Journal of the Neurological Sciences 338 (2014) 148–155

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Brain control of volitional ankle tasks in people with chronic stroke and in healthy individuals

L.D. Beaulieu [a], H. Massé-Alarie [a], B. Brouwer [b], C. Schneider [a,c,*]

[a] Axe neurosciences du Centre de recherche du CHU de Québec, Québec, QC, Canada
[b] School of Rehabilitation Therapy, Faculty of Health Sciences, Queen's University, ONT, Canada
[c] Department of Rehabilitation, Faculty of Medicine, Université Laval, Québec, QC, Canada

ARTICLE INFO

Article history:
Received 11 September 2013
Received in revised form 4 December 2013
Accepted 23 December 2013
Available online 29 December 2013

Keywords:
Chronic stroke
Primary motor cortex
Motor evoked potential
Intracortical excitability
Central conduction time
Neural reorganization
Clinical assessment
Ankle function

ABSTRACT

This study explored the relationships between motor cortical control of ankle dorsiflexors and clinical impairments of volitional ankle dorsiflexion in people with chronic stroke. Eighteen persons with stroke and 14 controls were evaluated. Clinical tools were used to assess ankle dorsiflexion amplitude and isometric strength. Transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) tested the functional integrity of cortical circuits controlling the tibialis anterior (TA). All clinical scores and most TMS outcomes were impaired in people with chronic stroke. The lower clinical scores were related to the reduction of the strength of corticospinal projections onto spinal motoneurons. Concurrent TMS and clinical testing in chronic stroke provided original data demonstrating relationships between the integrity of cortical and corticospinal components of TA motor control and volitional ankle tasks. Our study proposes that volitional ankle mobilization in chronic stroke may be explained by the residual abnormal M1 circuits which may be responsive for rehabilitation intervention. This should be confirmed in longitudinal studies with larger samples to determine whether TMS outcomes associated with lower limb muscles are predictive of clinical changes or vice versa.

1. Introduction

Stroke, the leading cause of adult disability worldwide often results in persistent contralateral sensorimotor deficits [1]. A growing body of literature links functional brain imaging and cerebral activation patterns to the recovery of motor control [2–4]. However, in order to test the function of the primary motor cortex (M1) associated with clinical impairment, other studies combined neurophysiological tools and clinical paradigms. For example, transcranial magnetic stimulation (TMS) is a noninvasive painless method of investigating the integrity of M1 cortical and corticospinal components of volitional control of movement [4] with negligible risk when safety guidelines are followed [5]. TMS of M1 can elicit a motor evoked potential (MEP) in muscles contralateral to the stimulus [6] measurable by surface electromyography (EMG).

In stroke, most TMS studies have focused on hand function and on the relationship of its recovery to TMS outcomes at acute and subacute stages. TMS has shown a consistent decrease of M1 excitability in the lesioned hemisphere as detected by the increase of motor threshold 1–15 days post-lesion [7,8], and reduction of MEP amplitudes beyond three months post-stroke [9]. Longitudinal studies using TMS and clinical evaluation of the paretic side indicated that the presence of MEPs of large amplitudes early after stroke was predictive of better recovery of hand function [10,11], whereas higher motor thresholds correlated with a poorer recovery [11,12]. Also, the enlargement of motor cortical maps (area and volume) after rehabilitation was positively related to functional upper limb improvements on the paretic side [13,14]. Paired pulse paradigms further test the integrity of inhibitory and facilitatory circuits involved in M1 function [15,16]. In stroke, the reactivation of M1 inhibitory circuits at acute/subacute stages was observed only in those with better hand function [17]. It follows that combining TMS outcomes with clinical assessment may be useful in determining the underlying mechanisms of functional impairments between individuals at the initial stages of recovery. Conversely, data obtained at chronic stages (>6 months post-stroke) are limited and yield inconsistent results [18]. In particular, cerebral reorganization of the M1 leg representation post-stroke has been largely unexplored with TMS, mostly because MEPs are more difficult to elicit from cells at a deeper location in the interhemispheric fissure, with sub-optimal fiber orientation and less robust corticospinal projections [19]. This explains why the relationships between brain control of movement and clinical impairments on the paretic side remain largely unknown for lower limb muscles in stroke.

The present study used concurrent TMS and clinical measures to better understand the impairment of volitional ankle movement in people with chronic stroke compared to healthy counterparts and to examine the relationship between brain control of ankle dorsiflexors

* Corresponding author at: Laboratoire de neurostimulation et neurosciences cliniques, Centre de recherche du CHU de Québec, Axe neurosciences RC-9800, 2705 boulevard Laurier, Québec, QC G1V 4G2, Canada. Tel.: +1 418 525 4444.47648; fax: +1 418 654 2753.
E-mail address: Cyril.Schneider@rea.ulaval.ca (C. Schneider).

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http://dx.doi.org/10.1016/j.jns.2013.12.038

and clinical outcomes of volitional ankle dorsiflexion. The tibialis anterior (TA) muscle, volitional dorsiflexion amplitude and isometric strength were chosen because of the involvement of the corticospinal system and when impaired, can result in problematic foot drop in stroke. Basically, the TA muscle is generally responsive to TMS because its corticospinal projections onto spinal motoneurons are stronger than those for other lower limb muscles [20]. The main hypothesis was that the impairment of volitional actions at the ankle joint could be related to dysfunction of residual M1 circuits post-stroke.

2. Material and methods

2.1. Participants and study design

Eighteen subjects with chronic stroke (53 ± 13 years, Tables 1 and 2) and 14 healthy subjects (Controls, 50 ± 7 years, Table 1) were enrolled after providing informed written consent under approval of local ethics committees and the declaration of Helsinki. The inclusion criteria for those with stroke were ≥18 years old, a first unilateral stroke more than 12 months prior to enrolment, paretic ankle muscles with spasticity as reported in medical files, a CT or MRI scan taken within the last 5 years, and the ability to walk more than 10 m with or without an assistive device. The exclusion criteria for all participants were the administration of anti-spastic medication, vertebral surgery, major circulatory, respiratory or cardiac disease, neurological disease/deficit other than stroke, severe lower limb orthopedic condition, or cognitive disorder. Exclusion criteria related to TMS included a history of seizures, cardiac pacemaker and intracranial metallic implants [5]. Medical evaluation by a physician before and after the study monitored compliance with the selection criteria and any adverse effects, respectively. All testing was completed in a single session consisting of clinical tests conducted by research therapists and followed by TMS testing. Only the paretic leg in subjects with stroke and the dominant leg in controls were tested. Dominance was determined by the foot used to kick a ball or write in the sand. Testing was completed within 2–3 h including rest breaks as needed.

2.2. EMG recordings

EMG recordings of background activity during clinical measures and responses to TMS were performed using adhesive surface Ag–AgCl electrodes (Kendall MediTrace 200 Series, MyWellCare, Concord, ON, Canada) in a bipolar configuration (Biometrics-NexGen amplifiers, Gwent, UK) over the belly of TA and soleus muscles [21]. A common ground electrode was positioned on patella. Signals were bandpass-filtered (20 Hz–450 Hz) and amplified (×1500) before digitization (2 kHz). Signals were displayed in real-time and stored for online display and offline analysis (PowerLab acquisition system, LabChart-ADInstruments, Colorado Springs, CO, US).

2.3. Clinical testing

Three trials (4 s each) were averaged per variable and up to 2 supplementary trials were performed in cases of variation >2SD from the mean. The participants adopted a standardized supine position on a therapeutic table with the knee in full extension and monitored by therapists.

Range of motion and associated TA EMG. The ankle's active range of (volitional) motion in dorsiflexion (DF) was measured using an extendable-hinged goniometer (*Lafayette-Instrument*) aligned with the rotational axis. Skin markers on the fibular head, the external malleolus and on the fifth metatarsal head helped reliable positioning of the goniometer. The angle formed by the fifth metatarsal, lateral malleolus and fibular head reflected the joint position with 90° assigned a value of 0° [note that the neutral position corresponded to a negative (plantar flexor) angle]. Participants were instructed to pull their foot upwards as much as possible and were encouraged by the therapist. The root-mean square (RMS) of TA EMG activity was calculated post-hoc over a 1-s time period central to maximal value of active DF.

Isometric muscle strength and associated TA EMG. A hand-held dynamometer (*Châtillon-Instrument*) was used to measure maximal isometric strength of the ankle dorsiflexors when placed perpendicular to metatarsal heads on the dorsal surface of foot. The participants were instructed to push as hard as possible against the dynamometer with verbal encouragement. The therapist matched the strength of the maximal isometric voluntary contraction (MVC) without 'breaking' it (the 'make' test). The 'make' test yields better reliability than the 'break' test for isometric strength measurement [22] and has been shown to reliably assess maximal strength [23,24]. The root-mean square (RMS) of the TA EMG activity was calculated post-hoc over a 1-s time period central to MVC recordings duration.

2.4. TMS testing

Participants were comfortably seated in a reclining chair with their legs and arms supported. Their knees were flexed 20° from full extension and the test foot firmly strapped in an ankle-foot orthosis to ensure standard positioning across subjects. Participants were first instructed to dorsiflex the ankle three times at maximal isometric contraction (MVC) against the strap and the 15% MVC was calculated from the mean TA EMG activity and displayed as a target line on a scaled screen. During TMS testing, real-time EMG activity of TA was low-pass filtered at 2-Hz and displayed online as visual feedback on the same screen. Participants had to activate their TA to superimpose their EMG output on the target line representing the output associated with 15% MVC. This contributed to stabilize motoneuronal excitability and spinal cord output [25]. Trials in which the EMG fell outside the acceptable window (15% MVC ± 5% implemented in software) were rejected. While subjects contracted their TA, magnetic stimuli were applied using a double-cone coil (7-cm outer diameter each wing; Magstim Company Limited, Whitland, UK) optimal for activating TA M1 cells [19]. The TMS coil was positioned over M1 for the TA area that was first approximated at 1.5–2 cm lateral from the vertex using 10–20 EEG system [26] and with the long axis of the two-wing intersection pointing anteroposteriorly [25]. The position was adjusted slightly to determine the 'hot spot': the location eliciting the largest TA MEP amplitudes using the lowest TMS intensity. This approach provided the most selective activation of M1 foot area cells at the lowest threshold to elicit MEP in the contralateral ankle muscles [25,27]. Scalp locations were marked using a surgical pen to ensure reliable positioning and orientation of the coil. The active motor threshold (AMT) was determined as the stimulus intensity required to elicit at least 5 TA MEPs out of 10 trials with amplitudes ≥100 μV [25]. Test TMS at 120% AMT enabled recording and measurement of the MEP amplitude (unconditioned) and of the duration of the EMG silent period following the MEP corresponding to M1 $GABA_B$ inhibition [28]. Paired TMS (coil connected to two Magstim 200^2 monophasic stimulators) was used to test the short-interval intracortical inhibition and facilitation (SICI, SICF). In SICI, a subthreshold conditioning TMS (70% AMT, no MEP elicited) was delivered 2 ms before the test TMS at 120% AMT (see Fig. 1, raw traces) and the conditioned MEP is expressed relative to the unconditioned $MEP_{120\%AMT}$. In

Table 1
General characteristics of participants.

	Controls	Stroke
Participants (N)	14	18
Age (years ± SD)	50 ± 7	53 ± 13 [p1]
Gender (N: males/females)	6/8	7/11
Height (cm)	168.1 ± 15.3	166.1 ± 6.8 [p2]
Footedness (N: right/left)*	14/0	18/0

N = number; p1 = 0.49 (*t*-test); and p2 = 0.69 (*t* test).
* Before lesion for patients.