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Effects of transcranial magnetic stimulation during voluntary and non-voluntary stepping movements in humans

I.A. Solopova [a,*], V.A. Selionov [a], O.V. Kazennikov [a], Y.P. Ivanenko [b]

[a] Institute for Information Transmission Problems, Russian Academy of Sciences, Moscow, Russia
[b] Laboratory of Neuromotor Physiology, Santa Lucia Foundation, Rome, Italy

HIGHLIGHTS

- Air-stepping can be used as a model for investigating rhythmogenesis/CPG in humans.
- We compared voluntary and non-voluntary (vibration-induced) stepping.
- We examined MEPs in response to TMS of the motor cortex and H-reflex.
- We found greater responsiveness to central/sensory inputs during voluntary stepping.
- Findings support engagement of supraspinal motor areas in CPG-modulating therapies.

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ABSTRACT

Here, we compared motor evoked potentials (MEP) in response to transcranial magnetic stimulation of the motor cortex and the H-reflex during voluntary and vibration-induced air-stepping movements in humans. Both the MEPs (in mm biceps femoris, rectus femoris and tibialis anterior) and H-reflex (in m soleus) were significantly smaller during vibration-induced cyclic leg movements at matched amplitudes of angular motion and muscle activity. These findings highlight differences between voluntary and non-voluntary activation of the spinal pattern generator circuitry in humans, presumably due to an extra facilitatory effect of voluntary control/triggering of stepping on spinal motoneurons and interneurons. The results support the idea of active engagement of supraspinal motor areas in developing central pattern generator-modulating therapies.

1. Introduction

Although the neural mechanisms that determine the timing and pattern of muscle activity and the coordination of limb movements during locomotion reside largely in the spinal cord [1–6], the brain is of utmost importance in monitoring locomotor patterns and therefore contains information regarding central pattern generation (CPG) functioning. In addition, there is an increasing consensus that motor centers in the brain, and the motor cortex in particular, play an essential and greater role in human walking compared to other mammals [7–12]. Engagement of supraspinal motor areas may also promote plasticity and gait recovery [13]. Therefore, a better understanding of interactions between spinal and supraspinal influences on the state of CPGs may be important for developing gait rehabilitation strategies in individuals with spinal cord and brain injuries.

The spinal CPG circuitry can be activated in healthy humans by applying tonic central or peripheral sensory inputs [4,5,14]. Experimentally, the contributions of body weight and balance control to stepping movements may be excluded in a gravity neutral position in the absence of external resistance (air-stepping). It has been suggested that central or peripheral stimulations can entrain locomotor neural networks and promote gait recovery [4]. Air-stepping can be evoked in ~10–50% of healthy subjects and the degree of activation may depend on supraspinal influences and the state of the spinal cord. However, it is not clear to what extent the activation state of the spinal circuitry and its responsiveness to sensory and central inputs are similar to those during voluntary stepping.

The motor evoked potential/transcranial magnetic stimulation (MEP/TMS) technique can be used to examine corticospinal

* Corresponding author at: Laboratory of Neurobiology of Motor Control, Institute for Information Transmission Problems, Russian Academy of Science, Bolshoy Karetny 19, Moscow 127994, Russia. Tel.: +7 495 650 2895; fax: +7 495 650 0579.
E-mail address: solopova@iitp.ru (I.A. Solopova).

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excitability [11,15,16]. To test our hypothesis, we compared MEPs in response to TMS of the motor cortex during voluntary and non-voluntary air-stepping evoked by continuous muscle vibration, while the relative excitability of alpha motoneurons to excitatory inputs from Ia afferents was assessed using electrical stimulation of the tibial nerve (soleus H-reflex). Since the MEPs and the H-reflex are typically modulated during walking and often in parallel with changes in the background electromyographic (EMG) activity, we applied stimuli at different phases of the stepping cycle (using the moving leg as reference) and compared the responses at similar amplitudes of angular motion and muscle activity.

2. Methods

2.1. Experimental setup and protocols

Participants were eight healthy volunteers (males, aged from 28 to 60 years). None of the subjects had any known neurological or motor disorder. The subjects were preselected based on whether air-stepping could be entrained using muscle vibration, since inter-individual differences in responsiveness of spinal CPG to its activation have been previously reported [4,14]. In our pre-selection procedure, we also excluded the subjects that previously demonstrated frequent transitions from forward to backward air-stepping [14] in order to compare voluntary and non-voluntary cyclic movements under similar (forward stepping) conditions. The experiments were performed according to the procedures of the Ethics Committee of the Institute for Information Transmission Problems and in conformity with the declaration of Helsinki for experiments on humans. All subjects gave their written informed consent.

The experimental setup (Fig. 1A) was similar to that described in our previous studies [5,14]. To minimize the effects of gravity and external resistance, the subjects lay on their right side with the upper leg suspended to permit its unimpeded motion in the horizontal plane. The other leg was lying motionlessly. Even though we studied one-leg movements, the basic features of cyclic movements are similar for one-leg and two-legged air-stepping [5]. The suspension system consisted of a two-segment exoskeleton (0.9 kg) with low-friction rotation (due to bearing junctions) at the hip and knee joints.

Two experimental conditions were investigated. (1) Non-voluntary air-stepping: rhythmic locomotor-like leg movements were elicited by continuous quadriceps muscle vibration (40–60 Hz, ~1-mm amplitude) produced by a small DC motor with an attached eccentric weight [14]. The vibrator was fastened with a rubber belt over the quadriceps tendon of the suspended leg, about 5 cm from the superior border of the patella. Subjects were instructed to relax and not intervene with movements that might be induced by stimulation. (2) Voluntary air-stepping: the subjects were asked to produce voluntary air-stepping movements at a natural cadence.

Two separate sessions were performed on different days. In the first session, we recorded motor evoked potentials (EMG responses) in the rectus femoris (RF), biceps femoris (BF, long head), tibialis anterior (TA) and gastrocnemius lateralis (GL) muscles (of the left leg) elicited by transcranial magnetic stimulation of the motor cortex. In the second session, we recorded the soleus H-reflex during voluntary and non-voluntary air-stepping. In this protocol, we recorded EMG of the soleus (Sol) and TA muscles (since there could be an effect of antagonistic contraction on H-reflex [17]).

2.2. Data recording

The latency of vibration-elicited cyclic leg movements may vary across subjects and trials (up to several seconds, [14,18]). Once the stepping movements achieved an approximately constant amplitude (across consecutive cycles) we began data recording and the stimulation protocol. In each trial we recorded 10 s of non-voluntary air-stepping without reflex stimulation, 40–60 s with stimulation (at ~0.4 Hz, see below) and again 15 s without stimulation, so that the duration of each trial was 65–85 s (Fig. 1A, lower panel). Voluntary air-stepping was recorded analogously. In the TMS session, the duration of stimulation was 40 s and each trial was repeated 10 times (with ~1–3 min rest between the trials). In the H-reflex session, the duration of stimulation was 60 s and each trial was repeated 6 times. The total duration of the experimental session was ~2 h.

EMG activity was recorded using surface bipolar electrodes (20 Hz high-pass, BAC Electronics, Rockville, MD). Angular movements of the hip and knee joints were recorded using potentiometers attached laterally to the leg. The kinematic and EMG data were sampled at 1000 Hz and stored for subsequent analysis. The kinematic data were also used online to trigger the stimulus delivery at the desired movement phase (see below).

2.3. Responses to TMS

TMS was delivered to the right primary motor cortex corresponding to the leg using a figure-8 magnetic coil (diameter of

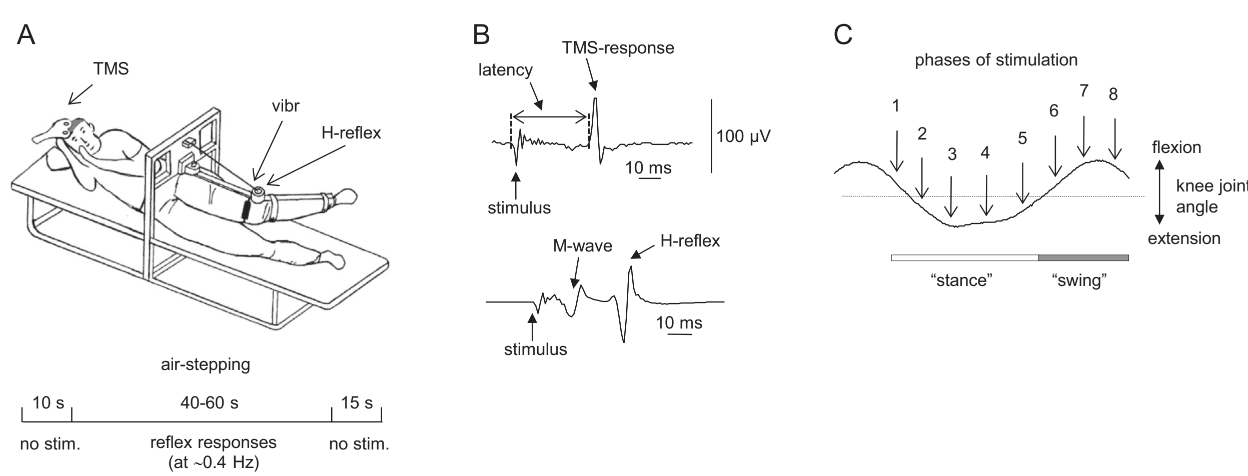

Fig. 1. Experimental setup. (A) The subject lay on her/his right side on a couch with the upper leg suspended in an exoskeleton. Experimental protocol is illustrated on the bottom: in each trial we recorded 10 s of air-stepping without reflex stimulation, 40–60 s with stimulation and again 15 s without stimulation. (B) Examples of motor responses (MEP and H-reflex). (C) Phases of stimulation.