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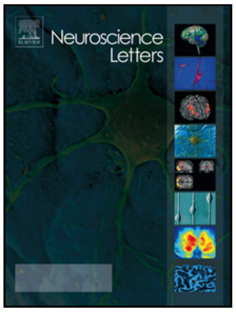

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Evidence for sustained cortical involvement in peripheral stretch reflex during the full long latency reflex period

Short: Sustained cortical involvement in 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 to 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.

Keywords: stretch reflex, cortical involvement, transcranial magnetic stimulation

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 55-100 ms) [7]. Within the long latency response (LLR), contribution 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 50-60 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.

Methods

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.

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 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).

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.

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 four millimetre (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.

Measurement protocol

<u>1. TMS initialisation.</u> 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 > 200μV 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).

<u>2. Combined TMS & stretch reflexes</u>. 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 both inhibition and facilitation of the response [27-29]. During all trials participants were instructed to apply a wrist flexion torque of 10% MVT. Automated wrist extensions were applied when flexion torque was within ± 2% of the target torque level for at least one second to ensure stable background EMG at stretch onset. Participants were instructed to let go (and not to respond to) the stretch perturbation whenever it occurred. Subthreshold stimulation intensity was set to 96% AMT to adopt the highest intensity relative to motor threshold at which no MEP could be evoked, whilst ensuring the highest sensitivity to any changes along the corticospinal pathway. Magnetic stimuli were timed to arrive at the FCR within a range from 35 to 80 ms after stretch onset (T_{MEP}) with 5 ms intervals. T_{MEP} was adjusted for the aforementioned MEP latency between motor cortex and FCR by subtraction of the determined individual motor conduction delay. Combined trials were alternated with TMS-only and stretch-only trials. Each condition was applied ten times, resulting in a total of 120 trials. All trials were applied in pseudo-random order in sets of 20 with breaks of one minute in between.

In five out of twelve participants the experiment was repeated at a different day but with a longer T_{MEP} ranging from 10 ms before to 120 ms after stretch onset with 10 ms intervals.

Data processing

All data processing was done within Matlab (version R2007B, The Mathworks Inc, Natick, USA). The bipolar EMG data were high-pass filtered (20 Hz, recursive third-order Butterworth) per trial to remove movement artefacts, rectified and subsequently averaged over the 10 repetitions. Averaged EMG was low-pass filtered (200 Hz, third-order Butterworth) before normalisation to defined background activity.

Normalised EMG from stretch-only trials was subtracted from the combined TMS-stretch trials within 20 ms after T_{MEP} to obtain a difference curve. The integrated difference (area under the curve) was defined as the main outcome parameter.

Statistical analysis

Effect of subTMS on EMG integrated difference was tested using a linear mixed model with compound symmetry covariance matrix [30] and T_{MEP} as factor (alpha = .05, SPSS version 20). The EMG difference value (main outcome parameter) per T_{MEP} condition was tested to differ from zero level obtained from the stretch-only trials by Bonferroni post-hoc testing.

SubTMS-only trials were tested on presence of a MEP by comparing root mean square (RMS) values of background EMG activity (180-20 ms before stimulus) with EMG activity within 5-45 ms after TMS application using a paired t-test. Difference between MVT before and after experiment was assessed with a paired t-test.

Results

Eleven participants were included in the data analysis. For one participant the experiment was aborted as the AMT was too high (> 80% of stimulator output).

General overview

MVT before (11.9 Nm (SD 4.2)) and after (12.6 Nm (SD 4.6)) the experiment was not significantly different ($t = 1.6$, $p = .14$) indicating it is unlikely that fatigue played a role. The AMT ranged from 37% to 63% of stimulator output. The MEP latency ranged between 16 and 21 ms. Participants in both experimental sessions showed no intra-individual differences in AMT and MEP latency.

Effects of subthreshold TMS on stretch reflex

Outcome parameters did not depend on the reconstructed bar electrode configuration. Comparable results were observed for different locations on the muscle and inter-electrode distances.

The stretch-only trials showed a distinguishable short and long latency reflex component. In the TMS only trials, no effect of subTMS on the EMG was observed ($t = 1.1$, $p = 0.296$). We confirmed the facilitating effect of suprathreshold TMS as found previously [16, 17] on the short and long latency reflex. The effect of subTMS on the stretch reflexes compared to stretch-only trials is shown in Figure 1. An augmentation of the stretch reflex EMG response due to subTMS compared to the stretch-only condition was found for both the main experiment ($F = 5.993$, $p < .001$) and the additional experiment (extended T_{MEP} range: $F = 3.369$, $p = .001$). Post-hoc analysis indicated a significant difference between stretch-only and combined trials at T_{MEP} of 60 to 90 ms. Figure 2 summarises the difference values from 10 ms before to 120 ms after stretch onset. The difference values are plotted with standard error bars, showing significant stretch reflex augmentation in time window between 60 and 90 ms after stretch onset for both experimental sessions (dark bars: short range; light bars: long range experiment), and relative to the stretch reflex profile plotted in the background.

Discussion

Subthreshold TMS pulses were found to substantially augment ramp-and-hold stretch induced EMG activity of the *m. flexor carpi radialis* (FCR) when timed to arrive at the muscle between 60 and 90 ms after stretch, taking individual motor conduction delay into account. This critical temporal window for cortical modulation of the stretch reflex is consistent within the long latency reflex period (LLR).

The interplay of sensory afferent with cortical efferent signals during a stretch reflex involves supraspinal ascending afferents. If bridging between spinal and cortical structures, such an afferent pathway is referred to as a transcortical pathway. Involvement of a transcortical pathway is constrained by afferent and efferent conduction times and cortical processing delay. Afferent conduction time as found by measuring somatosensory evoked potentials after wrist perturbations is 25-30 ms [11, 12] and cortical processing delay for upper extremity is estimated at 10 ms [13]. Combined with a mean efferent motor conduction delay (measured as MEP latency) of 17.5 ms, a transcortical pathway may affect the stretch reflex from approximately 55 ms onwards. By using a 40 ms lasting perturbation to induce stretch reflexes, afferent input reaches the cortex between 25 and 70 ms after stretch onset (see Figure 3A). This is the critical period, where the effect of cortical involvement can be measured in the EMG between 55 and 95 ms after stretch onset. This time window coincides with the measured augmentation as observed in our results. The ability of subthreshold TMS to augment the LLR within the critical temporal window indicates a temporarily decreased cortical motor threshold for the duration of this response, as the augmenting effect disappears directly after the evoked afferent signal train crossed the CNS.

No significant differences were found in EMG activity when subthreshold TMS was timed to arrive from 10 ms before to 50 ms after stretch onset, corresponding with the short latency response window and before, in line with earlier reported results [22]. The absence of any effect of TMS implies an indifference of short latency spinal reflexes to cortically induced activity and thus absence of spinal or supraspinal integration, limiting opportunity of cortical involvement to the long latency reflex.

Based on our temporal observations at the muscle we are not able to differentiate between a true transcortical loop (cortex is within the loop) and cortical manipulation of a subcortical loop (cortex is not inside the loop) (see Figure 3B). The current experimental set-up and results reduce the ongoing debate on the location of signal integration to a mere timing problem. This clarifies matter, bypassing the issue of location, as signal integration might take place both at the cortical level and the supraspinal level. From a functional perspective, it is not relevant whether the cortex is inside or outside the loop. It is essential that (stretch) reflex afferent pulse trains integrate with cortical input via a transcortical pathway. This study used an independent cortical source to support the neurophysiological modification of the spinal reflex depending on a subject’s voluntary intent [9, 31-33] or context dependency of the motor control [6]. Although voluntary intends may last for longer periods, the effect of cortical modulation can be instantaneous, as the duration seems to be limited to, and not exceeding the duration of the stretch reflex.

Strengths of the study

In this study we combined TMS pulses at various stimulation intensities with upper extremity muscle stretch reflexes in a controlled and systematic way with high temporal precision, allowing for exact timing of TMS pulses with respect to reflex provocation. The combination of non-invasive techniques to evoke cortical activity and peripherally induced reflex activity is a powerful tool in unravelling mechanisms of sensorimotor integration and reflex adaptation. The dual setup of this study allowed for an accurate study of the effect of subthreshold TMS on the FCR stretch reflex response while providing additional temporal resolution in the small sub-population.

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Figure captions

Figure 1. Combined TMS and stretch trials (bold line) compared to stretch-only condition (thin line) for T_{MEP} at 30 (short latency onset), 60 (long latency onset) and 100 ms (after long latency) after stretch onset. Mean data from 10 trials per stretch-only and T_{MEP} conditions are shown in this figure, averaged over the five participants in the long range experiment. T_{MEP} is indicated by the dot and window of 20 ms after T_{MEP} is highlighted to indicate area used to calculate the difference value (see Figure 2).

Figure 2. Difference value over the complete T_{MEP} range for short (dark, n = 12) and long (light, n = 5) range experiments (at 96% AMT). Difference is defined as the area under the difference curve calculated by subtracting the stretch-only EMG from the combined trials EMG recordings within 20 ms after T_{MEP}. Mean values plus standard error of the mean over all participants are presented. Normalized stretch-only EMG (shaded background) over five long range experiment participants is plotted to help interpret the results.

Figure 3. A) Ramp-and-hold (R&H) wrist perturbations of 40 ms allow cortical modulation by TMS between 25 and 70 ms after stretch onset. This modulation is measured at the muscle between 55 and 95 ms, in line with our results. B) Theoretical supraspinal - cortical interactions of TMS and stretch reflex. TMS modulates reflexes via subcortical (solid lines) or transcortical (dashed lines) levels (spinal reflex loop omitted). Neural conduction times are based on literature (see text). SLR: short latency reflex; LLR: long latency reflex; Cx: cortex; sCx: subcortical areas; M: muscle.

Figure 1

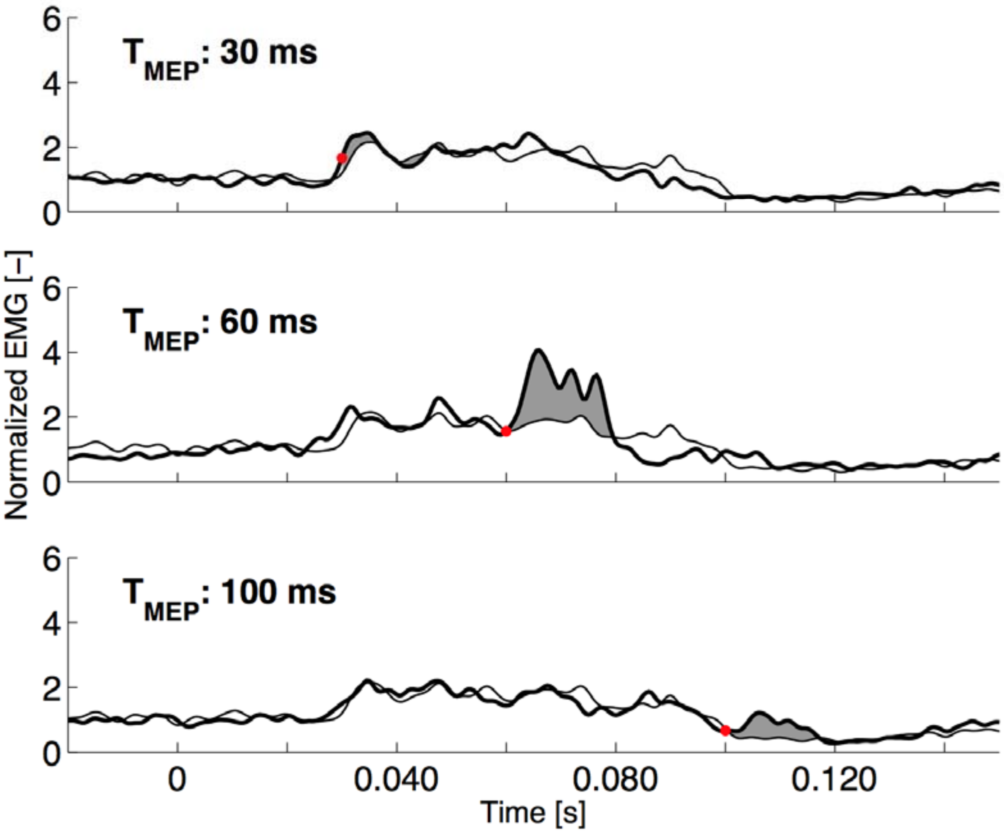
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Figure 2

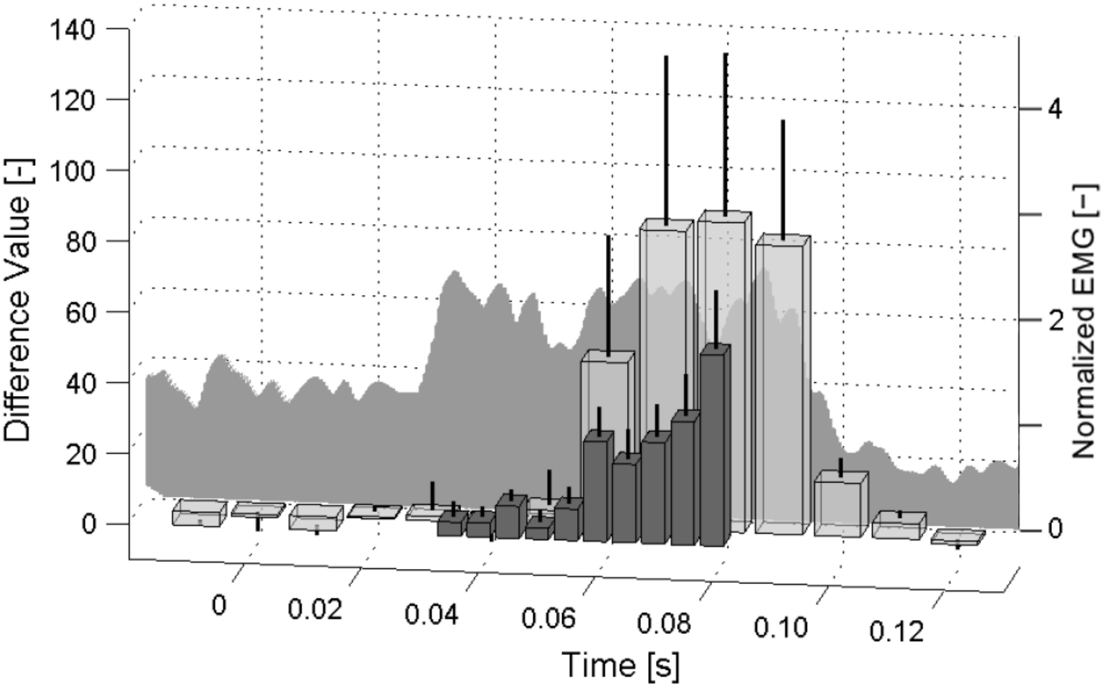

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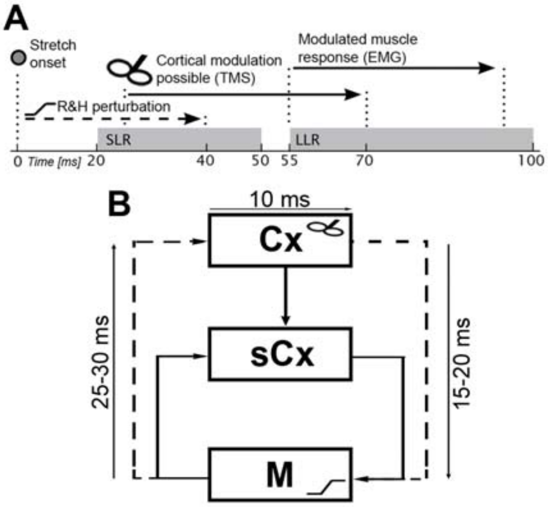
Figure 3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Stretch onset
Cortical modulation possible (TMS)
Modulated muscle response (EMG)
R&H perturbation
SLR
LLR
0
Time [ms]
20
40
50
55
70
100
B
10 ms
Cx
sCx
M
25-30 ms
15-20 ms

Perenboom et al.

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

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.