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Evidence for sustained cortical involvement in peripheral stretch reflex during the full long latency reflex period

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HIGHLIGHTS

- Integration of TMS and mechanically induced reflexes at high temporal precision.
- TMS application controlled for individual threshold and motor conduction time.
- Augmentation of EMG responses 60–90 ms after stretch onset by subthreshold TMS.
- Sustained cortical–peripheral signal integration only during the long latency reflex.

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ABSTRACT

Adaptation of reflexes to environment and task at hand is a key mechanism in optimal motor control, possibly regulated by the cortex. In order to locate the corticospinal integration, i.e. spinal or supraspinal, and to study the critical temporal window of reflex adaptation, we combined transcranial magnetic stimulation (TMS) and upper extremity muscle stretch reflexes at high temporal precision. In twelve participants (age 49 ± 13 years, eight male), afferent signals were evoked by 40 ms ramp and subsequent hold stretches of the *m. flexor carpi radialis* (FCR). Motor conduction delays (TMS time of arrival at the muscle) and TMS-motor threshold were individually assessed. Subsequently TMS pulses at 96% of active motor threshold were applied with a resolution of 5–10 ms between 10 ms before and 120 ms after onset of series of FCR stretches. Controlled for the individually assessed motor conduction delay, subthreshold TMS was found to significantly augment EMG responses between 60 and 90 ms after stretch onset. This sensitive temporal window suggests a cortical integration consistent with a long latency reflex period rather than a spinal integration consistent with a short latency reflex period. The potential cortical role in reflex adaptation extends over the full long latency reflex period, suggesting adaptive mechanisms beyond reflex onset.

1. Introduction

Adaptation of muscle stretch reflexes to environmental conditions and tasks at hand [1] plays a key role in motor control. Impaired adaptive capacity may contribute to movement disorders after e.g. stroke [2]. Adaptation of reflexes was found to depend on instruction (e.g. [3]) and behavioural [4] or environmental constraints [5]. Optimal control theory suggests reflexes to be context dependent, with possibility for the central nervous system to instantaneously adapt peripheral reflexes [6]. Location of cortico-spinal integration and subsequent temporal delay of cortical efferent relative to spinal afferent signals determine temporal constraints for optimal control.

Reflex activity can be assessed by electromyography (EMG) during ramp-and-hold muscle stretches, yielding a short (20–50 ms after stretch onset) and a long latency response (between 55 and 100 ms) [7]. Within the long latency response (LLR), contribution

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of sensory afferent and cortical efferent signal integration via a transcortical pathway has been proposed for a lower leg muscle [8]. Evidence for a cortical contribution evolved from LLR mediation in the upper limb by task instruction [9] and emerging bilateral stretch reflexes when a stretch is applied on one side of the body in participants with congenital mirror movements [10]. The involvement of a cortical pathway is limited by neural conduction times and cortical processing delay. Taking into account earlier research into conduction times of upper extremity muscles (e.g. wrist), cortical involvement might be present from 50 to 60 ms after stretch onset and onwards: 25–30 ms efferent conduction [11,12]; 10 ms cortical processing [13] and 15–20 ms afferent (motor) conduction [14].

Cortical efferent signals can be elicited by suprathreshold transcranial magnetic stimulation (TMS). When administered to the motor cortex, stimulation results in a motor evoked potential (MEP) in a target muscle as observed in the EMG. Combined with stretch reflexes, suprathreshold TMS was found to facilitate the long but not short latency response [14–17] showing that cortical involvement in stretch reflexes is likely.

Subthreshold TMS does not elicit a MEP but may inhibit or facilitate the excitability of the spinal motoneuron pool dependent on the stimulation intensity [18,19]. Suppression of voluntary motor activity in hand and arm muscles by subthreshold TMS demonstrated direct modulation of motor output [20], whereas also facilitation of H-reflexes has been found [21]. In line with these findings Van Doornik et al. [22] reported inhibition of lower extremity LLR when subthreshold TMS was administered 55–85 ms prior to reflex onset. In contrast, facilitation of upper extremity reflexes was reported when subthreshold TMS pulses were timed at the onset of the LLR [16]. This seemingly contradicting finding might be a result of greater cortical involvement in mediating control of upper extremity muscles [23], but might also be a result of substantial inter-subject variability. Whilst there is sufficient evidence to support cortical control of the long latency stretch reflex it is unknown if this effect is momentary or exceeds the time of afferent input from the periphery.

To further explore mechanisms of cortical control over peripheral reflex activity we quantified the effects of precisely timed subthreshold TMS pulses with respect to ramp-and-hold wrist extensions on EMG activity of the m. flexor carpi radialis. Subthreshold stimulation allows to determine inhibitory or facilitatory effects of the cortical efferents on the reflex evoked afferent signal, showing either suppressing or augmenting involvement of the cortex during the induced reflexive activity. From the existing evidence we expect effects of subthreshold TMS in the time window of the long latency reflexes as evidence for instantaneous integration of cortical efferent signals with spinal afferent signals by a cortico-spinal loop.

2. Methods

2.1. Participants

In twelve participants (mean age 49 ± 13 years, range 23–65, eight male) TMS effects were tested in the long-latency period of the stretch reflex. In a subgroup of five participants (mean age 46 ± 13, range 23–65, all male) TMS involvement in an extended time range was additionally tested. Prior to the experiments, eligibility to participate in TMS studies was checked using a questionnaire (based on [24]) and participants provided written informed consent. The study was performed at the Laboratory for Kinematics and Neuromechanics at the Leiden University Medical Center and was approved by the accredited local Medical Research Ethics Committee according to the Medical Research Involving Human Subjects Act.

2.2. Stretch reflexes

A wrist manipulator [25] rotated the wrist via a handhold handle. The applied angular ramp-and-hold (R&H) extensions to the wrist effectively stretched the flexor carpi radialis (FCR) muscle. Participants were seated in a chair with their head supported, holding the manipulator handle with their right hand while the lower arm was fixed. Wrist torque was measured by a force transducer mounted in the handle. A monitor in front of the subject provided visual feedback of the applied torque level (2 Hz low-pass filtered).

2.3. Transcranial magnetic stimulation (TMS)

Stimuli to the motor cortex were delivered using a Magstim Rapid^2 system (Magstim Co, Whitland, UK) with a flat figure-8 coil (70 mm individual wing diameter). Relative coil position was monitored with an optical measurement system (Polaris Spectra, NDI) using reflective markers and neuro-navigation software (ANT ASA 4.7.3, ANT, Enschede, NL). The coil was placed tangentially to the skull with the handle pointing backwards at an angle of approximately 45° from the mid sagittal plane of the head.

2.4. Muscle activity recordings and data acquisition

EMG activity of the FCR was recorded using a flexible surface grid of four by eight electrodes with an inter-electrode distance of 4 mm (TMSi, Enschede, The Netherlands). The grid was placed in line with the longitudinal axis of the muscle at approximately 1/3 of arm length from the humerus at the muscle belly. By averaging three consecutive electrodes perpendicular to the longitudinal axis of the FCR at third and at sixth electrode rows of the EMG grid, a mimicked bipolar configuration with interelectrode distance of 12 mm and a bar length of 12 mm [2,29] was reconstructed off-line. In order to test if the results depended on the position of the chosen 'bars', combinations of bars at rows 2 and 5, and 4 and 7 were calculated as well. EMG, angle and torque of the wrist manipulator were synchronously recorded at 2000 Hz (Porti7 system, TMSi, Enschede, The Netherlands). Prior to sampling, the EMG channels were low-pass filtered at 540 Hz in the Porti7 system to prevent aliasing. Data from 200 ms prior to, and 500 ms after stretch onset, or TMS pulse for TMS initialisation, were stored.

2.5. Measurement protocol

2.5.1. TMS initialisation

TMS hotspot was determined by stimulating the motor cortex and visually inspecting the MEP peak-to-peak value while participants remained at rest. Active motor threshold (AMT) was defined by gradually reducing stimulation intensity starting at 75% of maximum stimulator output until 5 out of 10 stimuli elicited a MEP with peak-to-peak amplitude >200 μV in the EMG [26], while the participants were instructed to hold 10% of their pre-determined maximum voluntary flexion torque (MVT). Motor conduction delay was defined as the time between TMS application and MEP onset, determined by the first moment the EMG response exceeded three times standard deviation of background EMG (determined as mean EMG amplitude 180–20 ms before stimulation).

2.5.2. Combined TMS and stretch reflexes

Ramp-and-hold stretches with a stretch duration of 40 ms and a velocity of 1.5 rad/s were combined with subthreshold TMS (subTMS). A stretch duration of 40 ms was chosen to be below the expected saturation level of short latency response and to allow for