Re-thinking the role of motor cortex: Context-sensitive motor outputs?

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ABSTRACT

The standard account of motor control considers descending outputs from primary motor cortex (M1) as motor commands and efference copy. This account has been challenged recently by an alternative formulation in terms of active inference: M1 is considered as part of a sensorimotor hierarchy providing top–down proprioceptive predictions. The key difference between these accounts is that predictions are sensitive to the current proprioceptive context, whereas efference copy is not. Using functional electric stimulation to experimentally manipulate proprioception during voluntary movement in healthy human subjects, we assessed the evidence for context sensitive output from M1. Dynamic causal modeling of functional magnetic resonance imaging responses showed that FES altered proprioception increased the influence of M1 on primary somatosensory cortex (S1). These results disambiguate competing accounts of motor control, provide some insight into the synaptic mechanisms of sensory attenuation and may speak to potential mechanisms of action of FES in promoting motor learning in neurorehabilitation.

Introduction

The execution of a voluntary movement requires the brain to integrate both the volitional intention to execute a given movement and knowledge about the state of the body (i.e. integrate sensory feedback). In humans, changing proprioceptive input influences motor cortex excitability (Léonard et al., 2013; Rosenkranz and Rothwell, 2012). Conversely, the response of somatosensory cortex neurons to proprioception is modified by the nature of the motor task (Chapman and Ageranioti-Bélanger, 1991; Cohen et al., 1994). Currently, motor control theory proposes that internal models generate motor commands that are sent to the periphery to produce the desired movement. In this account, internal models combine sensory inputs, prior knowledge and volitional intention to produce motor commands (Genewein and Braun, 2012). Forward models are thought to be responsible for predicting the sensory consequences of action, given the motor commands (Wolpert and Ghahramani, 2000; Wolpert and Kawato, 1998). It has been recently suggested that the updating of the internal model follows Bayesian principles (Genewein and Braun, 2012), combining a priori probability distributions and known levels of uncertainty of sensory feedback with sensorial consequences (Körding and Wolpert, 2004).

However, an alternative account of motor control has been proposed, drawing on the hierarchical generative models used in perceptual and active inference (Friston et al., 2009). In this account, motor cortex sends descending predictions of the sensory consequences of movement rather than the driving commands specified by optimal motor control. Here, proprioceptive prediction errors are generated at the level of the spinal cord and result in activation of motor neurons through classical reflex arcs. Although there are commonalities between the two accounts, the key difference is that under optimal control, given a same task and a same state of the system, motor signals are context-independent commands, whereas under active inference they are context-dependent predictions (Adams et al., 2012). In this study, we aim to disambiguate these accounts of motor control by experimentally manipulating both volitional movement and proprioception (i.e.

context) and examining the effects on the interactions between cortical motor and sensory areas. In other words, we define an experimental protocol that only alters proprioception in different conditions while maintaining constant movement kinematics to reveal which areas and which connections are sensible to proprioception alteration. Our prediction was that modification of sensory feedback (reafference signals) during motor task execution will influence descending information from primary motor cortex (M1) — as predicted by the active inference account of motor control.

We used functional electrical stimulation (FES) to provide externally driven proprioceptive information during movement execution — in other words, to experimentally alter reafference. FES delivered to a mixed nerve trunk (i.e. nerve that contains both efferent motor and afferent sensory fibers) will synchronously depolarize motor and sensory axons that are bundled together, eliciting muscle contraction through two pathways. The first (direct descending pathway) conveys signals along the efferent motor fibers that generate muscle contraction by direct motoneuron depolarization. The second (indirect ascending pathway) communicates signals via the afferent sensory fibers (Collins, 2007) that code proprioceptive signals from muscle spindles, Golgi tendon organs and cutaneous receptors (Burke et al., 1983), but in particular Ia fibers responsible for muscle spindle information (Leis et al., 1995). This second pathway produces muscle contractions through a central mechanism, providing excitatory synaptic input to spinal neurons that recruit motor units in the natural order (Bergquist et al., 2011). Therefore, the proprioceptive signal elicited by the sensory fiber stimulation creates the impression that the muscle is extended (i.e. muscle spindles discharge), and leads to firing of the motor neurons in order to produce a contraction. During FES, it has been demonstrated that this information can be useful at the level of the spinal cord, inducing a reinforcement of the muscle contraction through the myotatic reflex circuit, however few notions about altered proprioceptive information sent up to the cortex are available in the literature.

Our aim in this study was therefore to use FES during functional magnetic resonance imaging (fMRI) to investigate (i) where in the human brain altered proprioception information interacts with the intentional movement and (ii) how coupling or directed (effective) connectivity between these brain regions is influenced by altered proprioception. In particular, we were interested in the effect of altered proprioception on efferent signals from the primary motor cortex in order to disambiguate between two theoretical accounts of motor control.

Methods

Participants

Experiments were conducted with approval from the Villa Beretta Rehabilitation Centre ethics committee and all subjects gave informed written consent. Seventeen healthy volunteers (9 female, 8 male) with no neurological or orthopedic impairment were studied (mean age 36 ± 14 years, range 22–61).

Experimental set-up

The experimental set-up was comprised of a 1.5 T MRI scanner (GE Cv/I™), a motion capture system (Smart µg™; BTS) and an electrical stimulator (RehaStim proTM; HASOMED GmbH), as previously described and validated (Casellato et al., 2010; Gandolla et al., 2011).

fMRI task design

A 2 × 2 event-related fMRI design, with volitional intention [V: with the levels volitional and passive] and FES [F: with the levels present and absent] factors was performed using right ankle dorsiflexion (ADF). During a continuous 10 minute scanning session, subjects performed 20 alternate 9 s OFF and 21 s ON blocks. The 4 conditions that constituted our factorial design were performed during the ON blocks in a semi-randomized order: (i) FV = FES-induced ADF concurrently with voluntary movement by the subject; (ii) FP = FES-induced ADF, while the subject remains relaxed; (iii) V = voluntary ADF; (iv) P = passive dorsiflexion (by the experimenter) of the subject's ankle. The subjects were specifically instructed to remain completely relaxed during FP and P conditions and to equally voluntarily contribute during V and FV conditions. The dorsiflexions were paced every 3.5 s (for 6 repetitions) with an auditory cue. The auditory cues were presented through an earphone. Prior to scanning, subjects practiced the protocol until comfortable with the task; the experimenter was assisting the training to check the correct execution of the protocol. All subjects were free to choose the amplitude of their active movement to preclude fatigue. The experimenter moved the ankle to match to the movements during volitional dorsiflexion. Subjects were instructed to keep eyes closed and head movements were minimized with rubber pads and straps. To ensure minimum transmission of movements to the head, knees were bent with the subject's legs lying on a pillow.

FES stimulation paradigm

Functional electrical stimulation was applied to the peroneal nerve through superficial self-adhesive electrodes, with biphasic balanced current pulses at 20 Hz fixed frequency. The pulse width had a trapezoidal profile (maximum pulse width 400 µs) and the current amplitude was set subject by subject so as to reproduce the same movement amplitudes as during voluntary movements, within the tolerance threshold. Current amplitude and pulse width were kept the same for both FP and FV conditions.

Data acquisition

A GE Cv/I system, operating at 1.5 T was used to acquire both T1-weigthed anatomical images (0.94 × 0.94 × 4 mm voxels) and T2*-weighted MRI transverse echo-planar images (1.8 × 1.8 × 4 mm voxels, TE = 50 ms) with blood oxygenation level dependent contrast. Each echoplanar image comprised 22 contiguous axial slices, positioned to cover the temporo-parietal and occipital lobes, with an effective repetition time of 3 s per volume. Due to technical reasons, it was not possible to acquire the cerebellum. The first six volumes were discarded to allow for T1 equilibration effects. A total of 200 brain volumes were acquired in a single run lasting 10 min.

Kinematic measures and analysis

3D trajectories of retro-reflective markers were acquired to measure the ankle angle during fMRI acquisitions and to determine the movement onset for event-related fMRI time series analysis. Two separate acquisition sessions were performed. The first was a static acquisition performed before the scanning, but while lying in the scanner, to estimate the coordinates of the medial and lateral malleoli for both lower limbs. During the static acquisition, a plate with 3 markers was placed on each tibia and 4 sticks with two markers each were placed on the four malleoli (Fig. 1, panel A). The relative positions of the malleoli with respect to the plates (i.e. left and right plates) were computed and the transformation matrices were estimated under the assumption that the tibia and malleoli were rigidly connected. The second acquisition, dynamic acquisition, was performed during the fMRI scanning. Only the two plates on the tibia were used to estimate the tibia 3D position and the malleoli. Four additional markers were placed over the four metacarpi (Fig. 1, panel B). In this configuration, markers were always visible during ADF for all different conditions. The sampling frequency was set at 120 Hz. The synchronization between the kinematic measures and the fMRI acquisitions was implemented using a further