



# Unidirectional brain to muscle connectivity reveals motor cortex control of leg muscles during stereotyped walking



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## ABSTRACT

In lower mammals, locomotion seems to be mainly regulated by subcortical and spinal networks. On the contrary, recent evidence suggests that in humans the motor cortex is also significantly engaged during complex locomotion tasks. However, a detailed understanding of cortical contribution to locomotion is still lacking especially during stereotyped activities. Here, we show that cortical motor areas finely control leg muscle activation during treadmill stereotyped walking. Using a novel technique based on a combination of Reliable Independent Component Analysis, source localization and effective connectivity, and by combining electroencephalographic (EEG) and electromyographic (EMG) recordings in able-bodied adults we were able to examine for the first time cortical activation patterns and cortico-muscular connectivity including information flow direction. Results not only provided evidence of cortical activity associated with locomotion, but demonstrated significant causal unidirectional drive from contralateral motor cortex to muscles in the swing leg. These insights overturn the traditional view that human cortex has a limited role in the control of stereotyped locomotion, and suggest useful hypotheses concerning mechanisms underlying gait under other conditions.

*One sentence summary:* Motor cortex proactively drives contralateral swing leg muscles during treadmill walking, counter to the traditional view of stereotyped human locomotion.

## 1. Introduction

Walking is a complex task that requires the coordinated and flexible activation of several muscles to meet ever-changing environmental challenges. Gait control involves integration of sensory signals and consequent adjustments in descending supraspinal motor commands and spinal neuronal circuits (Grillner, 2011). Basic locomotor patterns are mainly generated by spinal interneuronal networks that integrate descending signals with peripheral afferent signals to achieve specific locomotion schemes (Brooks, 1986; Takakusaki, 2013). Sensory afferent information contributes to corrective reflexes following sudden perturbations and may be used to adapt and update gait patterns (Nielson, 2003).

Several research groups showed in animal models strong involvement

of the cerebellum the motor cortex and the pyramidal tract of the corticospinal tract in visually-guided locomotion and precision stepping (Drew et al., 2008; Drew and Marigold, 2015; Rossignol, 2010). Other groups (Armstrong, 1988; Brown, 1911; Grillner, 1985; Jordan, 1998; Lundberg, 1979; Rossignol, 2000) have provided evidence that cortical activity is not necessary for generating the basic stereotyped locomotion patterns of most lower animals. In fact, even in the absence of any supraspinal input to the spinal cord, spinal networks have the capacity of generating the basic locomotor rhythmicity in chronic spinalized animals.

While it is known that the cortex proactively controls voluntary and precise movements and is involved only in “high-level” motor planning (e.g., gait initiation, addressing obstacles, etc.), its involvement in stereotyped tasks is only hypothesized, because of the limits of available

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techniques (Beloozerova and Sirota, 2003; Drew and Marigold, 2015; Gossard et al., 2011; Marple-Horvat and Criado, 1999).

Imaging studies based on near-infrared spectroscopy (NIRS) demonstrated that walking is bilaterally associated with activity in primary sensorimotor cortices and supplementary motor areas (Miyai et al., 2001). Studies based on functional magnetic resonance imaging (fMRI) have also supported the involvement of supraspinal structures during walking-related motor imagery tasks (Cunnington et al., 2002, 2005). These techniques lack however of the necessary high dynamic (NIRS) and portability (fMRI) required to detect intra-stride changes in brain activity during ambulation.

Electroencephalography (EEG) is the only non-invasive brain imaging modality that has the potential to achieve the required temporal resolution (Makeig et al., 2009; Menicucci et al., 2014). So far, studies using high-density EEG combined with independent component analysis (ICA) and source localization techniques have shown that electrocortical dynamics, particularly in the sensorimotor cortex, exhibits intra-stride patterns of activation and deactivation (Cevallos et al., 2015; Chéron et al., 2012; Gramann et al., 2011; Gwin et al., 2011; Severens et al., 2012). However, there are conflicting pieces of evidence as to how compromising gait-related movement artifact is to ICA analysis of neural data (Snyder et al., 2015). In particular (Nathan and Contreras-Vidal, 2015a), suggest negligible motion artifacts during walking, while (Castermans et al., 2014) raise doubts on the cortical origin of time-frequency data, time-locked to the gait cycle. In fact, gait-locked artifacts overlap in time and frequency with brain activity. Other authors such as (Kline et al., 2015) and (Oliveira et al., 2016) studied the role of artifacts on artificially-generated brain activity using head phantoms. This latest work, suggests that ICs extracted from moving heads could reliably represent the content of a stationary condition, however the stereotyped nature of movement artifacts has not been proven yet.

Very recently, Kline et al. (2016), showed within-stride modulation of cortico-cortical connectivity. However, more conclusive evidence of cortical control would require the application of a methodology similar to the one used in animal experiments, where functional connectivity between recordings of individual or populations of brain cells and motor output, has been demonstrated during motion (Halliday et al., 1995; Lemon, 1993). A similar approach has been used to reveal frequency-coherent activity between localized recordings from the motor cortex and the EMG generated during human treadmill walking (Petersen et al., 2012), but such cortico-muscular functional connectivity is not informative of the existence of a causal relationship between brain regions and muscles.

The aim is that of defining new methodological approaches to verify the existence of a true brain-to muscle link during this task. We present a methodology (see Materials and Methods) that extends gait-related time-frequency methods and enabled us to analyze simultaneous EEG and EMG recordings. We were able, by highlighting the existence of strong gait phase locked, uni-directional cortico-muscular effective connectivity, to provide evidence for the first time that cortical motor areas are responsible for temporally-precise control of leg muscle activity during stereotyped treadmill walking.

## 2. Materials and methods

### 2.1. Summary

To investigate the neural correlates of gait, the experimental set-up shown in Fig. 1 was used to simultaneously record 64-channel EEG signals and 6 lower-limb EMG signals (Tibialis Anterior – TA, Biceps Femoris – BF, Vastus Medialis – VM, bilaterally) from eleven able-bodied subjects (mean age  $30 \pm 4$  years) who walked on a treadmill at 3.5 km/h in two 10-min time blocks. Four footswitches enabled identification of the gait phase of each leg. The full EEG and EMG datasets (collected during rest and walking conditions) were first time-aligned, and merged. In the pre-processing phase we used Artifact Subspace Rejection (ASR)

(Kothe and Jung, 2015) and reliable Independent Component Analysis (ICA) (Artoni et al., 2014) to decompose continuous EEG data into maximally-independent processes. Independent Components (ICs) representing muscle, ocular and other artifacts were removed from the data. We then epoched the EEG and band-pass filtered the EMG time-locked to each gait cycle and visually inspected them for prominent artifacts. Underlying brain source signals were determined by processing scalp EEG data using source localization functions in the eConnectome Matlab toolbox (He et al., 2011). Several regions of interest (ROIs) were defined according to Brodmann Areas near the motor cortex and effective connectivity or ROIs with each muscle was estimated using the Directed Transfer Function (DTF) method. Finally, we used ROIs data to decode EMG envelopes and we confirmed the hypothesis of data stationarity during walking via multiple model ICA (AMICA) (Palmer et al., 2007b).

**Signals recording (Fig. 1).** EEG signals were recorded using a 64-channel EEG amplifier (SD MRI, Micromed S. p.A, Italy) sampling at 2048 Hz/channel and a custom signal pre-amplifying active electrode cap (actiCAP, Brain Products GmbH, Germany). The montage was chosen in accordance with the 5% International 10/20 System (Oostenveld and Praamstra, 2001). Careful scalp preparation ensured electrode impedance was below 20 k $\Omega$  in at least 95% of derivations, both at the beginning and the end of the recordings. EMG electrodes were placed according to SENIAM guidelines ([www.seniam.org](http://www.seniam.org)) on 3 muscles of each leg, namely Tibialis Anterior (TA), Vastus Medialis (VM) and Biceps Femoris (BF), which were simultaneously recorded with a wireless EMG system (BTS Free EMG 300) at a sampling rate of 1000 Hz. A common trigger was sent both to EMG and EEG acquisition systems multiple times at the beginning and end of each session to enable robust, minimum jitter in offline synchronization of both devices.

EMG data were resampled and aligned to the EEG before further preprocessing. Throughout the analysis, to avoid misalignment artifacts, EEG and EMG data were treated as a single multivariate data series. Four footswitches (two under the heel and two under the toes for redundancy), were wirelessly connected to the EMG system, recorded with the same sampling frequency (1000 Hz). These data were used to segment the gait events (Right/Left Heel Strike – LHS/RHS and Right/Left Toe Off – LTO/RTO). All recorded events were carefully inspected and data pertaining to improperly-segmented gait cycles were removed.

**Special precautions (Fig. 1).** EEG artifacts in general can be classified as physiological or non-physiological. The former include e.g., ocular movement artifacts (eye blinks, lateral and vertical eye movement), muscle (e.g. jaw clenching, neck muscle contraction), heart. The latter include e.g., line noise, electrode detachment, cable movement interference etc. The walking task increases the influence of artifacts by introducing eye bounce (i.e. eye stabilization while fixing a point), cable movements, increased neck and facial muscle activation, increased non-stationarity of line noise interference (as the subject moves into space) and electrode/gel coupling shifts. The difficulty in removing Mobi artifacts is mainly due to the coupling of eye bounce, neck muscle contractions and mechanical artifacts to the walking task itself. While there is no definite way to exclude artifact interference as yet, during the recording sessions particular precautions were taken so as to avoid movement artifacts and other confounding effects as far as possible.

As shown in Fig. 1, the Acticap Control Box (ACB) receiving the cables departing from the EEG cap was securely fastened to the subject's waist. The ACB was connected to the EEG amplifier via a 2-m cable, which was fastened to the hand rails of the treadmill thus minimizing cable movements. The use of active pre-amplified electrodes also helped minimizing cable movement interference. Before each session, we confirmed the lack of any EEG-EMG interference and that the experimental set-up was clear of recording-impairing line noise. This was done by visual inspection of real time data before acquisition and by checking the effect of notch filters in the Micromed recording interface.

A preliminary 3-min walking period allowed acclimation to experimental conditions. Subjects were asked to fix their gaze to a point at eye level in front of them, and were asked to relax throughout the experiment

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