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Centre-surround organization of fast sensorimotor integration in human motor hand area

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ABSTRACT

Using the short-latency afferent inhibition (SAI) paradigm, transcranial magnetic stimulation (TMS) of the primary motor hand area ($M1_{HAND}$) can probe how sensory input from limbs modulates corticomotor output in humans. Here we applied a novel TMS mapping approach to chart the spatial representation of SAI in human hand-knob. We hypothesized SAI is somatotopically expressed in $M1_{HAND}$ depending on both the site of peripheral electrical nerve stimulation and the cortical spot targeted by TMS within $M1_{HAND}$. The left index or little finger was stimulated 23 ms before focal single-pulse TMS of the right $M1_{HAND}$. Using frameless stereotaxy, we applied biphasic-TMS pulses at seven stimulation positions above right $M1_{HAND}$ and recorded the motor evoked potentials (MEPs) from relaxed left first-dorsal-interosseous (FDI) and abductor-digiti-minimi (ADM) muscles. Homotopic stimulation of the finger close to the muscle targeted by TMS revealed a somatotopic expression of afferent inhibition matching the somatotopic representation of unconditioned MEPs (homotopic SAI). Conversely, heterotopic stimulation of a finger distant to the muscle targeted by TMS induced short-latency afferent facilitation (SAF) of MEPs in $M1_{HAND}$. Like homotopic SAI, heterotopic SAF was somatotopically expressed in $M1_{HAND}$. Together, the results provide first-time evidence that fast sensorimotor integration involves centre-inhibition and surround-facilitation in human $M1_{HAND}$.

1. Introduction

Humans have the capacity to acquire a large repertoire of fine motor skills, which require the flexible integration of sensory signals into motor commands. Such integration takes place in the primary sensorimotor cortex. The primary somatosensory cortex (S1) and primary motor cortex (M1) are commonly considered to be functionally segregated regions with S1 processing sensory input and M1 encoding motor output (Sanes and Donoghue, 2000). However, recent lines of research showed that both, M1 and S1 jointly contribute to sensory and motor aspects of motor control (Hatsopoulos and Suminski, 2011). In animals, invasive recordings of cortical activity showed that M1 directly receives somatosensory input enabling highly flexible, context-dependent encoding of movement kinematics (Balzamo et al., 2004; Churchland and Shenoy, 2007; Ferezou et al., 2007; Hatsopoulos et al., 2007). Conversely, S1 actively participates in motor control, for instance driving whisker retraction in mice (Matyas et al., 2010; Petersen, 2014).

Influential concepts of sensorimotor integration stress an active influence of cortical sensory input on motor output and vice versa. Somatosensory inputs inform both, reflexive and volitional actions (Friston and Kiebel, 2009; Friston et al., 2009; Hommel, 2009). This comprises bodily feedback generated by the movement itself and somatosensory input signalling the consequence of a movement, for instance the haptic experience when manipulating an object. Conversely, motor output impacts on perception. Reciprocal sensorimotor interactions in the sensory-motor hand area ($SM1_{HAND}$) support cooperative interactions

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Abbreviations

SAI	short-latency afferent inhibition
SAF	short-latency afferent facilitation
$M1_{HAND}$	primary motor hand area
FDI	first dorsal interosseous muscle
ADM	abductor digiti minimi muscle
PT	perceptual threshold
MCV	maximum voluntary contraction
AUC	area under the curve
WMP	weighted mean position

between associated sensory and motor events (Desmurget and Sirigu, 2015). Yet reciprocal sensorimotor interactions might also have "antagonistic" properties, causing active inhibition of sensorimotor events that lack contingent association. Indeed, the human $M1_{HAND}$ expresses an inhibitory activation pattern around the central core of excitatory activation (i.e. centre-surround structure) which counteracts non-contingent mappings between sensory and motor events (Beck and Hallett, 2011). Surround inhibition has also been demonstrated in the S1 with the reciprocal inhibition of the somatosensory evoked potential amplitude evoked by median and ulnar nerve stimulation (Tinazzi et al., 2000). Surround inhibition mechanism in S1, resulting in a centre-surround organization, is thought to help sharpen sensory perceptions (Beck and Hallett, 2011). While sensorimotor synergies are theoretically well motivated, in vivo studies of these synergies in action in human $SM1_{HAND}$ remain scarce.

Intracortical sensorimotor interactions can be probed using the short-latency afferent inhibition (SAI) paradigm (Tokimura et al., 2000). The amplitude of a motor evoked potential (MEP), induced by transcranial magnetic simulation (TMS) of $M1_{HAND}$, is reduced by a peripheral electrical stimulus applied to a peripheral nerve of the contralateral hand 20–28 ms before the TMS pulse. Pharmacological TMS studies have shown that SAI exerts its inhibitory effects on the corticospinal neurons through the GABA-ergic interneurons in $M1_{HAND}$ (Di Lazzaro et al., 2005a, b; Di Lazzaro et al., 2005a, b; Di Lazzaro and Ziemann, 2013). SAI is also a marker of cortical cholinergic activity, because anticholinergic drugs reduces the magnitude of SAI (Di Lazzaro et al., 2000). Further, patients with Alzheimer's disease show an attenuation of SAI, and the cholinesterase inhibitor rivastigmine can restore SAI (Di Lazzaro et al., 2004).

We recently introduced a novel mapping approach of muscle-specific representations in the $M1_{HAND}$ which aligns the position and orientation of the TMS coil to the individual shape of the central sulcus with the help of stereotactic neuronavigation (Raffin et al., 2015). Our sulcus-shape based mapping approach takes into account the individual curvature of the precentral knob that forms the human hand area (Yousry et al., 1997). In this study, we employed sulcus-shape based cortical mapping to examine how the human $M1_{HAND}$ integrates sensory and motor signals. Using cutaneous electrical nerve stimulation, previous SAI studies showed stronger SAI when the electrical conditioning stimulus was applied to a digit located near the target muscle (homotopic stimulation) compared to digit stimulation distant from the target muscle (heterotopic stimulation) (Classen et al., 2000; Di Lazzaro et al., 2005a, b; Tamburin et al., 2001). Building on these work, we tested the hypotheses that fast sensorimotor integration at the cortical level is mediated by topographically specific interactions, showing a centre-surround organization. We predicted that cutaneous electrical digit stimulation concurrently triggers homotopic "centre" representation of SAI and heterotopic "surround" representation of short-latency afferent facilitation (SAF) in the human $M1_{HAND}$. Critically, we expected that the concurrently expressed representations of SAI and SAF display distinct spatial profiles, which match the muscle-specific somatotopy in $M1_{HAND}$ (Experiment 1). Based on previous SAI studies (Classen et al., 2000), we further anticipated that this centre-surround organization of sensorimotor integration in $M1_{HAND}$ depends on the sensorimotor state. In that study, tonic contraction attenuated SAI, suggesting that the short-latency afferent modulation as probed by the SAI paradigm is most prominent when afferents are stimulated in a "resting" motor state. We therefore hypothesized that selective pre-activation of the homotopic muscle will abolish surround facilitation (SAF) in the relaxed heterotopic muscle. Likewise, we anticipated that selective pre-activation of the heterotopic muscle will abolish homotopic inhibition (SAI) in the relaxed homotopic muscle.

2. Materials and methods

2.1. Participants

Fourteen healthy volunteers (mean age: 27.8 ± 1.7 SE, 5 women) participated in the first experiment. Ten subjects also participated in the second experiment (mean age: 28.7 ± 2.0 SE, 4 women). All participants were right handed as assessed by the Edinburgh handedness inventory (Oldfield, 1971) and had no history of neurological or psychiatric disorders. All subjects were screened for contraindications to TMS (Rossi et al., 2009). They all gave written informed consent to the experimental procedures. The study complied with the Helsinki declaration on human experimentation and was approved by the Ethics Committee of the Capital Region of Denmark (H-15000551).

2.2. Shape-based neuronavigated TMS of the primary motor cortex

On the same day of the TMS experiment, participants underwent structural high-resolution magnetic resonance imaging (MRI) of the whole brain at 3-T (Verio, Siemens, Erlangen, Germany) to reconstruct individual brain surface for mapping. Structural MRI employed a three-dimensional, T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence consisting of 192 sagittal slices with 1 mm^3 isotropic voxel resolution (TR/TE = 2 300/2.98 ms, TI = 1100 ms; 256 × 256 matrix, flip angle 9°).

For shape-based TMS mapping, participants were seated comfortably in a chair and the TMS coil position was continuously monitored by a frameless neuronavigation system (Localite, Sankt Augustin, Germany). The brain surface was automatically reconstructed from the T1-weighted images using neuronavigation software (Localite, Sankt Augustin, Germany). The root mean square of difference between the co-registered anatomical landmarks estimated by the neuronavigation software was set below 2 mm for each subject to maintain positioning accuracy all along the experiment.

TMS target locations in the precentral gyrus were marked prior to the experiment on the segmented brain of each subject. The right $M1_{HAND}$ was identified by a trained investigator (RD) using the characteristic knob-like shape of the sulcus ("hand knob") as anatomic landmark (Yousry et al., 1997). The investigator placed seven targets in the posterior part of the crown of the precentral gyrus within the $M1_{HAND}$. The seven M1-targets matched the curvature of the hand knob, forming a line of equidistant targets every 10 mm. Target 4 corresponded to the centre of the "hand knob" (Fig. 1A). For each target, coil orientation was adjusted to produce a current direction perpendicular to the central sulcus. The individual coil positioning parameters were stored in the neuronavigation software. Table 1 reports the MNI normalized mean coordinates provided by the neuronavigation system.

2.3. Surface electromyography (EMG)

We recorded the electrical muscle activity of the left first dorsal interosseus (FDI) and abductor digiti minimi (ADM) muscle with surface electrodes (Ambu Neuroline 700, Ballerup, Denmark) arranged in a