Effects of SMA theta-burst stimulation on Soleus and Tibialis Anterior muscle activity during the APAs prior to gait initiation in 22 healthy subjects

		SMA cTBS		
		Before TBS	SMA-TBS	Sham-TBS
Swing Leg				
TA muscle	Duration (ms)	400±42	381±43	382±43
	RMS amplitude	0.15±0.01	0.14±0.01	0.13±0.01
SOL muscle	Duration (ms)	100±21	124±21**	67±21*
	RMS amplitude	0.05±0.01	0.06±0.01**	0.03±0.01*
Co-contraction	Start (ms)	157±32	129±33**	240±33*
	Duration (ms)	83±21	83±22	53±22*
	Ratio (%)	14±3	16±3	15±3
Stance Leg				
TA muscle	Duration (ms)	372±38	373±39**	315±38*
	RMS amplitude	0.17±0.02	0.19±0.02* **	0.15±0.02
SOL muscle	Duration (ms)	83±21	97±21	111±21
	RMS amplitude	0.05±0.01	0.06±0.01	0.05±0.01
Co-contraction	Start (ms)	349±53	345±55	370±56
	Duration (ms)	48±14	46±14	30±14
	Ratio (%)	9±2	10±2	9±2

Results are expressed as mean±SD. RMS: root mean square; SMA : supplementary motor area; SOL: soleus muscle; TA: tibialis anterior muscle; TBS : theta burst stimulation. * P<0.05 when compared to before SMA-TBS; ** P<0.05 when compared to sham-TBS.

Table 2. Effects of cerebellar theta-burst stimulation on Soleus and Tibialis Anterior muscle activity during the APAs prior to gait initiation in 22 healthy subjects

		Cerebellar cTBS		
		Before TBS	CER-TBS	Sham-TBS
Swing Leg				
TA muscle	Duration (ms)	400±40	381±41	386±41
	RMS amplitude	014±0.01	0.13±0.01	0.13±0.01
SOL muscle	Duration (ms)	94±21	115±22**	62±22*
	RMS amplitude	0.05±0.01	0.05±0.01**	0.03±0.01*
Co-contraction	Start (ms)	176±34	228±36	240±35*
	Duration (ms)	85±21	62±21	57±21*
	Ratio (%)	15±3	14±3	15±3
Stance Leg				
TA muscle	Duration (ms)	359±39	346±39	326±39
	RMS amplitude	0.17±0.02	0.16±0.02	0.16±0.02
SOL muscle	Duration (ms)	80±17	117±18*	113±18
	RMS amplitude	0.05±0.01	0.06±0.01	0.05±0.01
Co-contraction	Start (ms)	320±62	355±63	352±65
	Duration (ms)	51±19	85±20 * **	36±20
	Ratio (%)	9±3	12±3	9±3

Results are expressed as mean±SD. CER: cerebellum; RMS: root mean square; SOL: soleus muscle; TA: tibialis anterior muscle; TBS : theta burst stimulation. * P<0.05 when compared to before SAM-TBS; ** P<0.05 when compared to sham-TBS.

Table 3. Effects of SMA theta-burst stimulation on Soleus and Tibialis Anterior muscle activity during first step execution in 22 healthy subjects

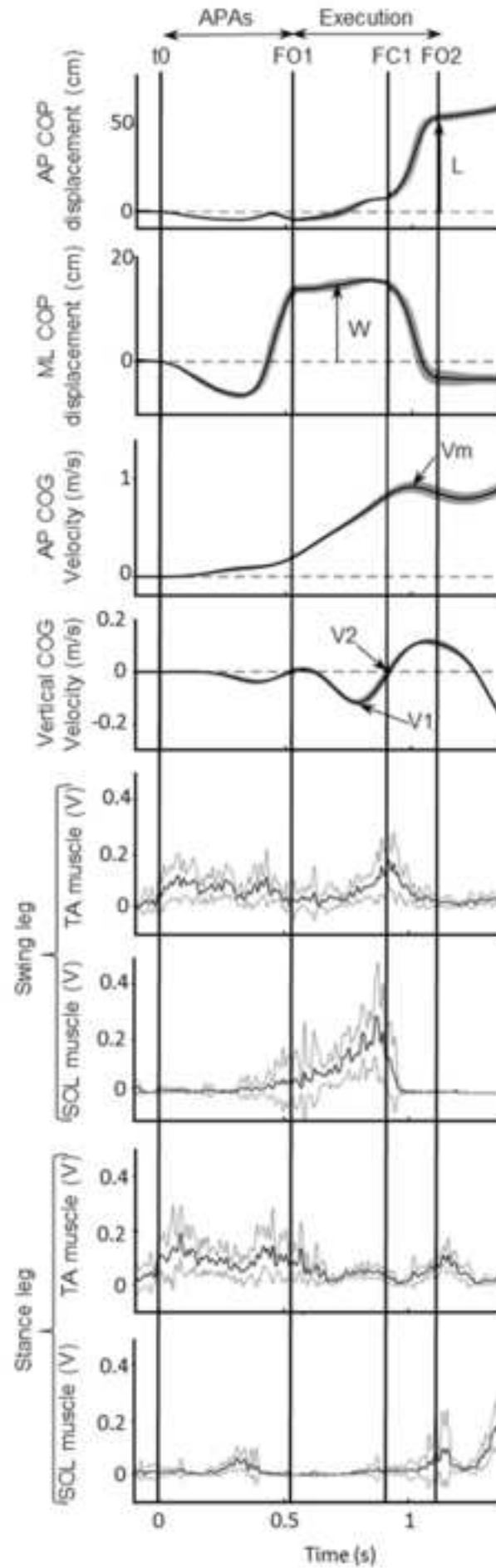
		SMA cTBS		
		Before TBS	SMA-TBS	Sham-TBS
Swing Leg				
TA muscle	Start (ms)	50±14	57±15	55±15
	RMS amplitude	0.11±0.01	0.12±0.01	0.12±0.01
SOL muscle	Start (ms)	177±39	180±41	157±41
	RMS amplitude	0.03±0.01	0.03±0.01	0.03±0.01
Co-contraction	Start (ms)	203±47	98±52*	165±48
	Duration (ms)	16±8	9±8**	35±8*
	Ratio (%)	6±3	3±3**	9±3*
Stance Leg				
TA muscle	Start (ms)	92±19	75±20	105±20
	RMS amplitude	0.08±0.01	0.09±0.01	0.10±0.01
SOL muscle	Start (ms)	61±14	75±14	65±14
	RMS amplitude	0.22±0.01	0.21±0.01	0.21±0.01*
Co-contraction	Start (ms)	123±20	138±21	135±21
	Duration (ms)	103±23	100±24	100±24
	Ratio (%)	12±3	12±3	15±3

Results are expressed as mean±SD. RMS: root mean square; SMA : supplementary motor area; SOL: soleus muscle; TA: tibialis anterior muscle; TBS : theta burst stimulation.* P<0.05 when compared to before SMA-TBS; ** P<0.05 when compared to before sham-TBS. P<0.05 when compared to sham-TBS.

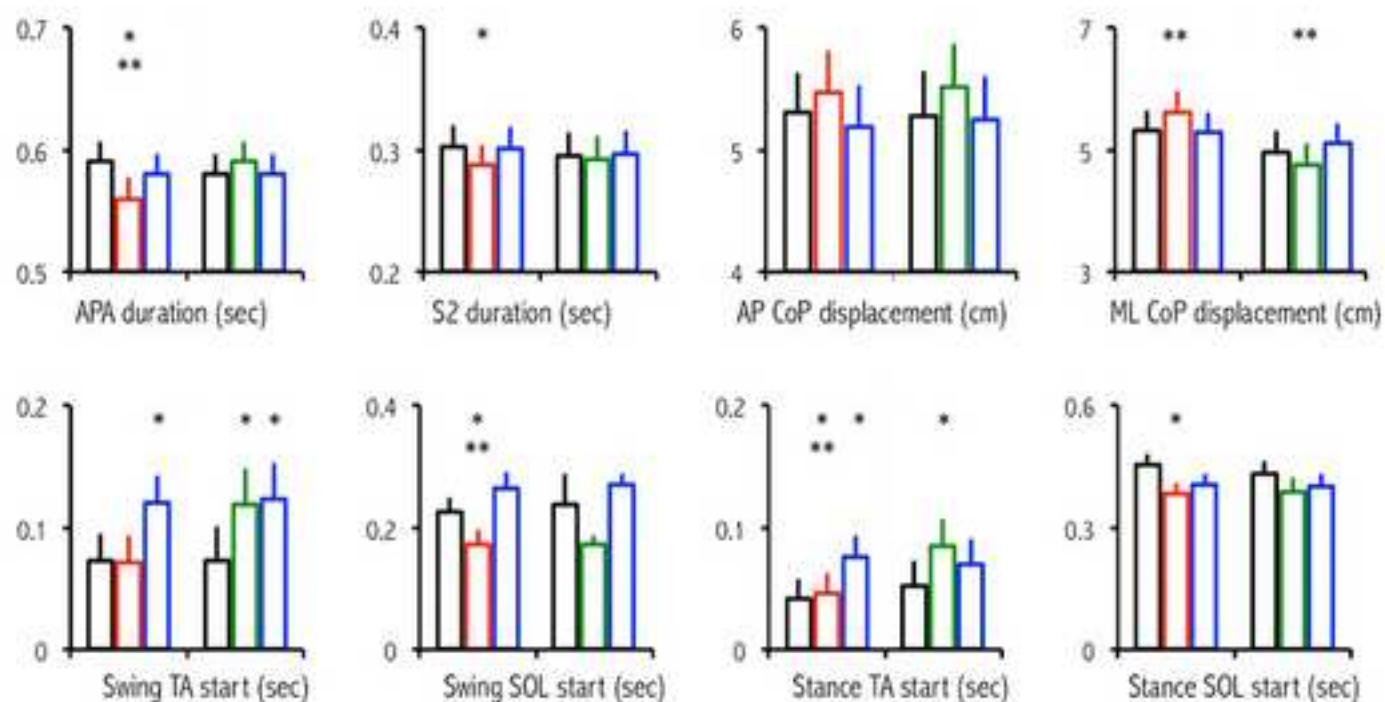
Table 4. Effects of cerebellar theta-burst stimulation on Soleus and Tibialis Anterior muscle activity during first step execution in 22 healthy subjects

		Cerebellar cTBS		
		Before TBS	CER-TBS	Sham-TBS
Swing Leg				
TA muscle	Start (ms)	55±11	46±12	50±12
	RMS amplitude	0.12±0.01	0.11±0.01**	0.14±0.01*
SOL muscle	Start (ms)	208±36	203±37	223±39
	RMS amplitude	0.02±0.01	0.03±0.01*	0.02±0.01
Co-contraction	Start (ms)	139±31	139±31	137±31
	Duration (ms)	20±8	26±9	33±9
	Ratio (%)	7±2	8±2	9±2*
Stance Leg				
TA muscle	Start (ms)	73±20	87±21	104±21
	RMS amplitude	0.08±0.01	0.10±0.01	0.09±0.01
SOL muscle	Start (ms)	56±13	50±13	59±13
	RMS amplitude	0.23±0.01	0.21±0.01	0.21±0.01*
Co-contraction	Start (ms)	106±20	110±21	123±21
	Duration (ms)	109±24	116±25	98±25
	Ratio (%)	15±3	16±3	14±3

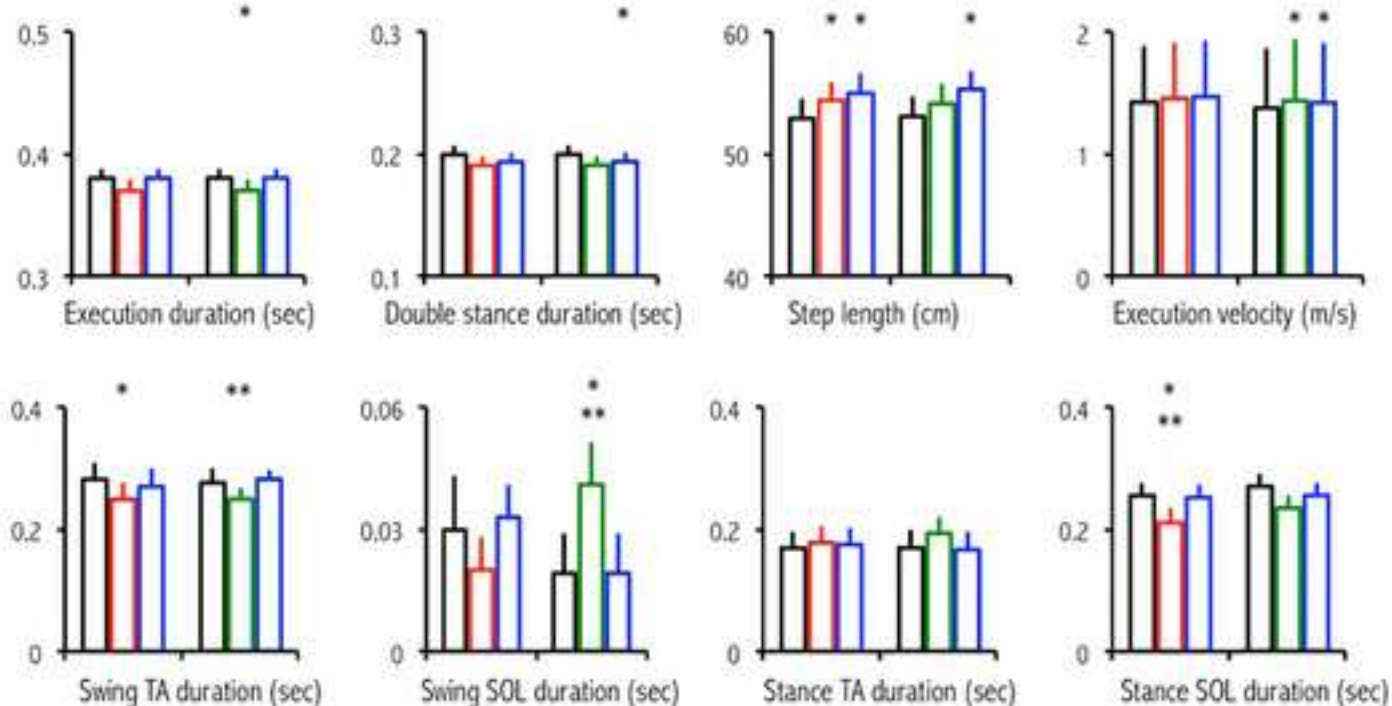
Results are expressed as mean±SD. CER: cerebellum; RMS: root mean square; SOL: soleus muscle; TA: tibialis anterior muscle; TBS : theta burst stimulation.* P<0.05 when compared to before cerebellar-TBS; ** P<0.05 when compared to before sham-TBS.



Anticipatory Postural Adjustments Phase



Execution Phase



* compared to Baseline (before stimulation)

** compared to sham stimulation