Evidence that distinct human primary motor cortex circuits control discrete and rhythmic movements

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Key points

- Discrete and rhythmic dynamics are inherent components of (human) movements.
- We provide evidence that distinct human motor cortex circuits contribute to discrete and rhythmic movements. Excitability of supragranular layer circuits of the human motor cortex was higher during discrete movements than during rhythmic movements. Conversely, more complex corticospinal circuits showed higher excitability during rhythmic movements than during discrete movements. No task-specific differences existed for corticospinal output neurons at infragranular layers.
- The excitability differences were found to be time (phase)-specific and could not be explained by the kinematic properties of the movements.
- The same task-specific differences were found between the last cycle of a rhythmic movement period and ongoing rhythmic movements.

Abstract Human actions entail discrete and rhythmic movements (DM and RM, respectively). Recent insights from human and animal studies indicate different neural control mechanisms for DM and RM, emphasizing the intrinsic nature of the task. However, how distinct human motor cortex circuits contribute to these movements remains largely unknown. In the present study, we tested distinct primary motor cortex and corticospinal circuits and proposed that they show differential excitability between DM and RM. Human subjects performed either 1) DM or 2) RM using their right wrist. We applied an advanced electrophysiological approach involving transcranial magnetic stimulation and peripheral nerve stimulation to test the excitability of the neural circuits. Probing was performed at different movement phases: movement initiation (MI, 20 ms after EMG onset) and movement execution (ME, 200 ms after EMG onset) of the wrist flexion. At MI, excitability at supragranular layers was significantly higher in DM than in RM. Conversely, excitability of more complex corticospinal circuits was significantly lower in DM than in RM.

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Introduction

Human motor behaviour comprises discrete movements (DM) and rhythmic movements (RM). RM feature continuous periodic dynamics (e.g. walking) whereas DM feature dynamics that go from an initial to an end position (e.g. reaching) and are bounded by distinct postural positions where no movement occurs (Hogan & Sternad, 2007).

The comparability of DM and RM has been debated for many years and has led to different theoretical viewpoints about their neural control. The first of two possible viewpoints implies that DM and RM share the same neural control circuits. Two scenarios could be possible: i) RM are a series of concatenated DM; or ii) DM are an extract of RM. However, behavioural studies have provided evidence against both possibilities (Smits-Engelsman et al. 2002; Sternad et al. 2002; Wei et al. 2003; Ikegami et al. 2010; Howard et al. 2011). A second viewpoint postulates that DM and RM are separate and controlled by distinct neural entities. Several studies have supported this viewpoint. Using functional magnetic resonance imaging (fMRI), it was shown that in comparison with RM, DM caused additional activity of higher cortical planning areas (Schaal et al. 2004). Behavioural studies indicated incomplete motor learning transfer from RM to DM (Ikegami et al. 2010) and different speed–accuracy trade-offs of the two movements (Smits-Engelsman et al. 2002). The differences in neural mechanisms underlying DM and RM seem to be specifically related to the initiating and the ending of the movements as ongoing RM also differ from the first (Ikegami et al. 2010) and the last cycle of RM (van Mourik & Beek, 2004). Moreover, from animal studies it was suggested that different functional anatomical representations in the motor cortex are accompanied by DM and RM dynamics (Hira et al. 2015) and that corticospinal pathways engage in DM and RM differently with regards to movement phase (Miri et al. 2017). In conclusion, experimental evidence favours the viewpoint that different neural entities control DM and RM. Knowledge about neural circuits of the primary motor cortex that engage in these behaviours is, however, still very limited.

In the present study, we therefore tested excitability modulations of different human primary motor cortex (M1) circuits during DM and RM. For this purpose, we applied a non-invasive electrophysiological method that includes transcranial magnetic stimulation (TMS) and peripheral nerve stimulation (PNS). With this method, changes in spinal motor neuron recruitment from TMS-triggered corticospinal activity can be tested. We recently showed that with this method it is possible to estimate excitability modulations of different micro-circuits of the human motor cortex (Niemann et al. 2018; Kurz et al. 2019). Here, we asked whether excitability modulations of these neural circuits differs between DM and RM in two phases of the movements (movement initiation (MI) and half way during execution).

Methods

Ethical approval

The study conformed to the standards set by the Declaration of Helsinki (latest revision in Fortaleza, Brazil), except for registration in a database, and was approved by the local ethics committee of the Albert-Ludwigs University in Freiburg (approval number 327/18). All participants had no contraindications to TMS (Rossi et al. 2009) and gave written informed consent to the procedures.

Subjects

In two separate experiments, modulation of primary motor cortex circuits was examined during DM and RM. Twenty-one healthy subjects (16 female) participated in experiment 1 and eleven subjects (5 female) in experiment 2. All subjects were aged between 18 and 30 years. In a subset of measurements of experiment 2, 13 additional subjects from experiment 1 participated. Note that we included only subjects in whom H-reflexes could be elicited and H-reflex onsets could be clearly determined.

Electromyography and kinematics

Surface EMG (EISA, Pfitec Biomedical Systems, Endingen, Germany) was recorded from the right flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles using bipolar surface electrodes (Blue sensor P, Ambu, Bad Nauheim, Germany). Electrodes were attached over...
the muscle belly with an interelectrode distance of 2 cm. A common ground electrode was placed at the caput ulnae. Impedance was kept below 5 kΩ. EMG signals were pre-amplified (100×), further amplified (2×) and bandpass filtered (10–1300 Hz). During experiments, the right hand of all subjects was attached to the handle of a robotic manipulandum. A goniometer measured the angular position of the wrist. All data were sampled at 10 kHz.

Motor tasks

Subjects rested in a custom-built laboratory seat approximately 40 cm in front of a computer screen (21-inch LCD monitor with 60 Hz frame rate and 1920 × 1200 pixel resolution). The right foream was positioned in a splint and stabilised with velcro straps. Subjects had to perform DM (wrist flexions) and RM (wrist flexions/extensions) by moving a robotic manipulandum. The angular position of the wrist was represented as a white cursor on a black computer screen. All movements started with the wrist in a neutral position and the cursor presented on the right side of the computer screen. Movements were performed at a self-selected comfortable speed. Wrist extension refers to the active returning of the wrist from the flexion end position to the neutral position. The visual environment was generated using Matlab (The MathWorks, Natick, Massachusetts, United States, 2016).

Experiment 1

For DM, a green target zone was displayed on the left side of the computer screen (Fig. 1A, left side). Subjects were instructed to perform DM with the wrist (Fig. 1B, left side) and move the cursor into the green target. Movements could be started once the subject was ready. Further, subjects were instructed to plan the required force in advance and not to stop actively in the target zone. A readjustment of the movement was not permitted once it was started. After completion of the movement, the robotic manipulandum pushed the wrist back to the neutral starting position. A new trial was started every 5 s. The horizontal position of the target varied between trials (between 10 and 30 pixels). This was to keep subjects’ attention high while completing the task.

For RM, a green bar was illustrated on the right and on the left sides of the computer screen (Fig. 1A, right side). Subjects had to move the cursor in a rhythmic manner between the two bars (Fig. 1B, right side). The green bars served as approximate reference points for the movement amplitude. RM were performed continuously in blocks (see Electrophysiological testing during DM and RM).

Experiment 2

Subjects had to perform 1) RM and 2) RMlast, which corresponds to the last cycle of RM. For RM, the task and the visual setup were as described for experiment 1. During RM, a tone (50 ms, 440 Hz sinus wave) signalled the end of the rhythmic movement period and that subjects had to finish the RM with one last wrist flexion movement (RMlast). For that purpose, the computer screen switched from the rhythmic setup (two bars) to the discrete setup (target field). The tone and the change in the visual environment were triggered at random intervals during performance of RM.

Peripheral nerve stimulation

H-reflexes of the FCR muscle were elicited by stimulating the nervus medianus approximately 1–3 cm proximal to the elbow joint. A constant current stimulator (DS7a, Digitimer, Hertfordshire, UK) giving square wave-pulses of 0.2 ms duration and a bipolar electrode configuration was used for the stimulation. The anode consisted of a graphite-coated rubber pad of 2 × 5 cm fixed proximal to the olecranon. To locate the best stimulation spot for the cathode, we moved a custom-made round pad (1 cm diameter) in the medial area of the os humeri just above the elbow joint. The optimum stimulation site was set where low stimulation intensities (5–30 mA, monophasic pulse) elicited no or minimal M-wave and H-reflex sizes remained constant. Also, H-reflexes in the antagonist muscle ECR had to be absent. The optimal position was marked and used as the stimulation site by fixing a self-adhesive cathode (Blue sensor P, Ambu, Bad Nauheim, Germany). Maximal H-reflexes and maximal M-waves were determined at the beginning of each experiment to set the intensity of the PNS during recording TMS-conditioned H-reflexes.

Transcranial magnetic stimulation

Single-pulse TMS was given over the contralateral M1 wrist area using a Magstim 2002 stimulator with a BiStim unit (Magstim, Whitland, UK) and a figure-of-eight coil (50 mm). A stand (Manfrotto Magic Arm, Lino Manfrotto & Co, Cassola, Italy) that was positioned on top of the subject’s chair fixed the handle of the coil. To ensure that the coil position remained constant we usedBrainsight TMS navigation (Brainsight 2, Rogue Research, Montreal, Canada) and monitored the coil position throughout all measurements and adjusted if necessary. The coil was placed tangentially on the scalp at an angle of 45° to the mid-saggital plane. The current was induced with a posterior–anterior direction. The hotspot for the FCR muscle was determined by performing a mapping procedure and analysing motor evoked potentials (MEPs).
The hotspot was defined as the position where the lowest possible stimulation intensity elicits clear MEPs. Resting motor threshold (RMT) was defined as the minimum stimulator output (in %) required to evoke MEPs of at least 50μV in at least three out of five consecutive stimulations at a certain intensity (Rossini et al. 1994).

**TMS conditioned H-reflexes**

The aim of the TMS H-reflex conditioning method is to promote the coincident arrival of the afferent volleys elicited by PNS with the corticospinal volleys triggered by TMS (Fig. 2A). If applied alone, PNS causes recruitment of a certain pool of motoneurons, initiating the H-reflex response in the muscle. TMS elicits a series of subsequent descending volleys (Di Lazzaro & Ziemann, 2013). If applied so that the fastest corticospinal volleys reach the spinal cord at the same time as the afferent volleys from PNS, more spinal motoneurons will be recruited. The result is a larger conditioned H-reflex. Increasing the delay between the stimulations, so that TMS is triggered even earlier, allows more corticospinal volleys to impact the H-reflex. The arrival of additional corticospinal volleys leads to a temporal summation of motoneuron recruitment and hence larger H-reflexes. In the present study, motoneuron recruitment from two parts of the first indirect corticospinal volley (I1-wave) and later indirect corticospinal volleys (I3-waves) were studied (Fig. 2B). The first part of the I1-volley likely originates from transsynaptic activation of corticospinal neurons at infragranular layers while the second part of the I1-volley includes modulation from supragranular layers (Kurz et al. 2019). Excitability of the two parts was modulated differently in a sensorimotor discrimination task (Kurz et al. 2019) and was also differently related to force output in human subjects (Kurz & Leukel, 2019). I3-waves have been associated with synaptic projections from premotor areas (Di Lazzaro & Ziemann, 2013; Volz et al. 2015) and can be affected by inhibitory intracortical circuits (Niemann et al. 2017). Thus, excitability of the different parts of the TMS-elicited corticospinal I1-volley and subsequent I-volleys refer to different neural circuits which may have different functions in motor control.

**Figure 1.** Experimental setup

A, Visual setup on the computer screen for DM (left) and RM (right). Recordings from a subject (goniometer, raw EMG of the FCR and of the ECR) are illustrated below the illustration of the setup. B, Wrist positions during DM (left) and RM (right). Subjects started from a neutral position. Flexion movements were terminated (DM) or rhythmically combined with extension movements (RM). Subjects’ hands were attached to a robotic manipulandum that recorded the angle of the wrist position. [Colour figure can be viewed at wileyonlinelibrary.com]
In each subject, we determined the individual stimulation delay between TMS and PNS. This was achieved by determining the early facilitation (the first part of I1-volley) in a two-step procedure (Fig. 3A and B) (see Kurz et al. 2019). In step 1, delays between TMS and PNS from -5 ms to -2 ms in steps of 0.5 ms were tested (negative delays indicate that PNS was triggered before TMS). Fifteen repetitions at each delay and the unconditioned H-reflex were recorded in a random manner. The early facilitation was statistically determined using uncorrected paired t tests between conditioned H-reflexes at each delay and unconditioned H-reflexes. Starting at the most negative delay (i.e.-5 ms), the first more positive delay with a significant increased H-reflex ($P < 0.05$) was denoted as early facilitation. The first significant delay was only chosen when the H-reflexes at the two subsequent more positive delays were also significantly higher than the unconditioned H-reflex. In step 2, we tested delays in the time range between the early facilitation delay defined in step 1 up to -1 ms with regards to that delay in steps of 0.1 ms (10 steps + unconditioned H-reflex). Like in step 1, 15 repetitions at each delay and the unconditioned H-reflex were tested in a random order. The statistical analysis was performed as explained before. According to these steps we could identify the early facilitation with 0.1 ms precision. The early facilitation interval for the experiments was named early facilitation delay (EFD) 0 ms. The mean individual EFD 0 ms was -3.55 ms (0.5 ms) (Fig. 3C). Based on the individual EFD 0 ms (first part of I1-volley), the delay between TMS and PNS for EFD +0.6 ms (second part of I1-volley) and EFD +3 ms (I3-waves) were calculated and used in the subsequent main protocol (Fig. 3D).

In both preparatory measurements, the interval between stimulations was set to 4 s to avoid changes in post-activation depression of the H-reflex (Crone & Nielsen, 1989). PNS intensity was set to elicit H-reflexes of 15% to 25% of the respective Mmax (Crone et al. 1990). The TMS intensity for all experiments was set to 115% of individual RMT with a posterior–anterior coil configuration to evoke I-waves and no D-waves (Niemann et al. 2018).

**Electrophysiological testing during DM and RM**

To test the excitability changes of primary motor cortex circuits during DM and RM, we decided to perform TMS H-reflex conditioning at two different

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**Figure 2. TMS H-reflex conditioning**

A, Schematic of the TMS H-reflex conditioning method. TMS evokes corticospinal activity that coincides with the afferent volley from PNS at the spinal motoneurons at distinct delays between stimulations. B, Principle of TMS H-reflex conditioning. If applied alone, PNS activates (Ia) afferent fibres that subsequently activate spinal motoneurons in the spinal cord. This leads to the H-reflex response in the muscle (left side). When TMS is combined with PNS so that the first part of the fastest corticospinal volley from TMS coincides with the fastest afferent volleys at the spinal cord there is an additional recruitment of spinal motoneurons (blue colour). This results in an increased, facilitated H-reflex (see examples of H-reflexes below). The delay between TMS and PNS to produce this earliest H-reflex facilitation was determined in each subject. When TMS is triggered 0.6 ms earlier, relative to the delay between TMS and PNS that produces the earliest facilitation, more corticospinal volleys will coincide with the afferent volley at the spinal motoneurons (red colour) and the H-reflex facilitation is greater. When TMS is applied 3 ms earlier, relative to the delay producing the earliest facilitation, even more corticospinal volleys affect spinal motoneuron recruitment (green colour). (Figure modified from Kurz et al. 2019) [Colour figure can be viewed at wileyonlinelibrary.com]
stimulation time points: i) 20 ms after flexion movement onset (MI); and ii) 200 ms after flexion movement onset (movement execution, ME). Recent research emphasizes the contribution of motor cortex and corticospinal pathways during different phases of DM and RM (Miri et al. 2017). A real-time signal processing system (STIMULI; Pfitec Biomedical Systems, Endingen, Germany) triggered all stimulations according to the online rectified EMG signal of the FCR. Movement onset was defined as the time at which the rectified FCR EMG signal exceeded 3 SD of the baseline EMG. Stimulations were exclusively applied during wrist flexion movements during DM and RM. For DM and RM, we recorded unconditioned H-reflexes by using PNS (without TMS). The size of the unconditioned H-reflex for DM and RM during MI and ME was matched between the conditions. This was achieved by using different electrical stimulators for MI and ME and adjusting stimulation intensities. To avoid anticipation of the stimulations by the subjects, we added trials in which no electrophysiological stimulations were applied. While DM were performed every 5 s, RM were performed continuously. Thus, the frequency at which wrist flexions were executed was higher during RM than during DM. To match the intervals between stimulations in DM and RM and to avoid effects from post-activation depression on the H-reflex (see previous paragraph), stimulations during RM were triggered again after three completed rhythmic cycles.

In experiment 1, TMS H-reflex conditioning was performed at EFD 0 ms, EFD +0.6 ms and EFD +3 ms during MI and ME was matched between the conditions. This was achieved by using different electrical stimulators for MI and ME and adjusting stimulation intensities. To avoid anticipation of the stimulations by the subjects, we added trials in which no electrophysiological stimulations were applied. While DM were performed every 5 s, RM were performed continuously. Thus, the frequency at which wrist flexions were executed was higher during RM than during DM. To match the intervals between stimulations in DM and RM and to avoid effects from post-activation depression on the H-reflex (see previous paragraph), stimulations during RM were triggered again after three completed rhythmic cycles.

In experiment 1, TMS H-reflex conditioning was performed at EFD 0 ms, EFD +0.6 ms and EFD +3 ms
during MI and ME. Testing for DM and RM was performed in separate blocks. One block consisted of 3 × randomly testing all stimulation conditions (all EFDs and unconditioned H-reflex). Blocks for DM and RM were performed in a pseudorandomized order. In experiment 2, TMS H-reflex conditioning was performed at EFD +0.6 ms (only during MI) and EFD +3 ms (only during ME). Testing was applied during RM and RM_last in the same recording block. One block consisted of 3 × randomly testing all stimulation conditions. In both experiments, six blocks for each condition were recorded resulting in 18 stimulation repetitions (for all EFDs and the unconditioned H-reflex) per condition.

Data analysis and statistics

Root mean squared (RMS) values of the initial 0.5 ms from the H-reflex onset at each EFD and the unconditioned H-reflex were analysed from the unrectified FCR EMG traces (Wiegel et al. 2018; Kurz et al. 2019) (Fig. 3E). Before RMS values were calculated, all trials were corrected for potential offsets of the baseline EMG by setting the H-reflex onset value to zero. This was done as the EMG offset (y-position) may change over the duration of the experiment and may bias the RMS analysis. The onset of the H-reflex was determined visually from superimposed single unconditioned H-reflexes and the mean unconditioned H-reflex (Wiegel et al. 2018) (Fig. 3E). The mean H-reflex onset was 16.96 ms (1.17 ms) (Fig. 3F). Trials in which stimulation was not applied during wrist flexions were excluded from the analysis (on average: 7.09% (8.01%)). This was the case when subjects had high background FCR EMG levels before wrist flexion movements were initiated (DM) or during the execution of extension movements (RM). Mean values (average of the 18 stimulation repetitions per condition) from all repetitions were calculated for conditioned and unconditioned H-reflexes. H-reflex facilitation at each EFD was expressed as a percentage of the unconditioned H-reflex (mean conditioned H-reflex/mean unconditioned H-reflex × 100%).

Pre-stimulus EMG activity of the FCR muscle and ECR muscle was assessed by calculating the RMS values in the 20 ms interval prior to stimulation from the rectified EMG signal. This relatively short time range was chosen due to the fast-changing EMG signal during dynamic contractions and the stimulation offset of 20 ms from EMG FCR onset during MI. To test for differences in movement kinematics, we calculated the movement time (in ms) and movement amplitude (in °) by determining the onset and end point of wrist flexion movements from the first derivative of the goniometer signal. Movement onset and movement end were defined as the time where the movement velocity exceeded and dropped below 10% of its maximum, respectively (d’Avella et al. 2006). Mean movement velocity was computed as movement amplitude/movement time. Only flexion movements of DM and RM were analysed. All data analyses were performed with custom-made scripts in Matlab (The MathWorks, Natick, Massachusetts, United States, 2016).

All data sets were tested for normal distribution and homogeneity with the Kolmogorov–Smirnov and Levene tests, respectively. Due to violations of normality and homogeneity, conditioned H-reflex data were log transformed prior to further processing. Note that we do not illustrate log transformed but original percentage H-reflex facilitation data in all figures.

To test how our subjects performed DM and RM, we computed repeated measures (rm) ANOVAs using the dependent measures 1) movement amplitude, 2) movement velocity and 3) movement time. For these statistical models, we used a 2 × 2 × 3 within-subject design. The independent factors were TASK (DM & RM), PHASE (MI & ME) and EFD (EFD 0 ms, EFD +0.6 ms and EFD +3 ms). An identical approach was used to test for differences in EMG activity prior to electrophysiological testing using pre-stimulus FCR EMG activity and pre-stimulus ECR EMG activity as dependent measures.

To test for differences in H-reflex facilitation between DM and RM, we used rmANOVAs with the 2 × 2 × 3 design mentioned above using the dependent variable H-reflex facilitation. We first asked whether the magnitude of H-reflex facilitation during DM and RM differed between the two tested movement phases (MI vs. ME). Thus, after using the rmANOVA, we performed post hoc t tests between H-reflex facilitation at MI and ME during DM and RM. In the next step, we used post hoc t tests to test whether H-reflex facilitation differs between DM and RM at MI and ME. During both procedures, we adjusted for multiple comparisons and corrected the level of significance according to the Benjamini–Hochberg procedure (Benjamini & Hochberg, 1995). Unconditioned H-reflexes were compared using a 2 × 2 rmANOVA with the factors TASK (DM & RM) and PHASE (MI & ME). The sample size for all statistics was n = 21.

Since we found significant differences in H-reflex facilitation between DM and RM for EFD +0.6 ms at MI and for EFD +3 ms at ME, we asked whether these differences might be explained by the differences in the kinematics and EMG profiles found in the first part of our analysis. Consequently, in a first step we used rmANCOVAs for H-reflex facilitation at EFD +0.6 ms and EFD +3 ms with the factor TASK (DM & RM) and the covariates pre-stimulus ECR EMG and kinematic parameters. In a second step, we removed nine of our subjects with differing kinematic properties between DM and RM from the sample. This left a subgroup of
12 subjects. With this reduced sample, we performed single comparisons (paired \( t \) tests) for H-reflex facilitation at EF \(+0.6\) ms at MI and at EF \(+3\) ms at ME between DM and RM to test whether the differences in H-reflex facilitation between DM and RM are also present in this subgroup with matched kinematics. For experiment 2, paired \( t \) tests were calculated for EF \(+0.6\) ms and EF \(+3\) ms between the conditions RM and RM\(_{last}\) for H-reflex facilitation data and control parameters (pre-stimulus EMG and kinematics) \((n = 11\) at EF \(+0.6\) ms; \(n = 24\) at EF \(+3\) ms).

For all statistical comparisons, the level for statistical significance was set to \( P < 0.05\). The Greenhouse–Geisser correction method was used for rmANOVA\(s\) if the assumption of sphericity was violated (Mauchly’s test). Effect sizes were estimated using Eta-squared \((\eta^2)\) partial). Data are presented as mean values (standard deviation). All statistical analyses were performed with SPSS software 24 (SPSS, Chicago, IL, USA).

**Results**

**Kinematic properties of DM and RM**

In the present study, subjects had to perform DM and RM with their wrist. As shown in Fig. 4A, DM and RM show characteristic velocity and acceleration profiles. We were interested to see if some of the basic kinematic properties differed between DM and RM. Our analyses revealed that subjects performed RM with greater movement amplitude and higher mean movement velocity than DM (Table 1). RM were executed with a mean movement range of 39.18° (2.65°) while DM had a mean range of 35.07° (3.46°) (Fig. 4B). The average movement velocity was 68.75°/s (9.82°/s) in RM and 61.22°/s (15.03°/s) in DM (Fig. 4C). No differences between DM and RM were found for movement time (Fig. 4D). DM and RM took on average 624.4 ms (118.28 ms) and 575.03 ms (100.64 ms), respectively.

Because electrophysiological testing was applied during DM and RM (Fig. 4A), we asked whether the stimulations provoked differentiated effects on movement kinematics when stimulations were applied at MI and ME. Our statistical results indeed support different effects. Application of TMS H-reflex conditioning caused a phase-specific modulation in movement kinematics, in both DM and RM (Table 1). Movement amplitude and movement velocity were greater with TMS H-reflex conditioning at ME than TMS H-reflex conditioning at MI (amplitude: MI 36.86° (3.44°) vs. ME 37.39° (3.73°); velocity MI 62.32°/s (12.76°/s) vs. ME 67.65°/s ± 12.98°/s, Fig. 4B and C). Movement time was longer with TMS H-reflex conditioning applied at MI compared with TMS H-reflex conditioning applied at ME (MI 624.41 ms (116.65 ms) vs. ME 575.03 ms (99.15 ms), Fig. 4D).

Thus, the stimulations caused changes in the kinematic properties in both DM and RM.

**EMG activity prior to electrophysiological testing**

We tested whether pre-stimulus EMG activity of the FCR and ECR differed between DM and RM (Fig. 5A and Fig. 5B). Pre-stimulus FCR EMG activity did not significantly differ between DM and RM (Table 2, Fig. 5C). The RMS for pre-stimulus FCR EMG activity was 0.08 mV (0.03 mV) at MI, and 0.08 mV (0.03) at ME during DM. For RM, the RMS was 0.07 mV (0.03 mV) at MI, and 0.09 mV (0.05 mV) at ME. Concerning ECR, pre-stimulus EMG activity was significantly greater for RM than for DM at MI, but not at ME (Table 2, Fig. 5D). This is no surprise, as the flexion movements during RM are preceded by extension movements while DM are not. EMG activity was 0.01 mV (0.01 mV) at MI and 0.02 mV (0.02 mV) at ME during DM. For RM, EMG activity was 0.02 mV (0.01 mV) at MI and 0.02 mV (0.01 mV) at ME.

**Excitability of primary motor cortex circuits in DM and RM**

We were interested in whether the excitability of primary motor cortex circuits depends on the phase of the movement in DM and RM. The rmANOVA yielded a significant TASK × PHASE interaction (Fig. 6, Table 3). H-reflex facilitation was greater at MI than at ME in DM (Fig. 6A), and the opposite occurred for RM (greater at ME than at MI, Fig. 6B). Post hoc analysis revealed that different EFDs caused these effects. H-reflex facilitation at EF \(+0.6\) ms was significantly larger at MI (219.17% (114.85%)) than at ME (172.37% (56.89%)) during DM \((t(20) = 2.95, P = 0.008)\). The comparison of H-reflexion at EF \(+0.6\) ms between MI and ME during RM did not survive the correction of the alpha level \((t(20) = -2.48, P = 0.02)\). H-reflex facilitation at EF \(+0.6\) ms during RM was 159.31% (32.81%) at MI and 185.23% (66.04%) at ME.

In contrast, H-reflex facilitation at EF \(+3\) ms was significantly higher at ME than at MI for RM \((t(20) = -4.6, P < 0.001)\). H-reflex facilitation at EF \(+3\) ms during RM was 292.07% (159.07%) at ME and 207.97% (76.97%) at MI. During DM, facilitation at EF \(+3\) ms was 259.9% (138.95%) at MI and 239.54% (133.68) at ME and not significantly different \((t(20) = 1.4, P = 0.17)\). H-reflex facilitation at EF 0 ms was 146.64% (66.57%) at MI and 124.16% (25.42%) at ME in DM and 126.82% (24.35%) at MI and 130.62% (41.39%) at ME in RM. The comparisons between movement phases for EF 0 ms were not significant (DM \(t(20) = 1.67, P = 0.11\); RM \(t(20) = -0.13, P = 0.9\)). In summary, these results reveal...
movement phase-specific excitability modulations of EFD +0.6 ms and EFD +3 ms during DM and RM.

We further asked whether H-reflex facilitation was different between DM and RM. As suggested by previous studies (Ikegami et al., 2010), we expected different excitability modulations of the tested circuits between DM and RM. This was the case as shown by the significant interaction of the factors TASK x EFD and TASK x PHASE x EFD in the rmANOVA (Table 2). Thus, the differences between DM and RM were EFD- and phase-specific (Fig. 7). H-reflex facilitation was higher in DM than in RM at MI (Fig. 7A), while it was the opposite at ME (greater for RM than for DM, Fig. 7B). Post hoc comparisons showed that facilitation at EFD +0.6 ms was significantly higher in DM than in RM at MI (t(20) = 3.48, P = 0.002) but not at ME (t(20) = -1.72, P = 0.1). Conversely, facilitation at EFD +3 ms was greater in RM than in DM at ME (t(20) = -3.66, P = 0.002) but not at MI (t(20) = 2.31, P = 0.03, after alpha level correction not significant). H-reflex facilitation at EFD 0 ms did not differ statistically between DM and RM (MI t(20) = 1.13, P = 0.27; ME t(20) = -0.43, P = 0.67).

Importantly, the unconditioned H-reflexes were neither different between stimulation time points (MI vs. ME) nor between DM and RM (Table 3).

**Are the differences in H-reflex facilitation between DM and RM caused by differences in kinematics or antagonistic ECR activity?**

We asked whether the significant differences in H-reflex facilitation at EFD +0.6 ms and EFD +3 ms might be explained by the differences in pre-stimulus ECR EMG activity and different movement kinematics between DM and RM. rmANCOVAs were consequently applied, controlling for the differences in pre-stimulus ECR EMG, movement amplitude and movement velocity, respectively.

Differences in pre-stimulus ECR EMG had no significant effect on H-reflex facilitation at EFD 0.6 ms (F[1,19] = 0.13, P = 0.73, η² partial = 0.01). The H-reflex facilitation at EFD +0.6 ms at MI was still significantly

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**Figure 4. Kinematic features of DM and RM**

A, Position, velocity and acceleration profiles for DM and RM are shown for one subject. For illustration purposes, signals were filtered with a 2nd order lowpass butterworth filter 5 Hz. Stimulation times at MI (left vertical line) and ME (right vertical line) are illustrated in all traces. B, Box plots for movement amplitude during DM and RM when stimulation was applied at MI and at ME. C, Box plots for movement velocity during DM and RM when stimulation was applied at MI and at ME. D, Box plots for movement time during DM and RM when stimulation was applied at MI and at ME. Note that for B, C and D, data from all EFDs were pooled for the corresponding condition (i.e. DM at MI, DM at ME, RM at MI, RM at ME). Asterisks illustrate significant (P < 0.05) main effects (Task and/or Phase) or significant interactions (Task × Phase) from the rmANOVA results. [Colour figure can be viewed at wileyonlinelibrary.com]
higher for DM than for RM (F[1,19] = 5.59, P = 0.03, \( \eta^2_{\text{partial}} = 0.23 \)). Differences in movement amplitude had no significant effect on H-reflex facilitation at EFD +0.6 ms (F[1,18] = 1.54, P = 0.23, \( \eta^2_{\text{partial}} = 0.08 \)). Differences in movement velocity had a significant effect on H-reflex facilitation at EFD +0.6 ms (F[1,18] = 5.18, P = 0.04, \( \eta^2_{\text{partial}} = 0.22 \)). However, the H-reflex facilitation was still significantly higher for DM than for RM at MI after controlling for both factors (F[1,18] = 9.26, P = 0.007, \( \eta^2_{\text{partial}} = 0.34 \)). At EFD +3 ms, H-reflex facilitation was neither influenced by movement amplitude (F[1,18] = 0.17, P = 0.68, \( \eta^2_{\text{partial}} = 0.01 \)) nor movement velocity (F[1,18] = 0.24, P = 0.63, \( \eta^2_{\text{partial}} = 0.01 \)). H-reflex facilitation was still significantly higher at EFD +3 ms at ME for RM than for DM (F[1,18] = 9.77, P = 0.006, \( \eta^2_{\text{partial}} = 0.35 \)).

In a second analysis, we asked whether the differences in H-reflex facilitation would still be present after removing subjects with different kinematic properties between DM and RM. Consequently, we removed nine subjects from the sample. This left a total of 12 subjects with matched kinematic properties between DM and RM (all kinematic comparisons P > 0.05). In this subgroup, H-reflex facilitation at EFD +0.6 ms at MI was still significantly higher for DM than for RM (t(11) = 3.03, P = 0.01). H-reflex facilitation at EFD +3 ms at ME was still significantly lower for DM than for RM (t(11) = -3.64, P = 0.004).

Altogether, differences in H-reflex facilitation between DM and RM could be revealed by the statistical analyses that were specific for the movement phase and EFD, and not significantly influenced by modulations in pre-stimulus EMG of ECR and kinematic variables, respectively.

### Last cycle of RM differs from ongoing RM

Previous research has demonstrated differences in the kinematic and behavioural properties of ongoing continuous RM and the first/last cycle of RM (van Mourik & Beek, 2004; Ikegami et al. 2010). Thus, it has been speculated that neural control of the first/last cycle of RM is similar to DM neural control mechanisms. To test this, we performed a second experiment in which H-reflex facilitation was recorded during ongoing continuous RM and the final flexion movement of RM (RMlast, Fig. 8A). We recorded H-reflex facilitation at EFD +0.6 ms at MI and EFD +3 ms at ME and hypothesized that we would find the same modulatory differences as in experiment 1. Indeed, we found significantly greater H-reflex facilitation at EFD +0.6 ms during RMlast than during continuous RM (t(10) = 2.43, P = 0.04, Fig. 8B). H-reflex facilitation at EFD +0.6 ms was 273.53% (107.26%) during RMlast and 177.07% (53.19%) during RM. H-reflex facilitation at EFD +3 ms was significantly greater during ongoing RM than during RMlast (t(23) = 3.2, P = 0.003, Fig. 8C). H-reflex facilitation at EFD +3 ms was 292.36% (127.79%) during RMlast and 338.73% (145.76%) during RM. There were no significant differences between RMlast and DM for EFD +0.6 ms at MI (t(10) = 2.06, P = 0.07) and for EFD +3 ms at ME (t(10) = 1.66, P = 0.19).

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### Table 1. rmANOVA results for kinematic parameters

| Movement time | Movement amplitude |
|---------------|--------------------|
|               | F[DF, error] | P  | \( \eta^2_{\text{partial}} \) | F[DF, error] | P  | \( \eta^2_{\text{partial}} \) |
| Task          | 0.84[1,20]  | 0.37 | 0.04 | 17.87[1,20]  | <0.001 | 0.47 |
| Phase         | 38.12[1,20]  | <0.001 | 0.66 | 4.51[1,20]  | 0.04  | 0.18 |
| EFD           | 0.47[2,40]  | 0.63  | 0.02 | 1.32[2,40]  | 0.33  | 0.06 |
| Task × Phase  | 0.27[2,40]  | 0.61  | 0.01 | 5.09[1,20]  | 0.04  | 0.2  |
| Phase × EFD   | 2.03[2,40]  | 0.14  | 0.09 | 0.63[2,40]  | 0.54  | 0.03 |
| Task × EFD    | 1.66[2,40]  | 0.2   | 0.08 | 2.08[2,40]  | 0.14  | 0.09 |
| Task × Phase × EFD | 0.26[2,40]  | 0.78  | 0.01 | 0.2[2,40]  | 0.82  | 0.01 |

### Movement velocity

| Movement velocity | F[DF, error] | P  | \( \eta^2_{\text{partial}} \) |
|------------------|--------------|----|------------------------------|
| Task             | 4.66[1,20]   | 0.04 | 0.19 |
| Phase            | 39.45[1,20]  | <0.001 | 0.66 |
| EFD              | 3.48[2,40]   | 0.04 | 0.15 |
| Task × Phase     | 2.15[1,20]   | 0.16 | 0.1 |
| Phase × EFD      | 0.96[2,40]   | 0.39 | 0.02 |
| Task × EFD       | 1.86[2,40]   | 0.17 | 0.09 |
| Task × Phase × EFD | 0.34[1,6,31.3] | 0.66 | 0.02 |

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Neural control of discrete and rhythmic movements

Discussion

In the present study, we asked whether DM and RM are controlled by distinct neural circuits of the primary motor cortex. For this purpose, subjects performed DM and RM with their wrist. During performance of these movements, we applied TMS H-reflex conditioning. Electrophysiological stimulations were triggered in two phases of DM and RM, i.e. at MI (20 ms after FCR EMG onset in wrist flexion movements) and at ME (200 ms after FCR EMG onset in wrist flexion movements).

We found differences in H-reflex facilitation that were task-specific. At MI, excitability at EFD +0.6 ms was significantly greater for DM than RM. No such modulation was observed at EFD 0 ms. At ME, no excitability changes between DM and RM were observed for EFD 0 ms and EFD +0.6 ms. In contrast, excitability at EFD +3 ms was greater for RM than DM at ME. Kinematic parameters and electromyographic activity differed between DM and RM. We tested whether the differences in H-reflex facilitation could be explained by the differences in antagonistic ECR EMG activity and in kinematic features between DM and RM. This was not the case. Thus, our results provide human electrophysiological evidence of different neural control mechanisms for DM and RM.

In a recent study, it was shown that EFD 0 ms and EFD +0.6 ms correspond to different parts of the I1-volley from TMS and represent distinct microcircuits of human motor cortex (Kurz et al. 2019). Specifically, supragranular layers and infragranulal layers of motor cortex contribute to facilitation of H-reflexes at EFD +0.6 ms while H-reflex facilitation at EFD 0 ms results from transsynaptic activation of corticospinal neurons at infragranular layers. Neurons at supragranular layers of motor cortex modulate the activity of deep infragranular layers in a top-down manner (see Weiler et al. 2008; Hooks et al. 2011). Neurons at infragranular layers of motor cortex have corticospinal connections and control the neural drive to the spinal motoneurons (Weiler et al. 2008).

As neural excitability at EFD 0 ms was not significantly different between RM and DM, the present results for EFD +0.6 ms point towards a selective excitability modulation at upper layers during MI. The increased excitability at EFD +0.6 ms for DM at MI is unlikely to be caused simply by an increase in excitability of pyramidal cells projecting to lower layers. This scenario would have also influenced corticospinal cells at lower layers, and led to a changed excitability at EFD 0 ms, too. It could be proposed that the increased excitability at EFD +0.6 ms was caused by an altered synaptic input at supragranular layers, from other motor and/or sensory areas. Indeed, superficial layers of the primary motor cortex predominantly receive inputs from somatosensory and pre-motor areas (Huber et al. 2017; Ninomiya et al. 2019). A previous neuroimaging study showed that in comparison with RM, DM are associated with additional activity in non-primary cortical motor planning areas such as premotor, supplementary motor and posterior parietal cortex (Schaal et al. 2004). Schaal and colleagues (2004) suggested that RM may engage primary motor circuits (automatic control) whereas DM require additional contributions from prefrontal and parietal cortical areas (cognitive control) (Lewis & Miall, 2003). According to these
findings, it may therefore be input from premotor and parietal sites that resulted in increased excitability at EFD +0.6 ms during DM in the current study. In any case, the increase in H-reflex facilitation at EFD +0.6 ms suggests that excitability of cortical rather than subcortical/spinal circuits is greater in DM than in RM as these very likely do not contribute to EFD +0.6 ms (Kurz et al. 2019).

The present study showed greater H-reflex facilitation at EFD +3 ms in RM during ME (approximately 200 ms after EMG onset) in comparison with DM. EFD +3 ms corresponds to later I-waves (Niemann et al. 2018) that could be associated with synaptic inputs from premotor areas (Shimazu et al. 2004; Di Lazzaro & Ziemann, 2013; Volz et al. 2015). The premotor areas have been associated with the production of temporal motor skills such as sequences (Lepage et al. 1999) and these skills can be especially relevant in RM in order to plan and time the continuous movement cycles. However, slower conducting pyramidal motor pathways can also be considered to contribute to EFD +3 ms and thus be the source of the differences between RM and DM. Indeed, DM and RM are controlled by distinct corticocortical synaptic circuits (Hira et al. 2015) and more indirect corticospinal pathways contribute to RM (locomotion) in rodents (Miri et al. 2017). It is possible that EFD +3 ms comprises these more indirect corticospinal connections. In contrast to EFD +0.6 ms, EFD +3 ms may also include extrapyramidal motor circuits. Forwarding the neural signal from the motor cortex to the spinal cord at EFD +3 ms principally allows for sufficient time of more relayed transmission via subcortical centres. For instance, the reticulospinal pathway constitutes one of the major descending motor pathways (Lemon, 2008) and it could be that EFD +3 ms incorporates reticulospinal pathways that show increased activity during RM. In fact, pathways from the reticulospinal system have shown greater engagement in locomotion than during reaching in cats (Dyson et al. 2014). Reticulospinal neurons in the brainstem receive synaptic inputs from the deep layers of motor cortex (Matsuyama et al. 2004).

However, we also want to emphasize that the latter discussion remains purely speculative as the literature stems from animal studies and includes locomotor and reaching behaviours. Engagement of the corticospinal system in these motor behaviours may indeed vary across different species (Lemon, 2008).

The same movement-specific differences in H-reflex facilitation at EFD +0.6 ms and EFD +3 ms also existed between the last cycle of RM and ongoing continuous RM (experiment 2). In recent studies, it was already shown that the last cycle of RM shows differences in kinematic properties compared with ongoing continuous RM (van Mourik & Beek, 2004). Our results strengthen the hypothesis that the neural strategies used for DM and
Figure 6. H-reflex facilitation differs between distinct movement phases

A, Individual and mean H-reflex facilitation (in % of unconditioned H-reflex) at EFD 0 ms, EFD +0.6 ms and EFD +3 ms when TMS H-reflex conditioning was applied at MI (dark blue) and ME (light blue) during DM. Data are presented as mean ± SD (asterisks indicate significant differences after multiple comparison correction).

B, Individual and mean H-reflex facilitation (in % of unconditioned H-reflex) at EFD 0 ms, EFD +0.6 ms and EFD +3 ms when TMS H-reflex conditioning was applied at MI (dark red) and ME (light red) during RM. Data are presented as mean ± SD (asterisks indicate significant differences after multiple comparison correction). x-axis values of the dots representing single subjects were jittered to better discern the data. [Colour figure can be viewed at wileyonlinelibrary.com]
Figure 7. H-reflex facilitation differs between DM and RM

A, Individual and mean H-reflex facilitation (in % of unconditioned H-reflex) at EFD 0 ms, EFD +0.6 ms and EFD +3 ms when TMS H-reflex conditioning was applied during DM (dark blue) and RM (dark red) at MI. Data are presented as mean ± SD (asterisks indicate significant differences after multiple comparison correction). B, Individual and mean H-reflex facilitation (in % of unconditioned H-reflex) at EFD 0 ms, EFD +0.6 ms and EFD +3 ms when TMS H-reflex conditioning was applied during DM (light blue) and RM (light red) at ME. Data are presented as mean ± SD (asterisks indicate significant differences after multiple comparison correction). x-axis values of the dots representing single subjects were jittered to better discern the data. [Colour figure can be viewed at wileyonlinelibrary.com]
the last cycle of RM may be of a similar origin. The greater excitability of superficial circuits of motor cortex may thus specifically relate to the necessity to plan the end of the movement at a desired position. Conversely, based on greater H-reflex facilitation at EFD +3 ms in RM, underlying neural circuits may make a greater contribution to ongoing alternating movements. In addition, previous studies have provided behavioural evidence that discrete control processes contribute to the generation of the initial first cycle of RM (van Mourik & Beek, 2004; Ikegami et al. 2010). In the latter study, the authors showed different motor learning transfers from a visuomotor adaptation task for the first initial cycle of RM and later cycles of RM (Ikegami et al. 2010). Based on the results from this and our study, it is reasonable that neural circuits engaged in DM may be required to initiate and terminate RM.

Several methodological problems need to be discussed. First, some subjects showed huge H-reflex facilitation (five to eight times the unconditioned H-reflex) in some of the conditions which might have greatly influenced the statistical results. We explored the origin of these extreme values in these subjects and found that in all cases the unconditioned H-reflex was relatively small and the conditioned H-reflex relatively high. This resulted in high percentage H-reflex facilitation. We asked whether our statistical results were influenced by those extreme values. This was not the case. After removing the subjects from the sample and performing the same analyses, the statistical results were not different from the previous analyses.

Second, we observed differences in the kinematic properties of DM and RM that may have biased the differences in H-reflex facilitation between RM and DM. The two main kinematic differences were greater amplitude (approximately 4° difference) and mean velocity (approximately 7°/s difference) in RM. One reason for this could be the visual feedback during the task. Subjects were instructed to move the computer cursor representing their wrist position to the target (DM) or between the bars (RM) at a comfortable speed. As the horizontal position of the target varied between trials in the DM, subjects sometimes performed movements with little amplitude whereas during RM the position of the bars did not change. Besides the visual feedback being responsible, the intrinsic nature of the task could have also caused kinematic differences between RM and DM. Previous studies demonstrated inherent different kinematic properties (e.g. symmetry ratio, peak speed, movement time, acceleration) between DM and RM (Smits-Engelsman et al. 2002; van Mourik & Beek, 2004). For example, higher movement speed in RM showed the same level of accuracy as in DM (Smits-Engelsman et al. 2002). It is thus possible that the differences in H-reflex facilitation between RM and DM are related to differences in kinematics.

However, by integrating the kinematic changes in our statistical analyses we could at least attenuate this possibility, as differences in H-reflex facilitation between RM and DM were still significant after controlling for these changes. Moreover, we performed a subgroup analysis with 12 subjects in whom movement kinematics between DM and RM were not significantly different. We found that H-reflex facilitation at EFD +0.6 ms during DM was still significantly greater than during RM at MI and H-reflex facilitation at EFD +3 ms during DM was still significantly lower than during RM at ME for this reduced sample. Thus, kinematic differences between DM and RM observed in the present study could not explain the differences in H-reflex facilitation.

However, we cannot rule out the possibility that the differences in H-reflex facilitation are simply due to differences in the inherent kinematic characteristics of
the tasks during the tested movement phases. Indeed, velocity and acceleration profiles for both movements differ markedly between DM and RM (Fig. 4A). RM do not have to be initiated or terminated but rather have continuous changes in velocity and acceleration profiles. DM go from an initial to an end position and are thus bounded by zero velocity and zero acceleration. Thus, at least during stimulation at MI, there were great differences in the kinematic states of the movements.

We also observed differences in pre-stimulus EMG activity of the antagonistic ECR muscle during MI. Thus, we cannot completely rule out the possibility that spinal reciprocal inhibitory pathways modulated the synaptic transmission at the motoneurons during RM. Thus, differences in pre-stimulus ECR EMG activity may have led to the different modulations in H-reflex facilitation at EFD +0.6 ms during MI. However, there are several reasons why this seems unlikely. First, those differences (and the kinematic differences) were observed globally, i.e. in all movement phases and all tested EFDs. Hence, one would expect that the differences in H-reflex facilitation would emerge between all these tested conditions. Second, by integrating the differences in pre-stimulus ECR EMG activity and kinematics in the ANOVA as a covariate, we show that modulation of H-reflex facilitation was still significantly different between DM and RM at the specific EFDs.

In conclusion, using an advanced human non-invasive electrophysiological approach our results indicate a differential modulation of distinct motor cortex and corticospinal circuits during DM and RM. The differential modulations most likely point to different neural strategies being used to control movements that are executed rhythmically and discretely. This assumption is in accordance with a recent study demonstrating that RM are less affected than DM in stroke patients (Leconte et al. 2016). Thus, our findings may be of interest for better understanding the motor deficits in diseases affecting the corticospinal system.

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