A neurophysiological basis for the coordination between hand and foot movement

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Abstract

Hand and foot movements are made more reliably when both limbs move in the same direction at the same time (isodirectional), compared to when they are made in opposite directions (anisodirectional). We hypothesised that M1 intracortical facilitation may subserve hand-foot coordination, and reveal correlates that explain the preference for hand-foot movements to be performed in an isodirectional pattern. To test our hypothesis we investigated behavioural kinematics of hand-foot coordination (Experiment 1) and neurophysiological measures of corticomotor excitability and intracortical facilitation (Experiment 2) in 17 healthy young adults. As expected, coordination became unstable in the anisodirectional pattern but not the isodirectional pattern, as confirmed in measures of wrist and ankle relative phase error and stability (both \(P < 0.001\)). Short-latency paired-pulse TMS was used to elicit MEPs and produce short-latency intracortical facilitation (sICF) in right extensor carpi radialis (ECR) and flexor carpi radialis (FCR) in the presence and absence of right ankle plantar/dorsiflexion (\(P < 0.015\)). An isodirectional preference was confirmed by facilitation of FCR MEPs and TMS-induced wrist flexion during ankle plantarflexion (both \(P < 0.025\)), but no evidence of modulation of any particular “I-wave” during foot movement compared to rest. A novel finding was the association between loss of stability of the anisodirectional pattern (Experiment 1) and the modulation of corticomotor excitability in support of the isodirectional pattern (Experiment 2) (\(P < 0.05\)). The preference for isodirectional hand-foot movements appears not to depend on M1 intracortical facilitation.
Introduction

Coincident ipsilateral hand and foot movements are made more reliably in the same direction (isodirectional, easy) than in the opposite direction (anisodirectional, difficult), as quantified by relative joint angles between ankle dorsiflexion-plantarflexion and wrist flexion-extension (Baldissera et al. 1982; Carson et al. 1995; Kelso and Jeka 1992). For instance, when movements are sped up, a phase transition commonly occurs from the anisodirectional to isodirectional pattern, but not vice versa (Baldissera et al. 2002; Baldissera et al. 1982), indicative of coupled oscillator dynamics (Kelso et al. 1981; Swinnen 2002).

The neurophysiological mechanisms underpinning the dynamics of hand-foot coordination are not fully understood. There are no anatomical connections between hand and foot representation areas within primary motor cortex (M1) (Huntley and Jones 1991), suggesting common input arising from secondary motor areas rather than horizontal connectivity within M1 (Murthy and Fetz 1996). During ipsilateral foot movement, the excitability of cortical forearm representations is modulated to facilitate an isodirectional pattern between hand and foot (Baldissera et al. 2002). For example, with the forearm resting in the prone position motor evoked potentials (MEP) in extensor carpi radialis (ECR) increased in size during ankle dorsiflexion (DF) compared to plantarflexion (PF), with the opposite pattern of modulation occurring for flexor carpi radialis (FCR). This coupling is presumed to be direction-dependent as opposed to muscle-dependent given that the modulation of MEPS in forearm muscles is reversed with a supine forearm posture (Borroni et al. 2004). Using dual-coil transcranial magnetic stimulation (TMS) Byblow et al. (2007) identified a putative functional network between dorsal premotor cortex (PMd) and M1 subserving the isodirectional coupling of hand and foot.
movement. PMd contains neural representations of relative position codes (Pesaran et al. 2006) and thus, may provide a general solution to the spatial problem of coordinating different body parts. Currently it is not known whether the PMd – M1 pathway facilitates the production of isodirectional patterns via a direct facilitatory pathway between PMd and M1, the modulation of inhibitory projections between PMd and M1 circuits mediating SICI (Byblow et al. (2007); (Fujiyama et al. 2009; Fujiyama et al. 2012), or both. Facilitation along the PMd – M1 pathway specifies the preferred coordination mode but so far it not known if this is the sole pathway through which one mode or the other is selected during interlimb coordination.

It is well understood that TMS over M1 produces temporally distinct volleys in the corticospinal pathway as a result of direct and indirect activation of the pyramidal neurons (Di Lazzaro et al. 2000). Paired-pulse TMS studies have identified three peaks of facilitation with a periodicity of approximately 1.5 ms at inter-stimulus intervals (ISIs) in the range of 1.1 – 1.5, 2.3 - 3.1 and 4.1 – 4.5 ms (Di Lazzaro et al. 1999; Peurala et al. 2008; Ziemann et al. 1998). This so-called “I-wave facilitation” is presumed to occur between excitatory interneurons within one, two or three synapses from M1 corticospinal projection neurons. Of interest however is a recent study showing that I-waves may originate within PMd as well as within M1 (Groppa et al. 2012a). These authors found that a conditioning stimulus (CS) applied to PMd facilitated MEPs derived from an M1 test stimulus (TS) at ISIs of 2.4 - 2.8 and 4.4 ms, but no facilitation occurred at any ISI if the CS was applied to dorsolateral prefrontal cortex. PMd is an anatomical region located anterior to the crown of the precentral gyrus and is thus susceptible to M1 TMS. This led to the idea that late (I2, I3) I-waves may originate, at least in part, from within PMd even when paired pulse TMS is applied over M1 alone (Baumer et al. 2006).
The present study was designed to investigate whether isodirectional coupling between ankle and wrist flexors and extensors might be explained by facilitation via specific I-wave facilitation using short-latency intracortical facilitation (sICF) (Peurala et al. 2008; Ziemann et al. 1998). Our hypothesis was that isodirectional tendencies would reflect, at least in part, facilitation occurring at I-wave periodicity attributable to a (putative) PMd origin. We conducted behavioural and neurophysiological experiments in order to: i) confirm the preference for isodirectional hand-foot coordination in our sample; and ii) test the hypothesis that there would be a correlation between the isodirectional tendency and the modulation of corticomotor excitability of wrist extensors (and flexors) during ankle plantar versus dorsiflexion.

Methods

Participants

Seventeen participants (8 M; mean age 22.3 y, range 20 - 26 years with no neurological impairments, no wrist or ankle injury, nor contraindications to TMS participated in two experiments. The University ethics committee approved the procedures, and participants gave written informed consent prior to participation, in accordance with the Declaration of Helsinki. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield 1971).

Recording and stimulation procedures

Preparation

Electromyography (EMG) data were recorded from the right ECR, FCR, right tibialis anterior (TA), and right soleus (SOL) muscles via 6 mm diameter surface Ag-AgCl electrodes, using standard techniques. EMG data were amplified (Grass P511AC, Grass Instrument
Division, West Warwick, RI), bandpass filtered (10 - 1000 Hz), sampled at 2000 Hz using a 16-bit A/D acquisition system (National Instruments, Austin, TX), displayed using custom LabVIEW software, and stored to disk for subsequent offline analysis.

Transcranial Magnetic Stimulation

Two MagStim 200 monophasic magnetic stimulators (MagStim Company, UK, maximum output intensity 2.0 T) were used to deliver TMS to the left motor cortex via a figure-of-eight coil. The stimulators were connected via a Bi-stim module allowing for the delivery of two stimuli through the same coil at pre-determined ISIs. The coil was oriented such that the handle was directed posteriorly at a 45º angle to the midline with the induced current flow in a posterior to anterior direction to optimally stimulate M1 (Kaneko et al. 1996) at the best location for eliciting MEPs in the right ECR.

Experimental Procedure

Participants were seated with their right hand and foot supported in a custom-built manipulandum (Figure 1). The right elbow, wrist, knee and ankle were positioned at 90º, 0º, 130º, and 90º flexion, respectively. The manipulandum consisted of hand and foot plates attached to horizontal spindles, aligned to the right wrist and ankle joint. Potentiometers were calibrated to record angular displacement of the right hand and right foot. An adjustable elastic support was used to oppose the combined weight of the participant’s hand and the plate to set the wrist with equal and negligible resistance in flexion or extension. The left foot was supported at the same height as the right foot and the left hand was rested on the participant’s lap.
Experiment 1: Hand-Foot Coordination

Experiment 1 was a behavioural paradigm involving concurrent right wrist flexion and extension and right ankle plantar and dorsiflexion in time with a metronome beat (pitch 800 Hz, pulse duration 50 ms). The metronome began at 1.2 Hz and increased to 2.0 Hz in 0.2 Hz increments every 10 s for trial duration of 50 s. Participants were instructed to synchronise their movements with the metronome, and move through a comfortable range of flexion-extension and dorsiflexion-plantarflexion i.e., within a natural and comfortable range of excursion. Movements began in one of two patterns: isodirectional (easy) or anisodirectional (difficult). In the isodirectional pattern, maximum plantarflexion of the ankle occurred at the same time as maximum wrist flexion on the metronome beat, and dorsiflexion of the ankle coincided with wrist extension between the beats. In the anisodirectional pattern, maximum plantarflexion of the ankle occurred at the same time as maximum wrist extension on the metronome beat, while dorsiflexion of the ankle and wrist flexion occurred between beats. Phase transitions from the anisodirectional to the isodirectional pattern were expected (Baldissera et al., 1982). Prior to each trial, participants were informed that if their movement pattern suddenly changed during the trial they were to keep making movements in time with the metronome without attempting to revert back to the initial pattern. Potentiometer signals were converted to angle and phase measures and the main dependent measure was relative phase between hand and foot calculated as the phase angle of ankle subtracted from that of the wrist. The absolute error of relative phase was used as a measure of accuracy. This was determined by calculating the absolute distance from target relative phase (0° = isodirectional, 180° = anisodirectional) and converted to a fraction between 0 and 0.5. Uniformity of relative phase was used as a measure of stability (Byblow et al. 1994).
When present, the time to transition (s) was determined for each trial as well as the average time to transition.

Experiment 2: Neurophysiological Basis of Isodirectional Tendency

Experiment 2 was completed with the forearm at rest always, and the leg either at rest or during ankle DF or PF in time with a metronome (Byblow et al. (2007). In this experiment, the spindle attached to the footplate of the manipulandum was connected to a Brushless AC Servomotor (Baldor, Fort Smith, AR) programmed to provide a resistive torque against ankle movements in either direction, restricting their excursion to a maximum of 40°. The resistive torque aided compliance with task instructions to help ensure a definite discrete SOL burst during PF since these movements are otherwise assisted by gravity. In all trials the forearm and hand were supported and rested in a prone posture. Auditory feedback of EMG data were used to monitor relaxation of the forearm muscles and confirmed by quantitative off-line analysis. Participants were instructed either to remain at rest or to perform rhythmic dorsiflexion (DF) or plantarflexion (PF) movements in time with the metronome. Each trial consisted of seven metronome beats (pitch 800 Hz, pulse duration 50 ms) at 1.0 Hz. Ankle movement was performed through 25 - 30° and synchronized with the metronome at peak DF or PF.

TMS was delivered as single (non-conditioned, NC) or paired-pulse (conditioned, C), in a randomized order. Resting motor threshold (RMT) was established as the stimulator intensity (%MSO) that produced ≥ 50 µV MEPs in ECR in four out of eight consecutive trials (Rossini et al. 1999). For the test stimulus (TS) the stimulator was set to the intensity that produced approximately 1 mV peak-to-peak amplitude MEPs in the right ECR. The conditioned stimulus intensity (CS) intensity was always set to 90% of RMT. In conditioned trials, the CS followed
the TS at an ISI of 1.5, 3.0, or 4.5 ms corresponding to preferential I1, I2 or I3 wave periodicity (Ziemann and Rothwell 2000). A recent study by Peurala and colleagues determined that peaks of facilitation occur within the range of 1.1 – 1.5 ms, 2.3 – 3.1 ms, and 4.1 – 4.5 ms for I1, I2 and I3 respectively (Peurala et al. 2008). Stimuli were applied 100 ms before the 5th, 6th or 7th metronome beat (pseudo-randomized) resulting in the delivery of TMS during peak TA or SOL activation during DF and PF conditions respectively. There were 12 blocks of 16 trials each to yield 4 blocks for each movement condition (Rest, DF, PF) and 16 NC and C MEPs in each condition. Trials were discarded if TMS was delivered outside the SOL burst during PF, or outside the TA burst during DF.

ECR and FCR MEP areas were determined due to the sometimes polyphasic nature of forearm muscle MEPs (Stinear and Byblow 2004). MEP area (mV·ms) was calculated over a 20 ms window from MEP onset determined individually for each muscle and participant. MEP areas were averaged for each direction and stimulation condition.

The kinematics of TMS-evoked hand movements were acquired as a surrogate measure of M1 directional tuning (Classen et al. 1998). TMS-evoked movements of the hand were measured using displacement data collected from potentiometer signals. The displacement data were filtered with a low-pass Butterworth filter (5 Hz cut-off), differentiated to derive velocity, and filtered and differentiated again to derive acceleration. Stimulus-evoked velocity (SEV), was used as an estimate of directional tuning defined as the velocity at the time of the maximal acceleration peak within the first 150 ms after TMS (Byblow et al. 2007). SEV (°/s) during DF and PF were normalized to SEV at rest (DF or PF minus rest).

Pre-trigger root mean squared EMG (rmsEMG) was acquired 50 ms pre-stimulus. Trials with pre-trigger rmsEMG >10 µV in either forearm muscle were discarded to ensure all MEPs
were surrogates of corticomotor excitability without contamination of voluntary EMG. Pre-
trigger rmsEMG was also monitored in the TA and SOL during rest with trials of rmsEMG of
>10 µV in either muscle discarded. Pre-trigger rmsEMG data were subjected to the same
statistical analyses as MEP area data. Less than 3% of trials were discarded due to excessive
EMG.

**Statistical analyses**

All analysis of variance contained repeated measures (RM-ANOVA).

In experiment 1, average absolute error of relative phase was analyzed as a measure of
movement accuracy with a 2 Pattern (isodirectional, anisodirectional) x 5 Frequency (1.2, 1.4,
1.6, 1.8, 2.0 Hz) RM-ANOVA. Uniformity of relative phase provided a measure of pattern
stability and was analysed with a 2 Pattern (isodirectional, anisodirectional) x 5 Frequency (1.2,
1.4, 1.6, 1.8, 2.0 Hz) RM-ANOVA.

In experiment 2, measures were normalised two separate ways. Normalisation of
conditioned MEPs to NC allowed us to examine I-wave facilitation. Normalisation of MEP area
or SEV obtained during foot movement to those obtained at rest allowed us to examine
directional tuning.

sICF at rest was investigated with a 2 Muscle (ECR, FCR) x 4 Interval (NC, I1, I2, I3)
RM-ANOVA of MEP area. A 2 Muscle x 3 Interval (I1, I2, I3) RM-ANOVA of MEP area
normalized to rest (C/NC) was also conducted. One sample t-tests were used to determine
whether the MEP areas were facilitated for each I-wave interval.

For MEP area, directional tuning was assessed with a 2 Muscle (ECR, FCR) x 2
Direction (DF, PF) RM-ANOVA where DF and PF MEP areas were normalized to rest (DF or
RM-ANOVAs were run to compare MEP area across each level of Muscle, Direction
and Interval, in which Direction and Interval were normalized to rest in separate ANOVAs.
Namely, a 2 Muscle x 2 Direction (DF, PF) x 4 Interval (NC, I1, I2, I3) normalized to rest, and a
2 Muscle x 3 Direction (Rest, DF, PF) x 3 Interval (I1, I2, I3) normalized to NC. To determine
the contribution of each Interval to directional tuning, linear regressions were computed for ECR
and FCR NC MEP areas against I1, I2 and I3 MEP areas.
SEV data from all stimulation conditions were combined and analysed using a paired t-
test with the factor Direction (DF, PF) normalized to Rest. SEVs were also compared using a 2
Direction x 4 Interval (NC, I1, I2, I3) RM-ANOVA.
Separate one-way RM-ANOVAs of pre-trigger rmsEMG for ECR and FCR were
conducted for the factor of Direction (Rest, DF, PF).
To determine if measures of isodirectional tuning (MEP area, SEV, Exp 2) were
associated with behavioural measures of pattern stability (Exp 1) linear regressions were
undertaken between time to transition and a composite measure of directional tuning in terms of
NC MEP area \(((ECR \ DF / ECR \ Rest) - (FCR \ DF / FCR \ Rest)) + ((FCR \ PF / FCR \ Rest) - (ECR
PF / ECR \ Rest)))\) and SEV \(((DF - Rest) + (PF - Rest))\). These composite measures yield larger
values with more directional tuning.
Statistical significance was set at \(\alpha = 0.05\). For non-spherical data, the Greenhouse-
Geisser correction for repeated measures was applied. Post-hoc t-tests were used to explore main
effects or interactions as required. When post-hoc t-tests numbered 3 or less for a given analysis,
they were not corrected for multiple comparisons. Otherwise they were corrected using a
Bonferroni procedure. All results are reported in text as mean ± standard error (SE).

Results
The procedures were tolerated by all subjects. The Edinburgh Handedness Inventory indicated a mean laterality quotient of 0.73 (range 0.30 – 1) for the mostly right handed group, with three participants scoring between 0.3 - 0.5.

Experiment 1

During each trial of hand-foot coordinated movement, transitions occurred from an anisodirectional to isodirectional pattern. The average time to transition ranged between 6.0 – 49.0 s (mean 21.1 ± 3.2 s) across trials and participants.

There were main effects of Pattern ($F_{1,16} = 44.48, P < 0.001$), Frequency ($F_{4,64} = 14.69, P < 0.001$) and a Pattern x Frequency interaction ($F_{4,64} = 8.80, P = 0.001$) in the analysis of absolute error of relative phase. Error was greater for anisodirectional than isodirectional patterns at each frequency (all $P < 0.001$; all $P < 0.01$ corrected; Figure 2).

There was a main effect of Pattern ($F_{1,16} = 34.47, P < 0.001$) with no effect of Frequency or Pattern x Frequency interaction (both $P > 0.41$) in the analysis of uniformity of relative phase. Uniformity of relative phase was greater for isodirectional than anisodirectional patterns at all frequencies other than 1.6 Hz (all $P < 0.02$).

Experiment 2

**MEP Area and sICF at Rest**

Example EMG and kinematic traces for representative participants are shown in Figure 3.

For raw ECR and FCR MEP area, there was a main effect of Interval ($F_{3,48} = 5.28, P = 0.013$), with no effect of Muscle or Muscle x Interval interaction ($F_{1,16} = 0.81, P = 0.38$, and $P = 0.07$, respectively). Post-hoc pairwise comparisons identified facilitation of MEP area of each I-wave
interval compared to NC (all $P < 0.05$), and between I1 and I2 MEP area with I1 being larger ($P < 0.001$). When normalized to NC, conditioned MEP areas did not differ from each other ($F_{2,32} = 1.92; P = 0.163$). One sample t-tests identified facilitation of MEP areas in the ECR and FCR for each I-wave relative to rest (all $P < 0.04$; Figure 4). There was no effect of Muscle or a Muscle x Interval interaction ($P = 0.61$ and $F_{2,32} = 3.02, P = 0.09$, respectively).

**Directional Tuning Normalized to Rest: NC MEP and SEV**

For NC MEP area (normalized to rest) there was a Muscle x Direction interaction ($F_{1,16} = 6.24, P = 0.024$; Figure 5a), with no effect of Direction ($F_{1,16} = 3.75, P = 0.071$) or Muscle ($P = 0.128$). The interaction reflected an iso-directional bias of MEP area facilitation in the FCR during PF.

For SEV there was a main effect of Direction (normalized to Rest) ($F_{1,16} = 6.80, P = 0.019$). TMS evoked wrist extension during DF and wrist flexion during PF (Figure 5b). Based on timing of EMG burst onsets in SOL and TA, there was a greater number of trials rejected during PF (mean rejected = 14/64) compared to DF (mean rejected = 6/64) ($t_{16} = -3.98, P = 0.001$) indicative of greater difficulty in timing SOL contraction / PF movement.

**sICF and Directional Tuning**

For MEP area normalized to rest, there was a Muscle x Direction interaction ($F_{1,16} = 7.00, P = 0.018$) with no main effect of Direction or Interval (both $P > 0.12$). With Interval collapsed across Direction, post-hoc pairwise comparisons showed MEP area in the FCR was greater during PF than DF ($P = 0.027$).

When MEP area was normalized to NC, there was a Muscle x Interval interaction ($F_{2,32} = 4.42, P = 0.041$). There was a trend, but no interaction of Muscle x Direction x Interval ($F_{4,64} = 2.26, P = 0.093$). Post-hoc pairwise comparisons with Direction collapsed across Interval indicated that ECR MEP area was greater for I1 Interval than I2 ($P = 0.001$), but with no effects seen in the FCR.

For SEV including conditioned trails, there was no main effect of Interval ($P = 0.471$) and no Interval x Direction interaction ($P = 0.306$). The previously identified main effect of Direction on SEV was again present ($F_{1,16} = 7.10, P = 0.017$).

**RMT and Pre-trigger rmsEMG**

Resting motor threshold was $41.8 \pm 1.7 \%$MSO and TS was $58.9 \pm 2.1 \%$MSO ($142 \pm 41 \%$RMT). Both ECR and FCR remained at rest throughout collection. Analysis of pre-trigger rmsEMG from experiment 2 showed no effects or interactions for the ECR ($P > 0.3$) but a main effect of Direction for FCR ($F_{2,32} = 7.41; P = 0.002$). The statistical effect did not decompose meaningfully. rmsEMG levels were $4.15 \pm 0.17, 4.47 \pm 0.22, \text{and } 4.47 \pm 0.20 \mu V$, for Rest, DF, and PF respectively. Regression of rmsEMG against MEP area indicated no linear association (all $R^2 < 0.1$), confirming that the small variation in pre-trigger rmsEMG was not associated with modulation of MEP area.

**Linear Regression**

There was an association between participants’ average time to transition from the anisodirectional pattern to the isodirectional pattern (Exp 1) and the degree of directional tuning observed in MEP modulation (Exp 2) ($R^2 = 0.23, F_{1,16} = 4.54, P = 0.05$). Participants who tended to have a greater extent of modulation between conditions in Exp 2, i.e., stronger
neurophysiological directional tuning toward isodirectional patterns, also tended to have faster
times to transition in Exp 1 (Figure 6).

Discussion

In support of our hypotheses, there was evidence of isodirectional tendencies between
hand and foot coordination (Exp 1) and for directional tuning of resting upper limb
neurophysiological excitability and kinematics obtained during foot movement (Exp 2) as well as
an observed association between neurophysiological and behavioural measures obtained in
separate experiments. Although previous studies have identified PMd as a potential origin for I-
waves, we found no indication of a specific I-wave mediated intracortical facilitation underlying
isodirectional tendencies between hand and foot in the present study.

Isodirectional Tendencies During Hand-Foot Coordination

Hand-foot movements made in the anisodirectional pattern were less accurate and more
variable than in the isodirectional pattern, in accordance with previous studies. This confirms the
isodirectional preference for ipsilateral hand and foot movements. Spontaneous transitions were
consistent with coupled oscillator dynamics, evident by switching from the anisodirectional to
the isodirectional pattern as movement rate increased (Carson et al. 1995; Kelso et al. 1981).

Intracortical Facilitation of Forearm Representations

Paired-pulse TMS was used to examine intracortical facilitation of forearm
representations at I-wave periodicity. I-wave facilitation at rest was found to be present in
cortical pathways projecting to ECR and FCR for the first three I-waves. Previous studies have
demonstrated I-wave facilitation of cortical pathways projecting to intrinsic hand muscles, and
to biceps brachii (Chen and Garg 2000), but to our knowledge, this is the first demonstration of
“I-wave facilitation” in ECR and FCR. When conditioned MEP area was normalized to NC, each I-wave was found to facilitate MEPs in both the ECR and FCR with no difference between each I-wave interval. This indicates that at rest, I1, I2 and I3 components contribute to corticospinal facilitation.

Directional Tuning During Foot Movement

In Experiment 2, directional tuning was demonstrated neurophysiologically by an increase in FCR MEP area during PF compared to DF. This finding is in agreement with previous results, although there was no evidence of directional tuning in ECR (which did not differ between DF and PF), as had been found previously (Byblow et al. 2007). The greater difficulty of timing PF compared to DF movements might explain, at least in part, why there was more pronounced directional tuning in FCR than ECR. Task difficulty may have led to a nonspecific and more widespread increase in excitability within M1 during PF, given that effort and task complexity influence corticomotor excitability (Qing Cui and Deecke 1999). It is not clear as to why the PF condition was more difficult in the present study compared to our previous experiments (Byblow et al. 2007). It may relate to small differences between studies in the amount of resistive torque applied by the torque motor (and hence effort required by the participants) and posture that made the PF condition more difficult than DF in the present study. This notwithstanding there was evidence for directional tuning with respect to FCR.

Evidence for directional tuning was also observed in the kinematics of TMS-evoked hand movements. These occurred in the same direction as voluntary foot movements i.e., toward extension during DF, and toward flexion during PF in accordance with previous findings (Byblow et al. 2007). The kinematic measure of SEV is a surrogate marker of directional tuning across the entire forearm, as opposed to an MEP measure derived from a single muscle. It is
encouraging that the SEV and MEP analyses are complimentary and both measures reflect directional tuning in this paradigm.

**Contribution of Intracortical Facilitation to Directional Tuning**

There was limited evidence for specific I-wave contributions to directional tuning. Linear regressions indicated that conditioned MEP area at each I-wave interval was positively correlated with NC MEP area for both ECR and FCR. The linear slope was steepest for the I1-wave, shallowest for the I2-wave, and intermediate for I3-wave, providing some evidence that the I1-wave had the greatest influence on directional tuning. However, this finding was not supported by ANOVA of conditioned MEPs, with no three-way interaction to indicate differential modulation of I-waves with movement direction. As such, the present results provide minimal support for the hypothesis that directional tuning might reflect facilitation from early I-wave periodicity.

Short-latency intracortical facilitation of MEPs in an intrinsic hand muscle, may originate from stimulation of neurons originating within PMd (Groppa et al. 2012b). Of relevance for the present study is that PMd-M1 connectivity has been suggested to mediate the isodirectional preference of ipsilateral hand and foot movements, given that PMd-M1 facilitation is up-regulated during isodirectional as opposed to anisodirectional conditions (Byblow et al. 2007). However, given the absence of evidence that isodirectional tendencies of ipsilateral hand and foot movements were mediated by intracortical facilitation, it may be that M1 intracortical inhibitory circuits play a larger role in this process. This idea already has empirical support from reduced short-interval intracortical inhibition in ECR during foot dorsiflexion (but not plantarflexion) compared to rest (Byblow et al. 2007). Complementary findings from (Fujiyama et al. 2009; Fujiyama et al. 2012) indicate that the stability of coordination of ipsilateral upper
and lower limb movement may be related to regulation of M1-mediated inhibition. Thus, modulation of GABAergic inhibitory networks may support isodirectional tendencies between ipsilateral hand and foot, and these may be modulated in part by circuits originating in PMd (Koch et al. 2007; O'Shea et al. 2007; Suppa et al. 2008; Uehara et al. 2013).

Neurophysiological Basis for Hand-Foot Coordination

There was an association between the behavioural transition dynamics of hand-foot coordination observed in Exp 1 and the ECR/FCR MEP modulation observed during foot movement in Exp 2. Participants who had a faster time to transition, indicating a breakdown of the more difficult anisodirectional pattern, exhibited a greater degree of MEP modulation in support of producing the isodirectional pattern. While this correlation is not causal, it is reasonable to suspect that the modulation obtained in measures of directional tuning from TMS, may reveal at least in part, an individual’s preference for isodirectional over anisodirectional hand-foot movements. We are aware of no previous correlational data linking neurophysiological and behavioural measures of interlimb coordination. A similar finding exists from a study bimanual coordination, where there was an observed association between the breakdown of bimanual circling (antiphase to inphase), and the presence of MEPs in a hand muscle ipsilateral to the stimulated M1 (Kagerer et al. 2003). The idea put forth by Kagerer and colleagues was that descending commands intended for the crossed pathway and contralateral upper limb were also propagated along uncrossed pathways to the ipsilateral side. This made symmetric bimanual movements more likely in those individuals with a relatively greater proportion of uncrossed pathways based on the surrogate measure presence of ipsilateral MEPs. It is unlikely that uncrossed pathways play a role in hand-foot movements, given that both limbs are on the same side of the body, and there are no known horizontal connections within M1 functionally linking
corticospinal neurons of hand and leg representations (Huntley and Jones 1991). For these reasons the preference for isodirectional hand-foot movement might originate in premotor areas (Roland et al. 1980) such as PMd. The present results support earlier findings that M1 corticospinal excitability is modulated to favour the production of hand and foot movements in the same direction, over those in opposite directions.

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References


Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory.


Figure Captions

Figure 1: The participant configuration and apparatus for both experiments. Both hand and foot were moved voluntarily in Experiment 1. In Experiment 2 only foot movements were performed with hand movements “evoked” by TMS.

Figure 2: Absolute error of relative phase between wrist and ankle angle for isodirectional (filled) and anisodirectional (open) coordination patterns. Symbols represent the group mean (N = 17). Y-axis values, 0.5 = 180 degrees. Error bars represent SE.

Figure 3: Experiment 2. A: ECR EMG traces showing MEPs at rest for a single participant at each I-wave interval. Traces are averages of 16 trials. Gray horizontal lines indicate NC MEP amplitude. B: EMG and kinematic traces illustrating ECR and FCR MEPs, SOL and TA EMG and wrist displacement for a single participant. Traces are averages of 16 trials. Gray horizontal lines indicate MEP amplitude at rest.

Figure 4: Normalized MEP area recorded from the ECR (filled bars) and FCR (open bars). Dashed line indicates NC stimulation MEP area. Bars represent the group mean (N = 17). Error bars represent SE.
Figure 5A: ECR (filled bars) and FCR (open bars) MEP area during foot movement. Dashed line indicates MEP area at Rest (no foot movement). Symbols represent the group mean (N = 17). Error bars represent SE.

Figure 5B: TMS-evoked wrist flexion-extension (SEV) during foot movement. Mean SEV during DF (filled bar) and PF (open bar) foot movements. SEV has been normalized by subtracting rest SEV from movement SEVs. Positive SEV = extension; negative SEV = flexion. Bars represent the group mean (N = 17). Error bars represent SE.

Figure 6: Linear regression between Behavioural Time to Transition (Exp 1) and Directional Tuning (Exp 2). X axis is unitless ratio based on MEP area where positive values indicate excitability bias toward directional tuning (e.g., larger ECR than FCR MEP during DF) and negative values indicate a bias away from directional tuning (e.g., larger FCR than ECR MEP during DF); see text for formula. Symbols represent individual participant data (N = 17).