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Abstract

The motor system displays strong changes in neural activity during action preparation. In the past decades, several techniques, including transcranial magnetic stimulation (TMS), electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), have allowed us to gain insights into the functional role of such preparatory activity in humans. More recently, new TMS tools have been proposed to study the mechanistic principles underlying the changes in corticospinal excitability during action preparation. The aim of the present review is to provide a comprehensive description of these advanced methods and to discuss the new knowledge they give access to, relative to other existing approaches. We start with a brief synthesis of the work that has been achieved so far using classic TMS protocols during action preparation, such as the so-called single-pulse and paired-pulse techniques. We then highlight three new approaches that recently arose in the field of action preparation, including (1) the exploitation of TMS current direction, known as directional TMS, which enables investigating different subsets of neurons in the primary motor cortex, (2) the use of paired-pulse TMS to study the suppressive influence of the cerebellum on corticospinal excitability and (3) the development of a double-coil TMS approach, which facilitates the study of bilateral changes in corticospinal excitability. The aim of the present article is twofold: we seek to provide a comprehensive description of these advanced TMS tools and to discuss their bearings for the field of action preparation with respect to more traditional TMS approaches, as well as to neuroimaging techniques such as EEG or fMRI. Finally, we point out perspectives for fundamental and clinical research that arise from the combination of these methods, widening the horizon of possibilities for the investigation of the human motor system, both in health and disease.
Human daily life entails the flexible navigation through continuous sets of actions (Cisek and Kalaska, 2010). We walk the world, play sports, manipulate tools and drive cars in a seemingly fluid and effortless manner. Yet, for each action we take, a series of complex preparatory processes must occur in our brain (Haith et al., 2016), allowing us to decide which motor goal to pursue, to select between effectors, and to specify the features of the movements that will ultimately implement these so-called “motor decisions” (Wong et al., 2015). Hence, the execution of any action is preceded by a phase of preparation, which is colloquially referred to as action preparation (or action/motor/movement planning; Churchland et al., 2012, 2010, 2006; Cisek, 2006; Svoboda and Li, 2018). Understanding the neural basis of action preparation is crucial as the disruption of preparatory processes may contribute to highly debilitating psychiatric and movement disorders (e.g., impulsivity disorders, Heinrich et al., 2014; Hoegl et al., 2012; or focal hand dystonia, Beck et al., 2008).

The motor system shows strong fluctuations in neural activity during action preparation (Chen et al., 2019; Gao et al., 2018; Lara et al., 2018; Perich et al., 2018). Several techniques, including transcranial magnetic stimulation (TMS), electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), have allowed us to gain insights into the contribution of these changes to preparatory processes in humans. In this review, we focus mostly on studies that have used TMS protocols to probe the activity of the motor system and the neural source of modulatory changes during action preparation. We discuss the main findings that came out from this work, putting the emphasis on how a set of recent approaches have allowed significant advances in the field, compared to other neuroimaging methods.

Using TMS to study corticospinal excitability during action preparation: current limitations and solutions

An effective way to investigate preparatory activity in humans is through the quantification of motor-evoked potentials (MEPs) – a probe of corticospinal (CS) excitability – which can be elicited in hand muscles by applying single-pulse TMS over the contralateral primary motor cortex (M1) at any time during action preparation (Bestmann and Duque, 2016; Derosiere and Duque, 2020). Using this approach, neuroscientists have made major advances in the understanding of the CS correlates of action preparation in the past decades.

Yet, despite this progress, researchers have been facing some practical limitations in the past few years. First, standard single-pulse TMS elicits MEPs that reflect the summation of multiple
monosynaptic and polysynaptic inputs on the CS pathway (see Figure 1, below). Hence, fluctuations in some of these inputs may not necessarily translate into consistent MEP changes, especially if overlapping influences have opposite effects on the CS pathway, thus cancelling out at the level of the MEP measure (Di Lazzaro and Rothwell, 2014). Another issue is related to the difficulty, if not the impossibility, to investigate subcortical areas with TMS, confining investigations to areas that are part of the cortical mantle, though several subcortical structures also contribute to the changes in CS excitability observed during action preparation. Finally, almost all studies of CS excitability have considered MEPs on one side of the body only, because probing them on both sides would double the length of the experiment. Hence, most conclusions have been reached by only considering half of the picture, excluding potential functional differences between the two hemispheres.

The motivation to overcome these issues has led to the recent development of new TMS approaches in the field of action preparation. Those include the exploitation of directional TMS approaches, which enables investigating different populations of neurons in M1 (Hannah et al., 2018), the use of paired-pulse TMS to study the influence of subcortical structures such as the cerebellum on CS excitability (ppTMS\textsubscript{CB-M1}; Spampinato et al., 2017) and the development of a double-coil TMS approach, which facilitates the study of bilateral changes in CS excitability (Grandjean et al., 2018; Vassiliadis et al., 2018). The aim of the present paper is twofold: we seek (1) to provide a comprehensive description of these advanced TMS approaches and (2) to discuss their bearings for the field of action preparation with respect to more traditional TMS procedures, as well as to neuroimaging techniques such as EEG or fMRI. To do so, we adopt a particular layout. We start with a succinct synthesis of the work that has been achieved so far using classic TMS procedures during action preparation, including single-pulse and ppTMS techniques. Our goal here is not to provide an exhaustive description of this work (this has been done in other recent reviews; e.g., see Bestmann and Duque, 2016) but rather to provide some background on the use of standard methods in the context of action preparation and on the main findings that have emerged from this approach. We then feature different articles that have recently exploited the three advanced methods mentioned above (Hannah et al., 2018; Spampinato et al., 2017; Vassiliadis et al., 2018). For each of these, we first describe the technique ("How does it work?") and then highlight its benefits in the context of the study of action preparation ("Interest for the field of action preparation"). Finally, we suggest future directions for fundamental and clinical research, emphasizing on the potential of combining these methods for the study of the CS system and related neural structures, both in health and disease.
Three decades of work using single-pulse and paired-pulse TMS during action preparation

In its classic form, the single-pulse technique involves placing a coil composed of two circular wings of wire (i.e., namely a “figure-of-eight” coil) on the scalp over M1, with the handle oriented towards the back of the head and turned laterally to form a 45° angle with respect to the midline (see Figure 1). The center of the coil is positioned over a so-called “hotspot”, defined as the site at which M1 stimulation elicits the largest motor potentials in a targeted contralateral muscle, such as the first dorsal interosseous (FDI; i.e., an index finger muscle). Surface electrodes are disposed on the targeted muscle and are plugged with cables into an electromyography (EMG) system.

A brief surge of electrical current is released in the wings of the coil, generating a transient magnetic field (i.e., a pulse), which in turn induces an electrical current in the underlying cortical tissue and depolarizes a set of CS cells. So far, most single-pulse studies have exploited a set-up in which the current flows in a clockwise direction in the left wing of the coil and in an anticlockwise direction in the right wing, inducing a current that flows in the postero-anterior (PA) direction in the cortex (see section on Directional TMS for more information). Still, coils of different sizes can be exploited, impacting the strength and the distribution of the magnetic field within M1 (Salvador and Miranda, 2009). In addition, experimenters have usually exploited suprathreshold intensities, that is, stimulation intensities set above an individual resting motor threshold (RMT). This RMT is defined as the minimal intensity allowing one to elicit motor potentials with a probability of 50 % in the targeted muscle at rest; in most action preparation studies, TMS is applied between 110 % and 130 % of the RMT (e.g., Chowdhury et al., 2019; Lebon et al., 2019).

TMS can depolarize some CS cells directly when the stimulation intensity is very (unusually) high, such as when it is set at 200 % of RMT (Di Lazzaro et al., 1998). However, with the standard stimulation parameters described above, the largest CS depolarization occurs indirectly, by activating neurons projecting onto CS cells (Di Lazzaro et al., 2001). This indirect depolarization of CS cells has been evidenced using a combination of single-pulse TMS and epidural recordings from the cervical cord (Di Lazzaro et al., 2017). Such recordings revealed that a single TMS pulse can produce a series of descending volleys, referred to as the Direct [D]-wave (i.e., resulting from the direct depolarization of CS cells) and as the early and late Indirect [I]-waves (i.e., resulting from an indirect depolarization), depending on their order of occurrence (Day et al., 1989; Di Lazzaro et al., 2001; see Figure 1). The early I-
wave consists in a single wave and originates from the activation of excitatory neurons projecting onto CS cells monosynaptically. The late I-waves involve two or three waves and result from the activation of polysynaptic circuits, comprising both excitatory and inhibitory neurons that ultimately bind onto CS cells. Importantly, while these different mono- and polysynaptic projections mostly originate within the stimulated M1 itself (i.e., providing intracortical inputs to CS cells), they can also include inputs from other regions (Di Lazzaro and Rothwell, 2014; Shimazu et al., 2004; Siebner, 2020), including the prefrontal, premotor and parietal cortices bilaterally, as well as the contralateral M1 (i.e., transcortical inputs), or from subcortical structures projecting onto M1 such as the cerebellum or the basal ganglia through the thalamus (i.e., subcortico-cortical inputs).

The descending volleys induced by the cortical stimulation eventually sums up and activates contralateral motoneurons through synapses in the ventral horn of the spinal cord. The summation of these volleys ultimately elicits an action potential in the targeted muscle (and thus, a muscular contraction) – i.e., the so-called motor-evoked potential (MEP), recorded with the surface EMG electrodes. Hence, the amplitude of MEPs provides a global readout of CS excitability at the time of the stimulation, reflecting altogether the intrinsic excitability of CS cells, the net impact of different neural inputs projecting onto them (Di Lazzaro et al., 2018) and the activity of spinal circuits modulating the corticomotoneuronal transmission (Aguiar and Baker, 2018; Taube et al., 2017, 2015).

In the past decades, a great deal of studies has exploited the single-pulse technique described above to examine changes in CS excitability during action preparation (e.g., Burle et al., 2004; Chye et al., 2018; Derosiè re et al., 2015b; Draper et al., 2015; Federico and Perez, 2017; Greenhouse et al., 2015; Ibáñez et al., 2018; Kennefick et al., 2019; Leocani et al., 2000; Mars et al., 2007; McMillan et al., 2004). In these studies, single pulses are typically applied over one M1, eliciting MEPs in one hand at different timings while subjects prepare left or right hand finger responses in variants of reaction time (RT) tasks, including instructed-delay RT tasks. In the latter tasks, a pre-cue allows subjects to prepare (part of) their response in advance of the imperative signal. Importantly, recording MEPs in such RT tasks necessitates to control for any background EMG activity, which may potentiate MEP amplitude. Hence, with such protocols, MEPs can be recorded in muscles that are selected for the forthcoming action (e.g., in the left FDI muscle before left index finger movements), as well as in muscles that are non-selected but are part of the potential effector repertoire (e.g., in the left FDI muscle before right index finger movements). In addition, MEPs are also sometimes recorded in other, task-
irrelevant muscles (e.g., in a left pinky muscle before left index finger movements), in order
to investigate the spatial specificity of the changes in CS excitability. One main advantage of
MEP measurements in this context, compared to other approaches such as EEG or fMRI, is
the possibility to probe changes in different muscles, thus reflecting neural activity in
different pools of CS cells. This is what we refer to as the high spatial resolution of TMS.
Notably, a single TMS pulse can elicit MEPs in adjacent muscles simultaneously. This is
because figure-of-eight coils stimulate a zone of about 10 mm of diameter (Brasil-Neto et al.,
1992; Derosiere et al., 2017b; Thielcher and Kammer, 2002). Also, CS cells projecting to
different muscles of a given limb strongly overlap within M1 (Willett et al., 2019). Further,
MEP amplitudes reflect the instantaneous level of excitability (i.e., at the time of the
stimulation) and thus, TMS also presents a high temporal resolution compared to other
techniques. Changes in CS excitability are then quantified by expressing the peak-to-peak
amplitude of MEPs obtained during action preparation relative to the amplitude of MEPs
measured for the same muscle in a baseline state (e.g., measured between the trials during the
task), either as a percentage or as a ratio. Percentage (ratio) values higher than 100 % (than 1)
indicate a facilitation of CS excitability with respect to baseline, while values lower than 100
% (than 1) reveal a suppression.

Using single-pulse TMS over M1, different labs around the world have shown that action
preparation entails a gradual build-up of excitability for CS cells controlling the selected muscle,
becoming significantly facilitated close to movement onset (i.e., MEPs reaching values higher
than 100 % of baseline; e.g., Klein et al., 2012; Leocani et al., 2000; Poole et al., 2018; Quoilin et
al., 2018), consistent with EEG and fMRI studies, showing increased activation in the hemisphere
centralateral to a selected hand (Alamia et al., 2019; Derosiere et al., 2018). Further, some studies
have revealed that, before this build-up, there is in fact an initial drop in CS excitability (i.e.,
percentage values lower than 100 %; e.g., Duque et al., 2010; Duque and Ivry, 2009; Klein et al.,
2016; Lebon et al., 2019; Vassiliadis et al., 2020), which is coherent with single-neuron studies in
non-human primates, showing that the firing rate of a substantial part of the CS cells decreases
during action preparation (Soteropoulos, 2018). Interestingly, TMS studies also revealed that this
early suppression concerns not only the selected muscle but also non-selected and task-irrelevant
effectors, and here, excitability can display a further drop until movement onset (Greenhouse et
al., 2015; Klein-Flugge et al., 2012; Labruna et al., 2019; Lebon et al., 2019). Altogether, these
findings led to the suggestion that action preparation involves an initial suppression of the activity
of the motor system (a phenomenon sometimes referred to as “preparatory inhibition” or
“preparatory suppression”; Duque et al., 2017), with facilitation of CS cells controlling the selected muscle emerging progressively from this down-regulated state, finally leading to movement execution. While the build-up of CS excitability clearly reflects the tuning of cells controlling the forthcoming response, the functional significance of the preparatory suppression effect is still a matter of intense debate (Derosiere, 2018; Duque et al., 2017; Greenhouse et al., 2015; Hannah et al., 2018; Ibáñez et al., 2018; Quoilin and Derosiere, 2015), aroused by two main hypotheses. One idea in the field is that these changes in CS excitability reflect action selection processes (i.e., “What and when to move?”; e.g., Duque et al., 2012; Duque and Ivry, 2009). Another hypothesis posits that these changes are related to action specification processes (i.e., “How to move?”; Greenhouse et al., 2015; Hannah et al., 2018). Notably, while these hypotheses are usually perceived as mutually exclusive, a potential alternative idea, which is in line with integrated models of action preparation (e.g., Cisek, 2007), would be that CS excitability is shaped by both action selection and specification processes, with some of them having suppressive effects.
Figure 1: Classic single-pulse TMS technique. A figure-of-eight coil is placed over the primary motor cortex (M1) at the ‘hotspot’, the position at which the largest motor-evoked potentials (MEPs) can be recorded in the electromyography (EMG) signal from a targeted muscle. The handle is oriented towards the back of the head and laterally at a 45° angle away from the midline. A pulse is applied over M1 with the current flowing in the coil in a clockwise direction in the left wing and in an anticlockwise one in the right wing (white arrows). This generates a current in the underlying cortical tissue flowing from back to front – i.e., in the postero-anterior (PA) direction (represented by a black arrow beside the coil) – which depolarizes a set of corticospinal (CS) cells, either directly (inducing a D-wave, purple), or indirectly (inducing early and late I-waves, dark and light blue, respectively). The parentheses around the D-wave indicates that it is only obtained when unusually high stimulation intensities are used, such as 200% of resting motor threshold (RMT; Di Lazzaro et al., 1998); it is in fact negligible with standard intensities, which typically range between
110-130% of RMT. These descending volleys finally reach contralateral motoneurons in the spinal cord, giving rise to an MEP in the targeted muscle (first dorsal interosseus [FDI] in the present example). The MEP is a bi-phasic response; its peak-to-peak amplitude reflects the intrinsic excitability of CS cells and the summation of neural inputs projecting onto them.

Since the introduction of TMS, the field of brain stimulation has seen the emergence of more sophisticated protocols, allowing one to probe, with a higher degree of specificity, different subsets of neural inputs projecting onto CS cells. For instance, many studies have used ppTMS protocols, which consist in generating two pulses separated in time by an inter-stimulation interval (ISI), most commonly of 2 to 200 ms (Lefaucheur, 2019). In such protocols, the first pulse (called the conditioning pulse; Pulse\textsubscript{Cond}) is exploited to pre-activate a specific subset of neural inputs while the second one (called the test pulse; Pulse\textsubscript{Test}) is applied over M1, eliciting MEPs, to measure the influence of the pre-activated neural inputs on CS excitability. To probe intracortical inputs, the two pulses are delivered through the same coil placed over M1 (single-coil set-up; Berardelli et al., 2008; Byblow et al., 2007; Cirillo et al., 2018; Cirillo and Byblow, 2016; MacDonald et al., 2014; Opie et al., 2015), while transcortical inputs are rather probed by delivering the two pulses through separate coils (dual-site set-up; Koch et al., 2007; Lebon et al., 2012; Stefanou et al., 2018). The contribution of the targeted subset of inputs – i.e., whether intra- or transcortical – is quantified by expressing the amplitude of conditioned MEPs elicited by ppTMS (Pulse\textsubscript{Cond} followed by Pulse\textsubscript{Test}) relative to the amplitude of unconditioned MEPs elicited by single-pulse TMS (Pulse\textsubscript{Test} only), either as a percentage or as a ratio. Here, percentage (or ratio) values higher than 100% (or 1) indicate a facilitatory influence of the targeted inputs, while values lower than 100% (or 1) reveal an inhibitory influence on CS excitability. Importantly, because changes in unconditioned MEP amplitudes can by themselves alter the MEP percentage (ratio) value (Sanger et al., 2001), the intensity of the Pulse\textsubscript{Test} is often adjusted over the course of ppTMS experiments to keep unconditioned MEPs constant, close to a target amplitude (i.e., usually 1 mV; e.g., Elahi et al., 2012; Huang et al., 2019).

PpTMS protocols have proved useful to reveal how various brain networks, including intracortical and transcortical circuits, shape CS excitability during action preparation (e.g., Allart et al., 2018; Buch et al., 2010; Davare et al., 2009; Dupont-Hadwen et al., 2019; Duque et al., 2007; Koch et al., 2010, 2006; Liuzzi et al., 2010; Mackenzie et al., 2016; Mars et al., 2009; Neubert et al., 2011, 2010; O’Shea et al., 2007; Strigaro et al., 2015; Tazoe and Perez, 2013; Tscherpel et al., 2019; Vesia et al., 2017, 2013). Studies using single-coil set-ups have revealed
that intracortical inhibitory inputs release their suppressive influence on circuits projecting to the CS cells controlling the selected muscle as execution approaches, while intracortical inhibition remains robust for non-selected effectors over time. That is, MEP percentage values (conditioned / unconditioned) are initially lower than 100 %, but rise over time in selected muscles only (Dupont-Hadwen et al., 2019; Neubert et al., 2011). This effect is consistent with TMS-evoked potential studies (TEP; i.e., cortical potentials evoked by TMS and recorded with EEG), showing that the amplitude of the N100 (a TEP component reflecting the level of intracortical inhibition) progressively decreases in the hemisphere contralateral to the selected effector (Leodori et al., 2019). However, a main advantage of the ppTMS technique relative to the TEP approach is to dissociate changes for distinct sets of CS cells that are related to muscles that may be either selected, non-selected or irrelevant.

Besides, studies exploiting dual-site set-ups have shown that a variety of fronto-parietal areas facilitates the CS cells controlling the selected muscle close to movement onset. This is the case of the inferior frontal gyrus (Neubert et al., 2010), the premotor cortex (Buch et al., 2010; Davare et al., 2009; Koch et al., 2006), and dorsal stream areas including the anterior intraparietal sulcus (Allart et al., 2018; Vesia et al., 2013), the superior parietal lobule (Mackenzie et al., 2016), the supramarginal gyrus (Koch et al., 2010), the superior parieto-occipital cortex (Allart et al., 2018; Vesia et al., 2017, 2013) and even secondary visual areas (Strigaro et al., 2015). This facilitatory drive appears to be quite specific and does not affect task-irrelevant effectors (e.g., pinky muscle while planning to pinch an object with the index and thumb; Koch et al., 2010). ppTMS studies indicate that pre-movement activation of selected muscles is also assisted by a release of inhibitory inputs from other areas, originating in part from the M1 area of the contralateral hemisphere (Buch et al., 2010; Duque et al., 2007; Koch et al., 2006; Liuzzi et al., 2010; Tazoe and Perez, 2013; Tscherpel et al., 2019). Such changes in interhemispheric interactions during action preparation is consistent with EEG studies showing a preparatory increase in functional connectivity between bilateral motor areas (Meziane et al., 2015; Perfetti et al., 2011; Wang et al., 2017). Interestingly, this increased connectivity between bilateral motor areas is maintained during action execution and may facilitate performance of hand movements, as revealed by effective connectivity analyses of fMRI data (Grefkes et al., 2008; Pool et al., 2013). Finally, as mentioned above, many CS cells display a decreased, rather than an increased, activity during action preparation and these changes have also been investigated using dual-site set-ups. Based on this work, the pre-supplementary motor area (Neubert et al., 2010), the premotor cortex and the
lateral prefrontal cortex (Duque et al., 2012) appear to contribute to the generation of preparatory suppression.

Hence, single-pulse TMS has allowed us to gain substantial insights as regards to how preparatory processes unfold within the motor system, revealing both the temporal dynamics and the spatial specificity of preparatory changes in CS excitability. Besides, ppTMS studies have identified a number of cortical sources at the origin of these modulatory changes. Yet, despite this progress, researchers have been facing some practical limitations in the past few years. First, standard single-pulse TMS elicits MEPs that reflect the summation of multiple monosynaptic and polysynaptic inputs on the CS pathway and fluctuations in some of these inputs may not necessarily translate into consistent MEP changes (Di Lazzaro and Rothwell, 2014). Another issue regards to the difficulty to target subcortical structures with TMS, and the related lack of consideration for their contributions to CS excitability changes. Finally, almost all TMS studies have considered MEPs on one side of the body only, impeding researchers from reaching a full understanding of the motor changes underlying action preparation.

**Directional TMS: probing different subsets of neurons in M1**

*How does it work?*

It is known since the early days of TMS investigations that changing the direction of the current flow in the cortex allows varying the subset of neurons that are preferentially recruited with TMS (Day et al., 1989). Past effort to identify precisely the effect of cortical current direction on neural recruitment (e.g., Di Lazzaro et al., 2001; Pascual-Leone et al., 1994; Rusu et al., 2014; Sakai et al., 1997; reviewed in Di Lazzaro et al., 2018) has ultimately led to the emergence of a proper technique known as directional TMS. In practical terms, directional TMS implies changing the coil orientation such that the angle between the handle and the midline shifts from $45^\circ$ (PA cortical current direction) to $90^\circ$ (latero-medial [LM] cortical current direction; Figure 2, central panel) or to $225^\circ$ (antero-posterior [AP] cortical current direction; Figure 2, right panel; Federico and Perez, 2016; Ni et al., 2019). Epidural recordings from the cervical cord allowed determining which subsets of neurons are recruited with each cortical current direction. As such, while the PA direction induces both early and late I-waves (D-waves are negligible for standard stimulation intensities; (Di Lazzaro et al., 1998)), the LM direction selectively generates D-waves and the AP direction preferentially induces late I-waves (Di Lazzaro et al., 2018; Jo and Perez, 2019; see Figure 2). In other
words, the PA direction is usually considered as rather non-specific, as it recruits both mono- and polysynaptic projections onto CS cells (although the difference in selectivity of neural recruitment between PA and AP current directions can be improved by varying specific stimulation parameters such as the pulse width, as discussed below; Hannah and Rothwell, 2017). Conversely, LM and AP currents are habitually viewed as more selective, with the former activating primarily the CS cells and the latter recruiting preferentially polysynaptic circuits. Note however that, for high stimulation intensities, AP currents can in some subjects recruit monosynaptic projections too (i.e., they can generate early I-waves; Di Lazzaro et al., 2001), although such recruitment is more pronounced and more systematic when using PA currents. The preferential recruitment of polysynaptic circuits using AP currents is supported by the fact that the latency of MEPs induced by those currents is generally longer by 2-3 ms compared to the two other current directions (~23-24 ms vs ~21-22 ms on average; Hannah and Rothwell, 2017). Hence, the amplitude of MEPs recorded using these three current directions (i.e., MEP_{PA}, MEP_{LM} and MEP_{AP}) can be taken as a proxy of the activity of different (still overlapping) subsets of neurons. Directional TMS is based on the comparison of these MEP amplitudes: by contrasting the changes (e.g., with respect to baseline) in the amplitude of MEP_{PA}, MEP_{LM} and MEP_{AP}, experimenters can infer about which neurons were preferentially targeted by a given process shaping CS excitability. Importantly, MEP_{PA}, MEP_{LM} and MEP_{AP} amplitudes do not reflect the activity of completely exclusive populations of neurons but rather overlapping ones, and how distinct those populations might be remains subject to intensive investigation.

Recent research has aimed at investigating the spatial and functional characteristics of the neural populations recruited by PA, LM and AP currents. For instance, recent works have shown that the difference in neural recruitment evoked by different current directions is reflected in early components of EEG-recorded TEPs, which exhibit different polarities depending on TMS current direction, potentially indicating the generation of different dipoles of current in the underlying cortical mantel (Bonato et al., 2006; Casula et al., 2018). Moreover, studies that have modelled the mechanisms by which TMS activates M1 neurons suggest that PA currents activate CS cells in the anterior portion of the central sulcus and a small proportion in the posterior part (Seo et al., 2017; Thielischer et al., 2011). In contrast, AP currents would recruit a larger portion of CS cells in the posterior part than PA currents do (Laakso et al., 2014; Salvador et al., 2011; Seo et al., 2017) but would still activate some neurons of the anterior portion too (Casula et al., 2018). In addition, there is growing
computational and neurophysiological evidence that AP currents can also activate axons of neurons in the premotor cortex projecting polysynaptically to the CS cells (Aberra et al., 2019; Siebner, 2020). As such, studies in non-human primates revealed that stimulation of the premotor cortex can facilitate the generation of late I-waves in M1 (Shimazu et al., 2004). Consistently, conduction times between the premotor cortex and M1 in human (Groppa et al., 2012) and non-human primates (Kraskov et al., 2011) are compatible with the additional latency observed with AP currents (i.e., 2 to 3 ms). Finally, an fMRI study showed a correlation between premotor-M1 functional connectivity in humans and the generation of MEP$_{AP}$ (Volz et al., 2015). Overall, these studies support the idea that different current directions can recruit populations of neurons that differ from each other both spatially and functionally. More studies are required to gain further insights into the properties of these different populations.

The use of directional TMS requires taking into account at least three key technical issues. First, one has to be aware of the direction of the current flow within the coil itself (i.e., the coil current direction). As such, the three cortical current directions mentioned earlier (i.e., PA, LM and AP) will only be generated with the three coil orientations described (i.e., 45°, 90° and 225°, respectively) if the current within the coil flows in a clockwise direction in the left wing and in an anticlockwise one in the right wing, as described in Figure 1. Yet, the default coil current direction can change from one TMS device to another and is even configurable on some of them. Hence, it is essential to be vigilant regarding this aspect when designing a directional TMS protocol. Second, the shape of the pulse is of critical importance. In fact, most TMS devices allow the production of either monophasic or biphasic pulses. However, the effects described above with directional TMS on neural recruitment have been strictly observed for monophasic pulses. The question as to whether effects vary with the use of biphasic pulses is still the object of investigations and recent findings point toward substantial differences between monophasic and biphasic directional TMS (refer to (Casula et al., 2018; Davila-Pérez et al., 2018; Sommer et al., 2018), for further information). Finally, the pulse duration is also decisive, specifically for the AP cortical current direction. In fact, Hannah and Rothwell (2017) provided neurophysiological evidence indicating that the AP direction recruits polysynaptic circuits with a higher selectivity when short pulses are used (30 µs) compared to when more standard long duration pulses are exploited (100-120 µs; see also Casula et al., 2018). The pulse duration does not seem to affect neural recruitment with PA direction; it was not tested for the LM direction, for which the standard 100-120 µs may
be thus preferred for now. Hence, the efficiency of a directional TMS protocol will depend on
the coil current direction, on the pulse shape and on the pulse duration.

**Figure 2: Directional TMS technique.** By changing the angle between the coil handle and
the midline, TMS over M1 can either induce a cortical current in a postero-anterior (PA)
direction (45°; left panel), in a latero-medial (LM) direction (90°; central panel) or an antero-
posterior (AP) current (225°; right panel). While the PA direction is usually considered as
rather non-specific, as it recruits both monosynaptic and polysynaptic projections (mostly
inducing early and late I-waves in the CS tract), the LM direction is thought to selectively
activate CS cells (primarily generating D-waves) and the AP direction is viewed as
preferentially recruiting polysynaptic circuits (inducing a majority of late I-waves). Hence, the
amplitude of MEPs recorded using these three current directions can be taken as a proxy of
the activity of different subsets of neurons. Although not highlighted on this figure, the
latency of MEPs obtained with the AP direction is usually longer by 2-3 ms compared to the
two other current directions (~23-24 ms vs ~21-22 ms on average; Hannah and Rothwell,
2017), putatively reflecting the recruitment of additional synapses with the AP direction.
Also, while this figure highlights changes in current direction as resulting from changes in
coil orientation, some TMS devices now allow to change current direction within the wings of
the coil resulting in a change in cortical current direction, hence making it possible to switch
from PA to AP stimulation while keeping the same coil orientation.
Interest for the field of action preparation

So far, only one single study has exploited directional TMS in the context of action preparation (i.e., Hannah et al., 2018). The results of this study demonstrate the level of insight that one can gain by exploiting the technique. Hannah et al. (2018) were interested in the mechanistic principles underlying preparatory suppression. As mentioned above, former studies took advantage of the spatial resolution of TMS and examined the anatomical specificity of preparatory suppression within M1 by measuring the amplitude of MEPs elicited in selected, non-selected and task-irrelevant muscles. These studies provided evidence that MEP amplitudes are suppressed in all of these effectors (i.e., compared to baseline), including selected muscles where amplitudes exhibit an initial suppression before building up close to movement onset. These observations gave rise to the suggestion that preparatory suppression operates in a global way, affecting muscle representations regardless of their function in the prepared action (e.g., Greenhouse et al., 2015). Hannah et al. used directional TMS (eliciting MEP_{PA} and MEP_{AP}) to go a step further than previous TMS investigations and to examine the selectivity of preparatory suppression at the level of the different subsets of neurons that may be involved in this phenomenon. Importantly, to further improve the selectivity of neural recruitment with the AP current (i.e., which should preferentially recruit polysynaptic circuits), the authors used a short pulse duration (i.e., 30 µs, see above), while a more standard long pulse duration was exploited for the PA stimulation (i.e., 120 µs). Their findings put forward three major benefits of using directional TMS for the study of preparatory activity, compared to more traditional TMS approaches, or EEG and fMRI procedures.

Firstly, one can use MEP_{AP} results to determine the specific contribution of the polysynaptic circuits (producing the late I-waves) to the generation of preparatory suppression. Here, the authors found that during action preparation, MEP_{AP} amplitudes are suppressed (i.e., with respect to baseline) regardless of whether the muscle is selected, non-selected, or task-irrelevant. As noted above, the amplitude of MEP_{AP} mostly reflects the activity of polysynaptic projections (although it can also recruit some monosynaptic inputs to the CS cells). Hence, these results indicate that preparatory suppression results, at least in part, from a reduced drive of polysynaptic circuits onto CS cells. This may arise from a decreased activity of excitatory neurons and/or from an increased activity of inhibitory neurons composing these circuits.
Secondly, one can infer about the putative contribution of the monosynaptic excitatory projections (producing the early I-waves) by directly comparing changes in MEP_{PA} and MEP_{AP} amplitudes. Indeed, if a release of monosynaptic excitatory inputs was to contribute to preparatory suppression, the amplitude of MEP_{PA}, which reflects the activity of both monosynaptic and polysynaptic inputs, should display stronger inhibitory changes than MEP_{AP} amplitude (Di Lazzaro et al., 2001). Yet, the authors found a comparable suppression of MEP_{PA} and MEP_{AP} when considering task-irrelevant muscles, suggesting that a release of monosynaptic excitatory inputs do not contribute to preparatory suppression (Derosiere 2018).

Interestingly though, the authors did report a difference between changes in MEP_{PA} and MEP_{AP} amplitudes when considering the selected and non-selected muscles. In fact, while MEP_{AP} were reduced in these muscles (as described above), the authors did not observe any significant suppression when considering MEP_{PA} amplitudes. Even though this absence of suppression of MEP_{PA} amplitudes might seem to contradict the results of previous studies, an important methodological difference here is that the stimulation intensities used by Hannah et al. (2018) were lower than the ones usually exploited. In fact, low intensities of stimulation reduce the recruitment of late I-wave when using PA current direction (Di Lazzaro et al., 2018). It is therefore possible that the absence of suppression of MEP_{PA} observed here was the result of a reduced contribution of late I-waves to MEP_{PA}. This brings us to the third benefit of directional TMS: it allows uncovering the presence of countermanding changes in monosynaptic and polysynaptic drives onto CS cells. As such, here, the absence of significant MEP_{PA} suppression for selected and non-selected muscles, despite the reduced amplitude of MEP_{AP}, suggests that action preparation also entails a selective increase in monosynaptic excitatory inputs directed at relevant effectors, thus masking the inhibitory effect of polysynaptic circuits. That is, action preparation may involve a global alteration in the activity of polysynaptic circuits, affecting all effectors irrespective of the function, and a concomitant increase in the activity of the excitatory neurons that bind onto CS cells controlling relevant muscles.

Hence, the use of directional TMS allowed Hannah et al. to disentangle which subsets of neurons may contribute to preparatory suppression. While former single-pulse studies revealed that CS excitability is broadly suppressed during action preparation, affecting different motor representations, the authors showed that only specific, polysynaptic circuits within these representations contribute to the suppression. Reaching such a level of understanding would not have been possible using more traditional TMS, EEG and fMRI.
approaches. Future human studies could exploit LM directional TMS to investigate how action preparation shapes the excitability of the CS cells themselves, in line with single-neuron research in non-human primates (Economo et al., 2018; Soteropoulos, 2018).

Paired-pulse TMS over the cerebellum and M1: probing cerebellar-brain inhibition (CBI)

How does it work?

As described above, ppTMS has been largely exploited to investigate CS modulatory sources originating from cortical sites, including M1, prefrontal, premotor and parietal areas. More recently, the use of ppTMS has been extended to a key subcortical structure, namely the cerebellum. We refer to this technique as ppTMS_{CB-M1}. Technically, ppTMS_{CB-M1} involves a dual-site set-up (see Figure 3), with the Pulse_{Cond} applied using a so-called “double-cone” coil (i.e., presenting an angle of 95° between the two wings) positioned over the cerebellum, at the back of the head, and the Pulse_{Test} delivered through a figure-of-eight coil positioned over M1. The double-cone coil can target deep neural tissues (up to 6 cm deep; (Deng et al., 2014)) and is thus particularly appropriate for cerebellar stimulation (Hardwick et al., 2014). Typically, it is positioned on the contralateral side of the head with respect to the M1 figure-of-eight coil (i.e., thus ipsilateral to the hand in which MEPs are recorded), 3 cm lateral to the inion or 3 cm lateral and 1 cm inferior to the inion. The double-cone coil is exploited to induce a subthreshold Pulse_{Cond}, generating a current flowing in the upward direction in the underlying cerebellar tissue (though the opposite direction is also efficient; (Fernandez et al., 2018)). This pulse is followed 5 to 7 ms later by the suprathreshold M1 Pulse_{Test} eliciting the MEP (suprathreshold defined here as an intensity necessary to elicit MEPs of 1 mV amplitude at rest; Fernandez et al., 2018; Spampinato and Celnik, 2018). One prominent view has been that the Pulse_{Cond} over cerebellum recruits Purkinje cells, which have a suppressive influence on deep cerebellar nuclei. Hence, because these nuclei send excitatory signals to M1 through the thalamus, the net effect of the Pulse_{Cond} is to suppress M1 (or to reduce the excitatory drive to M1) – a phenomenon called cerebellar brain inhibition (CBI). Note that the exact subset of neurons on which this cerebellum-thalamus pathway projects in M1 is still a matter of investigation (i.e., it is unclear whether CBI involves alterations of early and/or of late I-waves at present; Celnik, 2017; Spampinato et al., 2017b; please see Figure 3).
CBI manifests itself as a reduction in the amplitude of MEPs elicited by ppTMS\textsubscript{CB-M1}. As in other ppTMS protocols, the effect of cerebellar inputs on CS excitability is quantified by expressing the amplitude of MEPs obtained with ppTMS (\textit{i.e.}, the conditioned MEPs) relative to the amplitude of MEPs obtained with single-pulse TMS (\textit{i.e.}, the unconditioned MEPs), most commonly as a ratio. Here, ratio values lower than 1 are considered as a probe of CBI. In most CBI studies, the intensity of the Pulse\textsubscript{Test} is often adjusted over the course of the experiment to keep unconditioned MEP close to a target amplitude (\textit{i.e.}, usually 1 mV; Spampinato et al., 2017). Interestingly, while fMRI also offers the possibility to probe effective connectivity between the cerebellum and M1 (\textit{e.g.}, using dynamic causal modelling [DCM] analyses; Dirkx et al., 2016; Rothkirch et al., 2018), ppTMS\textsubscript{CB-M1} builds on the two main advantages of TMS and MEP measurements – high temporal and spatial resolutions – to bring a deeper level of details. Here, it is possible to probe the influence of the cerebellum on M1 at very specific time points and this, in specific pools of CS cells (\textit{i.e.}, projecting to different muscles).

The use of the ppTMS\textsubscript{CB-M1} technique requires to take into account at least two potential issues. Firstly, the determination of the stimulation intensity to be used for the Pulse\textsubscript{Cond} is critical. If a too high intensity is exploited with a double-cone coil at this scalp location, the induced current can go so deep that it directly activates the axons of CS cells at the level of the cervicomедullary junction in the brainstem. This direct activation can produce both orthodromic, descending volleys (\textit{i.e.}, travelling down to the spinal cord) and antidromic, ascending volleys (\textit{i.e.}, travelling up to the cortex). The latter volleys may suppress those descending from the cortex following the M1 Pulse\textsubscript{Test} (Taylor, 2006) and may thus potentially reduce the amplitude of conditioned MEPs in the exact same way as CBI would do (Fisher et al., 2009). An important challenge is therefore to determine a Pulse\textsubscript{Cond} intensity that is sufficient to recruit Purkinje cells and probe CBI, but not too high to avoid direct stimulation of the CS axons in the brainstem (Fernandez et al., 2018; Fisher et al., 2009; Ugawa, 2009). To tackle this issue, most ppTMS\textsubscript{CB-M1} studies use a Pulse\textsubscript{Cond} intensity of 5\% of stimulator output below the \textit{brainstem active motor threshold} – defined as the minimal intensity required to elicit MEPs in a targeted muscle during active contraction with the double-cone coil centered over the inion. In other words, the motor threshold for the Pulse\textsubscript{Cond} is first determined with the coil purposively centered over the brainstem in a condition where the CS cells are pre-activated and thus more excitable. Pulse\textsubscript{Cond} are then applied for the rest of the experiment with the coil positioned more laterally (\textit{i.e.}, 3 cm lateral to the inion as
described above), usually in a condition where the CS cells are not pre-activated, and at a subthreshold intensity, strongly reducing the likelihood of a direct activation of the CS axons (Fernandez et al., 2018). Yet, a contribution of ascending CS volleys to the reduction of MEP amplitudes reported with ppTMS$_{CB-M1}$ (and attributed to CBI) cannot be completely ruled out at this stage.

A second concern when using ppTMS$_{CB-M1}$ is the tolerability of the cerebellar stimulation by the subjects. Cerebellar stimulation is often perceived as uncomfortable or even painful by some subjects (Fernandez et al., 2018; Hardwick et al., 2014), mostly because of the tactile sensation of the stimulus on the scalp and of the contraction of face and neck muscles (Taylor, 2006). As a matter of fact, former studies have reported that some subjects could not complete the experiment (Kassavetis et al., 2011; Panyakaew et al., 2016) or that experimenters had to reduce the number of stimulations (Schlerf et al., 2015) because of the discomfort occasioned by the cerebellar stimulation. Relatedly, discomfort may lead subjects to produce muscular contractions (i.e., even in the hand muscles in which MEP are recorded), which may potentiate the amplitudes of MEPs (whether conditioned or unconditioned) and thus alter the main endpoint measure used to probe CBI (Pinto and Chen, 2001). Hence, a particular attention has to be paid to EMG recordings when using ppTMS$_{CB-M1}$ protocols, to ensure that trials with background muscular activity are discarded from analyses.

To sum up, the use of ppTMS$_{CB-M1}$ requires following a rigorous protocol for the determination of the Pulse$_{Cond}$ intensity. Further, researchers should expect that the cerebellar stimulation may not be well tolerated by some subjects, potentially leading to unwanted muscular contractions that could alter endpoint MEP measures. These issues aside, the technique offers a unique opportunity to probe the suppressive influence of the cerebellum on CS excitability – namely CBI.
Figure 3: Cerebellar paired-pulse TMS technique. ppTMS\textsubscript{CB-M1} (right) involves applying a suprathreshold Pulse\textsubscript{Test} with a figure-of-eight coil over M1 and a subthreshold Pulse\textsubscript{Cond} with a “double-cone” coil over the cerebellum, on the contralateral side of the head with respect to the M1 coil, usually 3 cm lateral to the inion. The Pulse\textsubscript{Cond}, which precedes the Pulse\textsubscript{Test} by 5 to 7 ms, is thought to recruit Purkinje cells (A: red cell), which send inhibitory projection onto deep cerebellar nuclei (A: green cell). Because the latter send excitatory signals to M1 through the thalamus (B), the net effect of the Pulse\textsubscript{Cond} is a suppression of CS excitability – a process called cerebellar brain inhibition (CBI). Note that the exact subset of neurons on which this pathway projects in M1 is still a matter of investigation (Celnik, 2017; Spampinato et al., 2017b). The question mark above the waves on the right panel is there to draw attention on the fact that the specific wave(s) concerned with CBI are unknown. Changes in CBI across experimental conditions can be probed by contrasting the amplitudes of MEPs obtained with the ppTMS\textsubscript{CB-M1} technique (i.e., the conditioned MEPs, bottom right) with respect to those obtained with a single-pulse TMS (i.e., the unconditioned MEPs, bottom left).
Interest for the field of action preparation

So far, most studies have used ppTMS_{CB-M1} to probe CBI changes in the context of motor learning (Celnik, 2015), or as a correlate of action execution (Kassavetis et al., 2011; Panyakaew et al., 2016). Only one study has applied this method in the context of action preparation (Spampinato et al., 2017), though this issue is of high relevance considering recent studies, including neuroimaging ones in humans (Moulton et al., 2017) and single-neuron work in non-human primates (Chabrol et al., 2019; Gao et al., 2018), showing tight interactions between the cerebellum and the frontal lobe during action preparation. Spampinato et al. asked subjects to perform two separate simple RT tasks in which they had to respond to imperative signals with either the right index finger or the right foot. Single-pulse TMS and ppTMS_{CB-M1} were applied at different timings between the imperative signal and movement onset. Importantly, MEPs were recorded in both the right FDI and the right tibialis anterior (TA; i.e., a foot dorsi-flexor muscle) in the two tasks (i.e., in separate blocks). The authors were thus able to compute an MEP ratio (i.e., [conditioned / unconditioned]) and probe CBI for muscles that are either selected for the forthcoming response (i.e., FDI and TA before index and foot responses, respectively) or task-irrelevant (i.e., TA and FDI before index and foot responses, respectively). Hence, such a protocol allows one to determine whether the cerebellum influences CS excitability during action preparation and whether this impact may vary for different time points and different effectors (selected versus task-irrelevant here). Two key findings illustrate the benefits of the technique.

The first finding concerns the selected muscles. Interestingly, the CBI MEP ratio built up in these muscles as movement execution drew nearer, starting at values of about 0.8 at the onset of the imperative signal and nearing a value of 1 close to movement initiation. Hence, this first finding of Spampinato et al. (2017) suggests that the cerebellum contributes to the rise in CS excitability usually observed for selected muscles, by releasing its inhibitory tone on M1 (i.e., release of CBI). Such a release of CBI may result from a decrease in the activity of the Purkinje cells, which would ultimately disinhibit deep cerebellar nuclei and thus the thalamus and M1. In line with this interpretation, single-neuron recordings in non-human primates have revealed that the activity of wrist-related Purkinje cells declines right before the onset of wrist movements, while the activity of wrist-related cells in deep cerebellar nuclei increases at this time (Ishikawa et al., 2014). This result is also in accordance with the fact that unilateral cerebellar lesions reduce pre-movement facilitation and lengthen RTs (Battaglia et al., 2006; Ikeda et al., 1994; Sasaki et al., 1981; Tsujimoto et al., 1993). Put
together, these results suggest that the pre-movement release of CBI observed by Spampinato et al. (2017) is necessary for the build-up of motor activity, and contributes to the rapid initiation of actions.

The second finding concerns the task-irrelevant muscles. Here, Spampinato et al. found that the CBI MEP ratio remains stable over time, hovering near 0.8 until movement initiation. Based on this finding, one is tempted to conclude that CBI persists at a stable level for task-irrelevant muscles during action preparation, and that the cerebellum does not contribute to the drop of CS excitability usually observed for these muscles over time. Yet, Spampinato et al. only considered task-irrelevant muscles in a different limb (i.e., TA muscle during the preparation of index finger movements and vice-versa) and changes in CBI may differ for task-irrelevant muscles that are closer to the selected effector, in the same body segment (i.e., pinky muscle during the preparation of index movements). Consistently, a recent study showed that preparatory changes in CS excitability depend on how close muscles are anatomically to the moving effectors (Labruna et al., 2019). In particular, preparatory suppression is stronger in task-irrelevant muscles that are in the same body segment as the moving effector, compared to muscles that are from other body parts. Hence, the influence of the cerebellum may vary based on this aspect.

The results of Spampinato et al. complement our previous knowledge of the network involved in the modulation of CS excitability during action preparation. When combined with the results of Hannah et al. (2018), one could tentatively propose that the release of CBI entails an increase in monosynaptic excitatory inputs onto selected effectors. Indeed, as discussed above, such a release of CBI may result from a disinhibition of the cerebellum-thalamus pathway, which projects to CS cells through excitatory projections (Hooks et al., 2013). Hence, while little is known about the exact subset of neurons on which the cerebellum-thalamus pathway projects within M1, one may hypothesize that this pathway influences CS excitability through monosynaptic excitatory circuits, at least during action preparation.

This work opens at least three new lines of research. Firstly, future research should determine if CBI for task-irrelevant muscles depends on whether these muscles are part of the same limb as the task-relevant ones or not. Secondly, it would be interesting to investigate if the findings of Spampinato et al. (2017) extend to situations involving decisions between actions (i.e., choice RT tasks) and/or a delay period (i.e., instructed-delay RT task), as the changes in CS excitability depend on these factors too (Greenhouse et al., 2015; Labruna et al., 2019; Quoilin et al., 2016). Finally, the use ppTMS\textsubscript{CB-M1} in choice RT tasks will allow
future experimenters to study the putative influence of the cerebellum on the CS cells controlling non-selected muscles (i.e., in addition to selected and task-irrelevant ones).

**Double-coil TMS: probing CS excitability bilaterally at once**

*How does it work?*

So far, almost all studies of CS excitability have recorded MEPs unilaterally – i.e., from muscles of a single limb (most commonly the hand) following the application of one coil over the M1. Hence, in most experiments, the MEP data have only provided researchers with half of the story, increasing the risk of shortcuts in data interpretations. This occurred because applying TMS over both M1s in separate blocks doubles the duration of the experiment, making it difficult to fit all the experimental conditions in a single session. Most other brain mapping techniques, including EEG and fMRI, do allow to record motor activity bilaterally, though they do not benefit from the combined temporal and spatial resolutions of TMS.

Recently, a double-coil TMS approach has emerged to overcome these limitations, allowing one to stimulate both M1s at once, and thus to obtain MEPs from the two upper limbs within each trial (e.g., from the left and right FDI; Grandjean et al., 2018, 2017). The core principles of the double-coil TMS approach are similar to the ones underlying the classic single-pulse technique presented in Figure 1. However, here, two small figure-of-eight coils are placed over both M1s with the handles oriented towards the back of the head producing a 45° angle with respect to the midline. Electrodes are disposed on muscles of both upper limbs (e.g., left and right FDI; see Figure 4). The two small coils are exploited to evoke suprathreshold pulses **within the same trial**, with a 1-ms ISI, leading to the concurrent depolarization of both CS pathways, and thus eliciting MEPs bilaterally. Hence, the double-coil approach allows one to multiply by two the amount of MEP data obtained for the same number of trials (i.e., compared to single-pulse TMS).

The use of a 1-ms ISI represents a major aspect for two main reasons. First, if triggered exactly at the same time, the two magnetic fields interfere with each other, producing an attractive force between the coils; the amplitude of the resulting MEPs is then smaller than the one obtained with classic single-pulse TMS (unpublished observations). Hence, one must insert a time interval between the two pulses. This takes us to the second point: if triggered with an interval longer than 1 ms, the two stimulations may influence each other through
transcallosal interactions. In fact, interactions between both M1s through the corpus callosum are known to occur with ISIs as short as 4 ms in ppTMS protocols using dual-site set-ups over M1 (Ferbert et al., 1992; Hanajima et al., 2001). Hence, adding an interval between the two stimulations is necessary to avoid electromagnetic interference, but the duration of this interval needs to be shorter than 4 ms to avoid transcallosal interactions. Note that because double-coil TMS involves applying two pulses over both M1, the set-up shares some similarities with some ppTMS protocols, especially with those aiming at probing interhemispheric interactions between both M1 areas. Yet, the goal here is very different as the double-coil technique is used to measure MEPs bilaterally while limiting any putative effect of these interactions on the recordings, hence the short ISI of 1 ms (see below).

Grandjean et al. (2018) showed that, using an ISI of 1 ms, the double-coil approach allows one to obtain raw MEPs of statistically similar amplitude compared to those recorded with single-pulse TMS applied sequentially over the two M1s. This is true independently of the order of stimulation (i.e., regardless of whether the left or right M1 is stimulated first) and of the intensity of the stimulator output. Hence, these findings indicate that the double-coil can be reliably used to assess CS excitability bilaterally.
Figure 4: Double-coil TMS technique. Coils are placed over both M1s (TMS$_1$ and TMS$_2$) to apply two pulses within the same trial, with a 1-ms inter-stimulation interval (Pulse$_1$ and Pulse$_2$), represented on the EMG recording at the bottom, leading to the concurrent depolarization of both corticospinal pathways (Waves$_1$ and Waves$_2$) and the recording of MEPs bilaterally (MEP$_1$ and MEP$_2$).

Interest for the field of action preparation
One recent study has used double-coil TMS to probe CS excitability during action preparation, and showed that MEPs obtained using this method reflect similar changes in CS excitability compared to MEPs elicited using single-pulse TMS (Vassiliadis et al., 2018). Hence, double-coil TMS can be reliably used to probe preparatory activity bilaterally. This technique has two main advantages for studies in the field of action preparation.

Firstly, it allows researchers to obtain markers of CS excitability in both hands at a near-simultaneous time within each single trial. In fact, as mentioned earlier, previous single-pulse studies on action preparation have applied TMS over one M1 only (i.e., as depicted in Figure 1; Duque et al., 2010; Duque and Ivry, 2009; Greenhouse et al., 2015). MEPs are then recorded in a contralateral hand muscle while subjects prepare to move either that hand or the opposite one in different task settings and percentage values are used as markers of changes in CS excitability associated with a selected or a non-selected hand condition, with respect to baseline. Yet, there is a substantial confound here because in addition to the function (selected versus non-selected), conditions also differ in terms of the hand being cued for the movement (left [often non-dominant] versus right [often dominant]) and this aspect (i.e., dominance) may also influence MEP amplitudes (Klein et al., 2016).

A stirring example concerns past observations of preparatory suppression, which refers to the suppression of MEPs observed during action preparation, compared to baseline. In this field, studies (including our own work) have mostly elicited MEPs in the left hand (of right-handers) while subjects withhold left or right hand responses following pre-cues in instructed-delay RT tasks. Doing so, many of them have observed that left MEPs show a stronger suppression when the pre-cue indicates a left than a right hand response and this finding has been taken to propose that preparatory suppression is more prominent for selected than for non-selected muscles (Duque et al., 2014; Duque et al., 2010; Labruna et al., 2014). However, although not considered so far, another possibility is that preparatory suppression may be stronger when preparing non-dominant compared to dominant hand responses. One way to test this alternative hypothesis in the future would be to record MEPs in both the left and the right hands. Such a goal could be achieved using the classic single-pulse approach by recording left and right MEPs in separate blocks of trials, but it would then double the duration of the experiment (Algoet et al., 2018; Klein et al., 2016; Poole et al., 2018). Most importantly, one would have then to compare the amplitudes of MEPs recorded in the left and the right hand in different trials, which may be associated with different behavioral outcomes (e.g., the RT may differ). Using double-coil TMS can help tackling both of these issues.
Secondly, given that double-coil TMS allows to elicit near-simultaneous MEPs in both hands, this technique provides us with a means to make direct comparisons between MEPs elicited in the selected versus the non-selected muscle on a single-trial basis and to consider their possible covariation in various experimental tasks. For example, the presence of a strong positive correlation in a given condition (e.g., high [low] MEP percentage values in the selected muscle associated with high [low] values in the non-selected one) may reflect that the excitability of both CS pathways is modulated by a common neural source in that specific condition. Conversely, a strong negative correlation between bilateral MEPs (i.e., high [low] percentage values in the selected muscle associated with low [high] values in the non-selected one) may reflect the presence of a mechanism through which increased facilitation in the former hand is associated with increased suppression in the latter one, for example inter-hemispheric inhibition (Fling and Seidler, 2012; Ni et al., 2009). MEPs obtained with double-coil TMS can be exploited to compute such correlations based on single-trial amplitudes and this, for each subject and each experimental condition. It is then possible to compare the slope and the strength (e.g., $R^2$ value) of these correlations across groups of subjects and conditions. In the same vein, EEG studies have reported that the coherence in the beta range between bilateral motor areas increases during action preparation, potentially reflecting enhanced functional connectivity between both motor cortices (Meziane et al., 2015; Perfetti et al., 2011). Double-coil TMS could provide deeper understanding of these mechanisms by allowing to study these single-trial correlations for each motor representation. Hence, double-coil TMS provides researchers with a new way of extracting relevant neurophysiological information based on MEP measures obtained during action preparation. While such information might be in part extracted using EEG or fMRI (i.e., given the possibility to record motor activity bilaterally), the double-coil approach provides a unique opportunity to measure changes occurring in different pools of CS cells in each hemisphere.

Conclusion and future directions

The level of understanding that can be reached when studying a given system or process depends closely on the tools that are available to examine it and, whatever the field of study, technical advances always open up the scope of possible investigations. Here, we focused on the study of the neural correlates of action preparation using TMS in humans. Our goal was to describe three new approaches and to highlight the (potential) breakthrough these advances represent for the field. Directional TMS provides a non-invasive opportunity to probe the
activity of partially distinct subsets of neurons in humans. PpTMS$_{\text{CB-M1}}$ allows investigating the modulatory influence of the cerebellum on CS excitability for specific motor representations. Double-coil TMS offers a unique opportunity to track bilateral changes in CS excitability and probe the putative (de)coupling of preparatory activity across hemispheres. Obviously, the benefits of these techniques go far beyond the field of action preparation, extending to any neuroscientist interested in exploiting MEPs as a probe of CS excitability, in contexts as various as action observation, motor imagery, inhibitory control, decision-making, speech, sustained attention, and motor learning (Derosiere et al., 2015, 2017a, 2019; Flöel et al., 2008; Foysal and Baker, 2019; Lebon et al., 2012; Neef et al., 2015; Raffin and Siebner, 2019; Ueno et al., 2018).

In addition to fundamental neuroscience, the methods reviewed above may be of interest for clinical research too. For instance, directional TMS could be used to identify the populations of M1 neurons altered in different pathologies. As such, a number of psychiatric and movement disorders have been associated with alterations of preparatory activity within the CS system (Beck et al., 2008; Heinrich et al., 2014; Hoegl et al., 2012; Hummel et al., 2009; Quoilin et al., 2018). Patients suffering from alcohol dependence exhibit a deficit in preparatory suppression relative to healthy subjects, which is predictive of relapse (Quoilin et al., 2019). Besides, patients affected by focal hand dystonia show an over-excitability of task-irrelevant CS cells close to action initiation (Beck et al., 2008). In a similar vein, post-stroke patients display a preponderant preparatory activity in the non-injured hemisphere (Hummel et al., 2009; Murase et al., 2004; Wiese et al., 2005). The use of directional TMS here should allow researchers to identify the subsets of neurons that contribute to such changes in preparatory activity. Importantly, this knowledge could be then exploited to design therapeutic interventions aiming at targeting specific subsets of cells, for instance using different repetitive TMS protocols (Di Lazzaro et al., 2008).

While the three techniques described in this review have allowed us to gain insight into the neural correlates of action preparation, a number of gaps remain in our knowledge. Interestingly though, these gaps could be bridged by combining some of these techniques in the future. First, ppTMS$_{\text{CB-M1}}$ experiments showed that the cerebellum contributes to pre-movement facilitation in selected representations. Yet, the exact subset of neurons that is targeted by cerebellar inputs within each motor representation remains unclear. This issue could be tackled by combining cerebellar stimulation with directional TMS (Celnik, 2017; Spampinato et al., 2017). Based on the hypothesis that the release of CBI in selected cells may...
rely on an increase in monosynaptic excitatory inputs to these cells (as proposed above), we predict that a such a release should only be observed when stimulating M1 with PA currents (Spampinato et al., 2018), but not with AP ones. A second gap in our understanding regards to how the activity of different subsets of neurons may co-vary in both hemispheres. Specifically, one may predict that the changes in polysynaptic inputs observed in selected and non-selected hemispheres (Hannah et al., 2018) co-vary at the single-trial level, putatively reflecting the influence of a common neural source on these circuits. The combination of double-coil and directional TMS could allow one to test this hypothesis in the future.

Altogether, the recent advances highlighted here pave the way towards even more sophisticated TMS approaches, widening the horizon of possibilities for the investigation of the human motor system, both in health and disease.

References

Aberra, A.S., Wang, B., Grill, W.M., Peterchev, A. V., 2019. Simulation of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons. Brain Stimul. https://doi.org/10.1016/j.brs.2019.10.002

Aguiar, S.A., Baker, S.N., 2018. Convergent Spinal Circuits Facilitating Human Wrist Flexors. J. Neurosci. 38, 3929–3938. https://doi.org/10.1523/JNEUROSCI.1870-17.2018

Alamia, A., Zénon, A., VanRullen, R., Duque, J., Derosiere, G., 2019. Implicit visual cues tune oscillatory motor activity during decision-making. Neuroimage 186, 424–436.

Algoet, M., Duque, J., Iannetti, G.D., Mouraux, A., 2018. Temporal Profile and Limb-specificity of Phasic Pain-Evoked Changes in Motor Excitability. Neuroscience 386, 240–255. https://doi.org/10.1016/j.neuroscience.2018.06.039

Allart, E., Devanne, H., Delval, A., 2018. Contribution of transcranial magnetic stimulation in assessing parietofrontal connectivity during gesture production in healthy individuals and brain-injured. Neurophysiol. Clin. / Clin. Neurophysiol. https://doi.org/10.1016/j.neucli.2018.12.005

Battaglia, F., Quartarone, A., Ghilardi, M.F., Dattola, R., Bagnato, S., Rizzo, V., Morgante, L., Girlanda, P., 2006. Unilateral cerebellar stroke disrupts movement preparation and motor imagery. https://doi.org/10.1016/j.clinph.2006.01.008

Beck, S., Richardson, S.P., Shamim, E.A., Dang, N., Schubert, M., Hallett, M., 2008. Short intracortical and surround inhibition are selectively reduced during movement initiation in focal hand dystonia. J. Neurosci. 28, 10363–10369. https://doi.org/10.1523/JNEUROSCI.3564-08.2008

Berardelli, A., Abbruzzese, G., Chen, R., Orth, M., Ridding, M.C., Stinear, C., Suppa, A., Trompetto, C., Thompson, P.D., 2008. Consensus paper on short-interval intracortical inhibition and other transcranial magnetic stimulation intracortical paradigms in movement disorders. Brain Stimul. https://doi.org/10.1016/j.brs.2008.06.005
Bestmann, S., Duque, J., 2016. Transcranial Magnetic Stimulation: Decomposing the Processes Underlying Action Preparation. Neuroscientist. https://doi.org/10.1177/1073858415592594

Bonato, C., Miniussi, C., Rossini, P.M., 2006. Transcranial magnetic stimulation and cortical evoked potentials: A TMS/EEG co-registration study. Clin. Neurophysiol. 117, 1699–1707. https://doi.org/10.1016/j.clinph.2006.05.006

Brasíl-Neto, J.P., Pasqual-Leone, A., Valls-Sole, J., Cohen, L.G., Hallett, M., 1992. Focal transcranial magnetic stimulation and response bias in a forced-choice task. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp.55.10.964

Buch, E.R., Mars, R.B., Boorman, E.D., Rushworth, M.F.S., 2010. A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex during action reprogramming. J. Neurosci. 30, 1395–1401. https://doi.org/10.1523/JNEUROSCI.4882-09.2010

Burle, B., Vidal, F., Tandonnet, C., Hasbroucq, T., 2004. Physiological evidence for response inhibition in choice reaction time tasks. Brain Cogn. 56, 153–164. https://doi.org/10.1016/j.bandc.2004.06.004

Byblow, W.D., Coxon, J.P., Stinear, C.M., Fleming, M.K., Williams, G., Müller, J.F.M., Ziemann, U., 2007. Functional connectivity between secondary and primary motor areas underlying hand-foot coordination. J. Neurophysiol. 98, 414–422. https://doi.org/10.1152/jn.00325.2007

Casula, E.P., Rocchi, L., Hannah, R., Rothwell, J.C., 2018. Effects of pulse width, waveform and current direction in the cortex: A combined cTMS-EEG study. Brain Stimul. 11, 1063–1070. https://doi.org/10.1016/j.brs.2018.04.015

Celnik, P., 2017. Motor learning. Cerebellar Inhibition and Intracortical M1 circuitry. Brain Stimul. 10, 500. https://doi.org/10.1016/j.brs.2017.01.461

Celnik, P., 2015. Understanding and Modulating Motor Learning with Cerebellar Stimulation. Cerebellum. https://doi.org/10.1007/s12311-014-0607-y

Chabrol, F.P., Blot, A., Mrsic-Flogel, T.D., 2019. Cerebellar Contribution to Preparatory Activity in Motor Neocortex. Neuron 103, 506–519.e4. https://doi.org/10.1016/j.neuron.2019.05.022

Chen, K., Vincis, R., Fontanini, A., 2019. Disruption of Cortical Dopaminergic Modulation Impairs Preparatory Activity and Delays Licking Initiation. Cereb. Cortex 29, 1–14. https://doi.org/10.1093/cercor/bhz005

Chowdhury, N.S., Livesey, E.J., Harris, J.A., 2019. Individual differences in intracortical inhibition during behavioural inhibition. Neuropsychologia 124, 55–65. https://doi.org/10.1016/j.neuropsychologia.2019.01.008

Churchland, M.M., Cunningham, J.P., Kaufman, M.T., Foster, J.D., Nuyujukian, P., Ryu, S.I., Shenoy, K. V, Shenoy, K. V, 2012. Neural population dynamics during reaching. Nature 487, 51–56. https://doi.org/10.1038/nature11129

Churchland, M.M., Cunningham, J.P., Kaufman, M.T., Ryu, S.I., Shenoy, K. V, 2010. Cortical Preparatory Activity: Representation of Movement or First Cog in a Dynamical Machine? Neuron 68, 387–400. https://doi.org/10.1016/j.neuron.2010.09.015
Churchland, M.M., Santhanam, G., Shenoy, K. V, 2006. Preparatory activity in premotor and motor cortex reflects the speed of the upcoming reach. J. Neurophysiol. 96, 3130–3146. https://doi.org/10.1152/jn.00307.2006

Chye, L., Riek, S., de Rugy, A., Carson, R.G., Carroll, T.J., 2018. Unilateral movement preparation causes task-specific modulation of TMS responses in the passive, opposite limb. J. Physiol. 596, 3725–3738. https://doi.org/10.1113/jp275433

Cirillo, J., Byblow, W.D., 2016. Threshold tracking primary motor cortex inhibition: the influence of current direction. Eur. J. Neurosci. 44, 2614–2621. https://doi.org/10.1111/ejn.13369

Cirillo, J., Semmler, J.G., Mooney, R.A., Byblow, W.D., 2018. Conventional or threshold-hunting TMS? A tale of two SICIs. Brain Stimul. 11, 1296–1305. https://doi.org/10.1016/j.brs.2018.07.047

Cisek, P., 2007. Cortical mechanisms of action selection: The affordance competition hypothesis. Philos. Trans. R. Soc. B Biol. Sci. 362, 1585–1599. https://doi.org/10.1098/rstb.2007.2054

Cisek, P., 2006. Preparing for speed. J. Neurophysiol. 96, 2842–2843. https://doi.org/10.1152/jn.00857.2006.Preparing

Cisek, P., Kalaska, J.F., 2010. Neural Mechanisms for Interacting with a World Full of Action Choices. Annu. Rev. Neurosci. 33, 269–298. https://doi.org/10.1146/annurev.neuro.051508.135409

Davare, M., Montague, K., Olivier, E., Rothwell, J.C., Lemon, R.N., 2009. Ventral premotor to primary motor cortical interactions during object-driven grasp in humans. Cortex 45, 1050–1057. https://doi.org/10.1016/j.cortex.2009.02.011

Davila-Pérez, P., Jannati, A., Fried, P.J., Cudeiro Mazaira, J., Pascual-Leone, A., 2018. The Effects of Waveform and Current Direction on the Efficacy and Test–Retest Reliability of Transcranial Magnetic Stimulation. Neuroscience 393, 97–109. https://doi.org/10.1016/j.neuroscience.2018.09.044

Day, B.L., Dressler, D., Maertens de Noordhout, A., Marsden, C.D., Nakashima, K., Rothwell, J.C., Thompson, P.D., 1989. Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. J. Physiol. 412, 449–473. https://doi.org/10.1113/jphysiol.1989.sp017626

Deng, Z. De, Lisanby, S.H., Peterchev, A. V., 2014. Coil design considerations for deep transcranial magnetic stimulation. Clin. Neurophysiol. 125, 1202–1212. https://doi.org/10.1016/j.clinph.2013.11.038

Derosière, G., 2018. A dynamical system framework for theorizing preparatory inhibition. J. Neurosci. https://doi.org/10.1523/JNEUROSCI.0069-18.2018

Derosière, G., Billot, M., Ward, E.T., Perrey, S., 2015a. Adaptations of motor neural structures’ activity to lapses in attention. Cereb. Cortex 25, 66–74. https://doi.org/10.1093/cercor/bht206

Derosière, G., Billot, M., Ward, E.T., Perrey, S., Derosière, G., Billot, M., Ward, E.T., Perrey, S., 2015b. Adaptations of motor neural structures’ activity to lapses in attention. Cereb. Cortex 25, 66–74. https://doi.org/10.1093/cercor/bht206
Derosiere, G., Duque, J., 2020. Tuning the Corticospinal System: How Distributed Brain Circuits Shape Human Actions. Neurosci. https://doi.org/10.1177/1073858419896751

Derosiere, G., Klein, P.A., Nozaradan, S., Zénon, A., Mouraux, A., Duque, J., 2018. Visuomotor correlates of conflict expectation in the context of motor decisions. J. Neurosci. 38, 9486–9504. https://doi.org/10.1523/JNEUROSCI.0623-18.2018

Derosiere, G., Thura, D., Cisek, P., Duque, J., 2019. M1 disruption delays motor processes but not deliberation about action choices. bioRxiv 501205. https://doi.org/10.1101/501205

Derosiere, G., Vassiliadis, P., Demaret, S., Zénon, A., Duque, J., 2017a. Learning stage-dependent effect of M1 disruption on value-based motor decisions. Neuroimage 162, 173–185. https://doi.org/10.1016/j.neuroimage.2017.08.075

Derosiere, G., Zénon, A., Alamia, A., Duque, J., 2017b. Primary motor cortex contributes to the implementation of implicit value-based rules during motor decisions. Neuroimage 146, 1115–1127. https://doi.org/10.1016/j.neuroimage.2016.10.010

Di Lazzaro, V., Oliviero, A., Profice, P., Saturno, E., Pilato, F., Insola, A., Mazzone, P., Tonali, P., Rothwell, J.C., 1998. Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. Electroencephalogr. Clin. Neurophysiol. - Electromyogr. Mot. Control 109, 397–401. https://doi.org/10.1016/S0924-980X(98)00038-1

Di Lazzaro, V., Oliviero, A., Saturno, E., Pilato, F., Insola, A., Mazzone, P., Profice, P., Tonali, P., Rothwell, J.C., 2001. The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. Exp. brain Res. 138, 268–73.

Di Lazzaro, V., Rothwell, J., Capogna, M., 2018. Noninvasive Stimulation of the Human Brain: Activation of Multiple Cortical Circuits. Neuroscientist. https://doi.org/10.1177/1073858417717660

Di Lazzaro, V., Rothwell, J.C., 2014. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. J. Physiol. 592, 4115–4128. https://doi.org/10.1113/jphysiol.2014.274316

Dirkx, M.F., den Ouden, H., Aarts, E., Timmer, M., Bloem, B.R., Toni, I., Helmich, R.C., 2016. The cerebral network of parkinson’s tremor: An effective connectivity fMRI study. J. Neurosci. 36, 5362–5372. https://doi.org/10.1523/JNEUROSCI.3634-15.2016

Draper, A., Jude, L., Jackson, G.M., Jackson, S.R., 2015. Motor excitability during movement preparation in Tourette syndrome. J. Neuropsychol. 9, 33–44. https://doi.org/10.1111/jnp.12033

Dupont-Hadwen, J., Bestmann, S., Stagg, C.J., 2019. Motor training modulates intracortical inhibitory dynamics in motor cortex during movement preparation. Brain Stimul. 12, 300–308. https://doi.org/10.1016/j.brs.2018.11.002

Duque, J., Greenhouse, I., Labruna, L., Ivry, R.B., 2017. Physiological Markers of Motor Inhibition during Human Behavior. Trends Neurosci. https://doi.org/10.1016/j.tins.2017.02.006

Duque, J., Ivry, R.B., 2009. Role of corticospinal suppression during motor preparation. Cereb. Cortex 19, 2013–2024. https://doi.org/10.1093/cercor/bhn230
Duque, J., Labruna, L., Cazares, C., Ivry, R.B., 2014. Dissociating the influence of response selection and task anticipation on corticospinal suppression during response preparation. Neupropsychologia 65, 287–296. https://doi.org/10.1016/j.neuropsychologia.2014.08.006

Duque, J., Labruna, L., Verset, S., Olivier, E., Ivry, R.B., 2012. Dissociating the role of prefrontal and premotor cortices in controlling inhibitory mechanisms during motor preparation. J. Neurosci. 32, 806–816. https://doi.org/10.1523/JNEUROSCI.4299-12.2012

Duque, J., Lew, D., Mazzocchio, R., Olivier, E., Ivry, R.B., 2010. Evidence for two concurrent inhibitory mechanisms during response preparation. J. Neurosci. 30, 3793–3802. https://doi.org/10.1523/JNEUROSCI.5722-09.2010

Duque, J., Murase, N., Celnik, P., Hummel, F., Harris-Love, M., Mazzocchio, R., Olivier, E., Cohen, L.G., 2007. Intermanual differences in movement-related interhemispheric inhibition. J. Cogn. Neurosci. 19, 204–213. https://doi.org/10.1162/jocn.2007.19.2.204

Economo, M.N., Viswanathan, S., Tasic, B., Bas, E., Winnubst, J., Menon, V., Graybuck, L.T., Nguyen, T.N., Smith, K.A., Yao, Z., Wang, L., Gerfen, C.R., Chandrashekar, J., Zeng, H., Looger, L.L., Svoboda, K., 2018. Distinct descending motor cortex pathways and their roles in movement. Nature 563, 79–84. https://doi.org/10.1038/s41586-018-0642-9

Elahi, B., Gunraj, C., Chen, R., 2012. Short-interval intracortical inhibition blocks long-term potentiation induced by paired associative stimulation. J. Neurophysiol. 107, 1935–1941. https://doi.org/10.1152/jn.00202.2011

Federico, P., Perez, M.A., 2017. Distinct Corticocortical Contributions to Human Precision and Power Grip. Cereb. Cortex 27, 5070–5082. https://doi.org/10.1093/cercor/bhw291

Ferbert, A., Priori, A., Rothwell, J.C., Day, B.L., Colebatch, J.G., Marsden, C.D., 1992. Interhemispheric inhibition of the human motor cortex. J. Physiol. 453, 525–546. https://doi.org/10.1113/jphysiol.1992.sp019243

Fernandez, L., Major, B.P., Teo, W.P., Byrne, L.K., Eenticott, P.G., 2018. Assessing cerebellar brain inhibition (CBI) via transcranial magnetic stimulation (TMS): A systematic review. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2017.11.018

Fisher, K.M., Lai, H.M., Baker, M.R., Baker, S.N., 2009. Corticospinal activation confounds cerebellar effects of posterior fossa stimuli. Clin. Neurophysiol. 120, 2109–2113. https://doi.org/10.1016/j.clinph.2009.08.021

Fling, B.W., Seidler, R.D., 2012. Task-dependent effects of interhemispheric inhibition on motor control. Behav. Brain Res. 226, 211–217. https://doi.org/10.1016/j.bbr.2011.09.018

Flöel, A., Rösser, N., Michka, O., Knecht, S., Breitenstein, C., 2008. Noninvasive brain stimulation improves language learning. J. Cogn. Neurosci. 20, 1415–1422. https://doi.org/10.1162/jocn.2008.20098

Foysal, K.M.R., Baker, S.N., 2019. A hierarchy of corticospinal plasticity in human hand and forearm muscles. J. Physiol. 597, 2729–2739. https://doi.org/10.1113/JP277462

Gao, Z., Davis, C., Thomas, A.M., Economo, M.N., Abrego, A.M., Svoboda, K., De Zeeuw, C.I., Li, N., 2018. A cortico-cerebellar loop for motor planning. Nature. https://doi.org/10.1038/s41586-018-0633-x
Grandjean, J., Derosiere, G., Vassiliadis, P., Quemener, L., de Wilde, Y., Duque, J., 2017. Validation of a double-coil TMS method to assess corticospinal excitability. Brain Stimul. 10, 507. https://doi.org/10.1016/j.brs.2017.01.480

Grandjean, J., Derosiere, G., Vassiliadis, P., Quemener, L., Wilde, Y. de, Duque, J., 2018. Towards assessing corticospinal excitability bilaterally: Validation of a double-coil TMS method. J. Neurosci. Methods 293, 162–168. https://doi.org/10.1016/j.jneumeth.2017.09.016

Greenhouse, I., Sias, A., Labruna, L., Ivry, R.B., 2015. Nonspecific inhibition of the motor system during response preparation. J. Neurosci. 35, 10675–10684. https://doi.org/10.1523/JNEUROSCI.1436-15.2015

Grefkes, C., Eickhoff, S.B., Nowak, D.A., Dafotakis, M., Fink, G.R., 2008. Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. Neuroimage 41, 1382–1394. https://doi.org/10.1016/j.neuroimage.2008.03.048

Groppa, S., Werner-Petroll, N., Münchau, A., Deuschl, G., Ruschwort, M.F.S., Siebner, H.R., 2012. A novel dual-site transcranial magnetic stimulation paradigm to probe fast facilitatory inputs from ipsilateral dorsal premotor cortex to primary motor cortex. Neuroimage 62, 500–509. https://doi.org/10.1016/j.neuroimage.2012.05.023

Haith, A.M., Pakpoor, J., Krakauer, J.W., 2016. Independence of movement preparation and movement initiation. J. Neurosci. 36, 3007–3015. https://doi.org/10.1523/JNEUROSCI3245-15.2016

Hanajima, R., Ugawa, Y., Machii, K., Mochizuki, H., Terao, Y., Enomoto, H., Furubayashi, T., Shio, Y., Uesugi, H., Kanazawa, I., 2001. Interhemispheric facilitation of the hand motor area in humans. J. Physiol. 531, 849–859. https://doi.org/10.1111/j.1469-7793.2001.0849h.x

Hannah, R., Cavanagh, S.E., Tremblay, S., Simeoni, S., Rothwell, J.C., 2018. Selective suppression of local interneuron circuits in human motor cortex contributes to movement preparation. J. Neurosci. 38, 1264–1276. https://doi.org/10.1523/JNEUROSCI2869-17.2017

Hannah, R., Rothwell, J.C., 2017. Pulse Duration as Well as Current Direction Determines the Specificity of Transcranial Magnetic Stimulation of Motor Cortex during Contraction. Brain Stimul. 10, 106–115. https://doi.org/10.1016/j.brs.2016.09.008

Hardwick, R.M., Lesage, E., Miall, R.C., 2014. Cerebellar transcranial magnetic stimulation: The role of coil geometry and tissue depth. Brain Stimul. 7, 643–649. https://doi.org/10.1016/j.brs.2014.04.009

Heinrich, H., Hoegl, T., Moll, G.H., Kratz, O., 2014. A bimodal neurophysiological study of motor control in attention-deficit hyperactivity disorder: A step towards core mechanisms? Brain 137, 1156–1166. https://doi.org/10.1093/brain/awu029

Hoegl, T., Heinrich, H., Barth, W., Lösel, F., Moll, G.H., Kratz, O., 2012. Time Course Analysis of Motor Excitability in a Response Inhibition Task According to the Level of Hyperactivity and Impulsivity in Children with ADHD. PLoS One 7. https://doi.org/10.1371/journal.pone.0046066

Hooks, B.M., Mao, T., Gutnis, D.A., Yamawai, N., Svoboda, K., Shepherd, G.M.G.,
2013. Organization of cortical and thalamic input to pyramidal neurons in mouse motor cortex. J. Neurosci. 33, 748–760. https://doi.org/10.1523/JNEUROSCI.4338-12.2013

Huang, Y., Chen, J.C., Chen, C.M., Tsai, C.H., Lu, M.K., 2019. Paired associative electroacupuncture and transcranial magnetic stimulation in humans. Front. Hum. Neurosci. 13. https://doi.org/10.3389/fnhum.2019.00049

Hummel, F.C., Steven, B., Hoppe, J., Heise, K., Thomalla, G., Cohen, L.G., Gerloff, C., 2009. Deficient intracortical inhibition (SICI): During movement preparation after chronic stroke. Neurology 72, 1766–1772. https://doi.org/10.1212/WNL.0b013e3181a609c5

Ibáñez, J., Hannah, R., Rocchi, L., Rothwell, J.C., 2018. Motor excitability before cue-guided v self-paced actions Premovement suppression of corticospinal excitability may be a necessary part of movement preparation. bioRxiv 470153. https://doi.org/10.1101/470153

Hummel, F.C., Steven, B., Hoppe, J., Heise, K., Thomalla, G., Cohen, L.G., Gerloff, C., 2009. Deficient intracortical inhibition (SICI): During movement preparation after chronic stroke. Neurology 72, 1766–1772. https://doi.org/10.1212/WNL.0b013e3181a609c5

Ibáñez, J., Hannah, R., Rocchi, L., Rothwell, J.C., 2018. Motor excitability before cue-guided v self-paced actions Premovement suppression of corticospinal excitability may be a necessary part of movement preparation. bioRxiv 470153. https://doi.org/10.1101/470153

Kassavetis, P., Hoffland, B.S., Safi, T.A., Bhatia, K.P., Van De Warrenburg, B.P., Rothwell, J.C., Edwards, M.J., 2011. Cerebellar brain inhibition is decreased in active and surround muscles at the onset of voluntary movement. Exp. Brain Res. 209, 437–442. https://doi.org/10.1007/s00221-011-2575-5

Koch, G., Cercignani, M., Pecchioli, C., Versace, V., Oliveri, M., Caltagirone, C., Rothwell, J., Bozzali, M., 2010. In vivo definition of parieto-motor connections involved in planning of grasping movements. Neuroimage 51, 300–312. https://doi.org/10.1016/j.neuroimage.2010.02.022

Koch, G., Franca, M., Del Olmo, M.F., Cheeran, B., Milton, R., Sauco, M.A., Rothwell, J.C., 2013. Organization of cortical and thalamic input to pyramidal neurons in mouse motor cortex. J. Neurosci. 33, 748–760. https://doi.org/10.1523/JNEUROSCI.4338-12.2013

Huang, Y., Chen, J.C., Chen, C.M., Tsai, C.H., Lu, M.K., 2019. Paired associative electroacupuncture and transcranial magnetic stimulation in humans. Front. Hum. Neurosci. 13. https://doi.org/10.3389/fnhum.2019.00049

Hummel, F.C., Steven, B., Hoppe, J., Heise, K., Thomalla, G., Cohen, L.G., Gerloff, C., 2009. Deficient intracortical inhibition (SICI): During movement preparation after chronic stroke. Neurology 72, 1766–1772. https://doi.org/10.1212/WNL.0b013e3181a609c5

Ibáñez, J., Hannah, R., Rocchi, L., Rothwell, J.C., 2018. Motor excitability before cue-guided v self-paced actions Premovement suppression of corticospinal excitability may be a necessary part of movement preparation. bioRxiv 470153. https://doi.org/10.1101/470153

Hummel, F.C., Steven, B., Hoppe, J., Heise, K., Thomalla, G., Cohen, L.G., Gerloff, C., 2009. Deficient intracortical inhibition (SICI): During movement preparation after chronic stroke. Neurology 72, 1766–1772. https://doi.org/10.1212/WNL.0b013e3181a609c5

Ibáñez, J., Hannah, R., Rocchi, L., Rothwell, J.C., 2018. Motor excitability before cue-guided v self-paced actions Premovement suppression of corticospinal excitability may be a necessary part of movement preparation. bioRxiv 470153. https://doi.org/10.1101/470153

Kassavetis, P., Hoffland, B.S., Safi, T.A., Bhatia, K.P., Van De Warrenburg, B.P., Rothwell, J.C., Edwards, M.J., 2011. Cerebellar brain inhibition is decreased in active and surround muscles at the onset of voluntary movement. Exp. Brain Res. 209, 437–442. https://doi.org/10.1007/s00221-011-2575-5

Koch, G., Cercignani, M., Pecchioli, C., Versace, V., Oliveri, M., Caltagirone, C., Rothwell, J., Bozzali, M., 2010. In vivo definition of parieto-motor connections involved in planning of grasping movements. Neuroimage 51, 300–312. https://doi.org/10.1016/j.neuroimage.2010.02.022

Koch, G., Franca, M., Del Olmo, M.F., Cheeran, B., Milton, R., Sauco, M.A., Rothwell, J.C.,
2006. Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. J. Neurosci. 26, 7452–7459. https://doi.org/10.1523/JNEUROSCI.1158-06.2006

Koch, G., Franca, M., Mochizuki, H., Marconi, B., Caltagirone, C., Rothwell, J.C., 2007. Interactions between pairs of transcranial magnetic stimuli over the human left dorsal premotor cortex differ from those seen in primary motor cortex. J. Physiol. 578, 551–562. https://doi.org/10.1113/jphysiol.2006.123562

Kraskov, A., Prabhu, G., Quallo, M.M., Lemon, R.N., Brochier, T., 2011. Ventral premotor-motor cortex interactions in the macaque monkey during grasp: Response of single neurons to intracortical microstimulation. J. Neurosci. 31, 8812–8821. https://doi.org/10.1523/JNEUROSCI.0525-11.2011

Laakso, I., Hirata, A., Ugawa, Y., 2014. Effects of coil orientation on the electric field induced by TMS over the hand motor area. Phys. Med. Biol. 59, 203–218. https://doi.org/10.1088/0031-9155/59/1/203

Labruna, L., Lebon, F., Duque, J., Klein, P.A., Cazares, C., Ivry, R.B., 2014. Generic inhibition of the selected movement and constrained inhibition of nonselected movements during response preparation. J. Cogn. Neurosci. 26, 269–278. https://doi.org/10.1162/jocn_a_00492

Labruna, L., Tischler, C., Cazares, C., Greenhouse, I., Duque, J., Lebon, F., Ivry, R., 2019. Planning Face, Hand, and Leg Movements: Anatomical Constraints on Preparatory Inhibition. bioRxiv 529107. https://doi.org/10.1101/529107

Lara, A.H., Elsayed, G.F., Zimnik, A.J., Cunningham, J.P., Churchland, M.M., 2018. Conservation of preparatory neural events in monkey motor cortex regardless of how movement is initiated. Elife 7. https://doi.org/10.7554/eLife.31826

Lazzaro, V. Di, Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., Insola, A., Ranieri, F., Meglio, M., Tonali, P.A., Rothwell, J.C., 2008. The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex 16, 3871–3879. https://doi.org/10.1113/jphysiol.2008.152736

Lebon, F., Lotze, M., Stinear, C.M., Byblow, W.D., 2012. Task-Dependent Interaction between Parietal and Contralateral Primary Motor Cortex during Explicit versus Implicit Motor Imagery. PLoS One 7, e37850. https://doi.org/10.1371/journal.pone.0037850

Lebon, F., Ruffino, C., Greenhouse, I., Labruna, L., Ivry, R.B., Papaxanthis, C., 2019. The Neural Specificity of Movement Preparation During Actual and Imagined Movements. Cereb. Cortex 29, 689–700. https://doi.org/10.1093/cercor/bhx350

Lefaucheur, J.P., 2019. Transcranial magnetic stimulation, in: Handbook of Clinical Neurology. Elsevier B.V., pp. 559–580. https://doi.org/10.1016/B978-0-444-64032-1.00037-0

Leocani, L., Cohen, L.G., Wassermann, E.M., Ikoma, K., Hallett, M., 2000. Human corticospinal excitability evaluated with transcranial magnetic stimulation during different reaction time paradigms. Brain 123, 1161–1173. https://doi.org/10.1093/brain/123.6.1161

Leodori, G., Thirugnanasambandam, N., Conn, H., Popa, T., Berardelli, A., Hallett, M., 2019. Intracortical inhibition and surround inhibition in the motor cortex: A tms-EEG study.
Distinct temporospatial interhemispheric interactions in the human primary and premotor cortex during movement preparation. Cereb. Cortex 20, 1323–1331.
https://doi.org/10.1093/cercor/bhp196

MacDonald, H.J., Coxon, J.P., Stinear, C.M., Byblow, W.D., 2014. The fall and rise of corticomotor excitability with cancellation and reinitiation of prepared action. J. Neurophysiol. 112, 2707–2717. https://doi.org/10.1152/jn.00366.2014

MacKenzie, T.N., Bailey, A.Z., Mi, P.Y., Tsang, P., Jones, C.B., Nelson, A.J., 2016. Human area 5 modulates corticospinal output during movement preparation. Neuroreport 27, 1056–1060. https://doi.org/10.1097/WNR.0000000000000655

Mars, R.B., Bestmann, S., Rothwell, J.C., Haggard, P., 2007. Effects of motor preparation and spatial attention on corticospinal excitability in a delayed-response paradigm. Exp. Brain Res. 182, 125–129. https://doi.org/10.1007/s00221-007-1055-4

Mars, R.B., Klein, M.C., Neubert, F.-X.F.X., Olivier, E., Buch, E.R., Boorman, E.D., Rushworth, M.F.S.S., 2009. Short-Latency Influence of Medial Frontal Cortex on Primary Motor Cortex during Action Selection under Conflict. J. Neurosci. 29, 6926–6931. https://doi.org/10.1523/JNEUROSCI.1396-09.2009

McMillan, S., Nougier, V., Byblow, W.D., 2004. Human corticospinal excitability during a precued reaction time paradigm. Exp. Brain Res. 156, 80–87. https://doi.org/10.1007/s00221-003-1772-2

Meziane, H.B., Moisello, C., Perfetti, B., Kvint, S., Isaias, I.U., Quartarone, A., Rocco, A. Di, Ghilardi, M.F., 2015. Movement preparation and bilateral modulation of beta activity in aging and parkinson’s disease. PLoS One 10. https://doi.org/10.1371/journal.pone.0114817

Moulton, E., Galléa, C., Kemlin, C., Valabregue, R., Maier, M.A., Lindberg, P., Rosso, C., 2017. Cerebello-cortical differences in effective connectivity of the dominant and non-dominant hand during a visuomotor paradigm of grip force control. Front. Hum. Neurosci. 11. https://doi.org/10.3389/fnhum.2017.00511

Murase, N., Duque, J., Mazzocchio, R., Cohen, L.G., 2004. Influence of Interhemispheric Interactions on Motor Function in Chronic Stroke. Ann. Neurol. 55, 400–409. https://doi.org/10.1002/ana.10848

Neef, N.E., Linh Hoang, T.N., Neef, A., Paulus, W., Sommer, M., 2015. Speech dynamics are coded in the left motor cortex in fluent speakers but not in adults who stutter. Brain 138, 712–725. https://doi.org/10.1093/brain/awu390

Neubert, F.-X., Mars, R.B., Buch, E.R., Olivier, E., Rushworth, M.F.S., 2010. Cortical and subcortical interactions during action reprogramming and their related white matter pathways. Proc. Natl. Acad. Sci. 107, 13240–13245. https://doi.org/10.1073/pnas.1000674107

Neubert, F.X., Mars, R.B., Olivier, E., Rushworth, M.F.S., 2011. Modulation of short intracortical inhibition during action reprogramming. Exp. Brain Res. 211, 265–276. https://doi.org/10.1007/s00221-011-2682-3

Ni, Z., Cash, R.F.H., Gunraj, C., Bercovici, E., Hallett, M., Chen, R., 2019. Involvement of
different neuronal components in the induction of cortical plasticity with associative
stimulation. Brain Stimul. 12, 84–86. https://doi.org/10.1016/j.brs.2018.08.019

Ni, Z., Gunraj, C., Nelson, A.J., Yeh, I.J., Castillo, G., Hoque, T., Chen, R., 2009. Two phases
of interhemispheric inhibition between motor related cortical areas and the primary
motor cortex in human. Cereb. Cortex 19, 1654–1665. https://doi.org/10.1093/cercor/bhn201

O’Shea, J., Sebastian, C., Boorman, E.D., Johansen-Berg, H., Rushworth, M.F.S., 2007.
Functional specificity of human premotor-motor cortical interactions during action
selection. Eur. J. Neurosci. 26, 2085–2095. https://doi.org/10.1111/j.1460-9568.2007.05795.x

Opie, G.M., Ridding, M.C., Semmler, J.G., 2015. Task-related changes in intracortical
inhibition assessed with paired- and triple-pulse transcranial magnetic stimulation. J.
Neurophysiol. 113, 1470–1479. https://doi.org/10.1152/jn.00651.2014

Panyakaew, P., Cho, H.J., Srivanitchapoom, P., Popa, T., Wu, T., Hallett, M., 2016.
Cerebellar brain inhibition in the target and surround muscles during voluntary tonic
activation. Eur. J. Neurosci. 43, 1075–1081. https://doi.org/10.1111/ejn.13211

Pascual-Leone, A., Cohen, L.G., Brasil-Neto, J.P., Valls-Solé, J., Hallett, M., 1994.
Differentiation of sensorimotor neuronal structures responsible for induction of motor
evoked potentials, attenuation in detection of somatosensory stimuli, and induction of
sensation of movement by mapping of optimal current directions. Electroencephalogr.
Clin. Neurophysiol. 93, 230–6.

Perfetti, B., Moisello, C., Landsness, E.C., Kvint, S., Lanzafame, S., Onofrj, M., di Rocco, A.,
Tononi, G., Felice Ghilardi, M., 2011. Modulation of gamma and theta spectral
amplitude and phase synchronization is associated with the development of visuo-motor
learning. J. Neurosci. 31, 14810–14819. https://doi.org/10.1523/JNEUROSCI.1319-
11.2011

Perich, M.G., Gallego, J.A., Miller, L.E., 2018. A Neural Population Mechanism for Rapid
Learning. Neuron 100, 964–976.e7. https://doi.org/10.1016/j.neuron.2018.09.030

Pinto, A.D., Chen, R., 2001. Suppression of the motor cortex by magnetic stimulation of the
cerebellum. Exp. Brain Res. 140, 505–510. https://doi.org/10.1007/s002210100862

Pool, E.M., Rehme, A.K., Fink, G.R., Eickhoff, S.B., Grefkes, C., 2013. Network dynamics
engaged in the modulation of motor behavior in healthy subjects. Neuroimage 82, 68–76.
https://doi.org/10.1016/j.neuroimage.2013.05.123

Poole, B.J., Mather, M., Livesey, E.J., Harris, I.M., Harris, J.A., 2018. Motor-evoked
potentials reveal functional differences between dominant and non-dominant motor
cortices during response preparation. Cortex 103, 1–12.
https://doi.org/10.1016/j.cortex.2018.02.004

Quoilin, C., Derosiere, G., 2015. Global and specific motor inhibitory mechanisms during
action preparation. J. Neurosci. https://doi.org/10.1523/JNEUROSCI.3664-15.2015

Quoilin, C., Lambert, J., Jacob, B., Klein, P.A., Duque, J., 2016. Comparison of motor
inhibition in variants of the instructed-delay choice reaction time task. PLoS One 11,
e0161964. https://doi.org/10.1371/journal.pone.0161964

Quoilin, C., Wilhelm, E., Maurage, P., De Timary, P., Duque, J., 2018. Deficient inhibition in
alcohol-dependence: Let’s consider the role of the motor system!
Neuropsychopharmacology 43, 1851–1858. https://doi.org/10.1038/s41386-018-0074-0

Raffin, E., Siebner, H.R., 2019. Use-dependent plasticity in human primary motor hand area: Synergistic interplay between training and immobilization. Cereb. Cortex 29, 356–371. https://doi.org/10.1093/cercor/bhy226

Rothkirch, I., Granert, O., Knutzen, A., Wolff, S., Gövert, F., Pedersen, A., Zeuner, K.E., Witt, K., 2018. Dynamic causal modeling revealed dysfunctional effective connectivity in both, the cortico-basal-ganglia and the cerebello-cortical motor network in writers’ cramp. NeuroImage Clin. 18, 149–159. https://doi.org/10.1016/j.nicl.2018.01.015

Rusu, C. V., Murakami, M., Ziemann, U., Triesch, J., 2014. A model of TMS-induced I-waves in motor cortex. Brain Stimul. 7, 401–414. https://doi.org/10.1016/j.brs.2014.02.009

Sakai, K., Ugawa, Y., Terao, Y., Hanajima, R., Furubayashi, T., Kanazawa, I., 1997. Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. Exp. Brain Res. 113, 24–32. https://doi.org/10.1007/BF02454139

Salvador, R., Silva, S., Bassar, P.J., Miranda, P.C., 2011. Determining which mechanisms lead to activation in the motor cortex: A modeling study of transcranial magnetic stimulation using realistic stimulus waveforms and sulcal geometry. Clin. Neurophysiol. 122, 748–758. https://doi.org/10.1016/j.clinph.2010.09.022

Sanger, T.D., Garg, R.R., Chen, R., 2001. Interactions between two different inhibitory systems in the human motor cortex. J. Physiol. 530, 307–317. https://doi.org/10.1111/j.1469-7793.2001.0307l.x

Sasaki, K., Gemba, H., Hashimoto, S., 1981. visually initiated hand movements in the monkey 205.

Schlerf, J.E., Galea, J.M., Spampinato, D., Celnik, P.A., 2015. Laterality Differences in Cerebellar-Motor Cortex Connectivity. Cereb. Cortex 25, 1827–1834. https://doi.org/10.1093/cercor/bht422

Seo, H., Schaworonkow, N., Jun, S.C., Triesch, J., 2017. A multi-scale computational model of the effects of TMS on motor cortex. F1000Research 5, 1945. https://doi.org/10.12688/f1000research.9277.3

Shimazu, H., Maier, M.A., Cerri, G., Kirkwood, P.A., Lemon, R.N., 2004. Macaque Ventral Premotor Cortex Exerts Powerful Facilitation of Motor Cortex Outputs to Upper Limb Motoneurons. J. Neurosci. 24, 1200–1211. https://doi.org/10.1523/JNEUROSCI.4731-03.2004

Siebner, H.R., 2020. Does TMS of the precentral motor hand knob primarily stimulate the dorsal premotor cortex or the primary motor hand area? Brain Stimul. 13, 517–518. https://doi.org/10.1016/j.brs.2019.12.015

Sommer, M., Ciocca, M., Chieffo, R., Hammond, P., Neef, A., Paulus, W., Rothwell, J.C., Hannah, R., 2018. TMS of primary motor cortex with a biphasic pulse activates two independent sets of excitable neurones. Brain Stimul. 11, 558–565. https://doi.org/10.1016/j.brs.2018.01.001

Soteropoulos, D.S., 2018. Corticospinal gating during action preparation and movement in the...
Spampinato, D., Celnik, P., 2018. Deconstructing skill learning and its physiological mechanisms. Cortex 104, 90–102. https://doi.org/10.1016/j.cortex.2018.03.017

Spampinato, D., Rothwell, J.C., Celnik, P.A., 2017. P153 Cerebellar-M1 connectivity (CBI): One or two different networks? Clin. Neurophysiol. 128, e90. https://doi.org/10.1016/j.clinph.2016.10.274

Spampinato, D.A., Block, H.J., Celnik, P.A., 2017. Cerebellar–M1 connectivity changes associated with motor learning are somatotopic specific. J. Neurosci. 37, 2377–2386. https://doi.org/10.1523/JNEUROSCI.2511-16.2017

Stefanou, M.I., Desideri, D., Belardinelli, P., Zrenner, C., Ziemann, U., 2018. Phase synchronicity of µ-rhythm determines efficacy of interhemispheric communication between human motor cortices. J. Neurosci. 38, 10525–10534. https://doi.org/10.1523/JNEUROSCI.1470-18.2018

Strigaro, G., Ruge, D., Chen, J.C., Marshall, L., Desikan, M., Cantello, R., Rothwell, J.C., 2015. Interaction between visual and motor cortex: A transcranial magnetic stimulation study. J. Physiol. 593, 2365–2377. https://doi.org/10.1113/JP270135

Taube, W., Leukel, C., Nielsen, J.B., Lundbye-Jensen, J., 2017. Non-invasive assessment of changes in corticomotoneuronal transmission in humans. J. Vis. Exp. 2017. https://doi.org/10.3791/52663

Taube, W., Leukel, C., Nielsen, J.B., Lundbye-Jensen, J., 2015. Repetitive activation of the corticospinal pathway by means of rTMS may reduce the efficiency of corticomotoneuronal synapses. Cereb. Cortex 25, 1629–1637. https://doi.org/10.1093/cercor/bht359

Taylor, J.L., 2006. Stimulation at the cervicomedullary junction in human subjects. J. Electromyogr. Kinesiol. 16, 215–223. https://doi.org/10.1016/j.jelekin.2005.07.001

Tazoe, T., Perez, M.A., 2013. Speed-dependent contribution of callosal pathways to ipsilateral movements. J. Neurosci. 33, 16178–16188. https://doi.org/10.1523/JNEUROSCI.2638-13.2013

Thielscher, A., Kammer, T., 2002. Linking physics with physiology in TMS: A sphere field model to determine the cortical stimulation site in TMS. Neuroimage 17, 1117–1130. https://doi.org/10.1006/nimg.2002.1282

Thielscher, A., Opitz, A., Windhoff, M., 2011. Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. Neuroimage 54, 234–243. https://doi.org/10.1016/j.neuroimage.2010.07.061

Tscherpel, C., Hensel, L., Lemberg, K., Freytag, J., Michely, J., Volz, L.J., Fink, G.R., Grefkes, C., 2019. Age affects the contribution of ipsilateral brain regions to movement kinematics. Hum. Brain Mapp. 640–655. https://doi.org/10.1002/hbm.24829

Tsujimoto, T., Gemba, H., Sasaki, K., 1993. Effect of cooling the dentate nucleus of the cerebellum on hand movement of the monkey. Brain Res. 629, 1–9.
Ueno, T., Meteyard, L., Hoffman, P., Murayama, K., 2018. The ventral anterior temporal lobe has a necessary role in exception word reading. Cereb. Cortex 28, 3035–3045. https://doi.org/10.1093/cercor/bhy131

Ugawa, Y., 2009. [Basic mechanism of magnetic human cerebellar stimulation and its clinical application]. Rinsho Shinkeigaku 49, 621–8.

Vassiliadis, P., Derosiere, G., Grandjean, J., Duque, J., 2020. Motor training strengthens corticospinal suppression during movement preparation. bioRxiv 2020.02.14.948877. https://doi.org/10.1101/2020.02.14.948877

Vassiliadis, P., Grandjean, J., Derosiere, G., de Wilde, Y., Quemener, L., Duque, J., 2018. Using a double-coil TMS protocol to assess preparatory inhibition bilaterally. Front. Neurosci. 12, 139. https://doi.org/10.3389/fnins.2018.00139

Vesia, M., Barnett-Cowan, M., Elahi, B., Jegatheeswaran, G., Isayama, R., Neva, J.L., Davare, M., Staines, W.R., Culham, J.C., Chen, R., 2017. Human dorsomedial parieto-motor circuit specifies grasp during the planning of goal-directed hand actions. Cortex 92, 175–186. https://doi.org/10.1016/j.cortex.2017.04.007

Vesia, M., Bolton, D.A., Mochizuki, G., Staines, W.R., 2013. Human parietal and primary motor cortical interactions are selectively modulated during the transport and grip formation of goal-directed hand actions. Neuropsychologia 51, 410–417. https://doi.org/10.1016/j.neuropsychologia.2012.11.022

Volz, L.J., Hamada, M., Rothwell, J.C., Grefkes, C., 2015. What Makes the Muscle Twitch: Motor System Connectivity and TMS-Induced Activity. Cereb. Cortex 25, 2346–2353. https://doi.org/10.1093/cercor/bhu032

Wang, B.A., Viswanathan, S., Abdollahi, R.O., Rosjat, N., Popovych, S., Daun, S., Grefkes, C., Fink, G.R., 2017. Frequency-specific modulation of connectivity in the ipsilateral sensorimotor cortex by different forms of movement initiation. Neuroimage 159, 248–260. https://doi.org/10.1016/j.neuroimage.2017.07.054

Wiese, H., Stude, P., Särge, R., Nebel, K., Diener, H.-C., Keidel, M., 2005. Reorganization of motor execution rather than preparation in poststroke hemiparesis. Stroke 36, 1474–9. https://doi.org/10.1161/01.STR.0000170639.26891.30

Willett, F.R., Deo, D.R., Avansino, D.T., Rezaei, P., Hochberg, L., Henderson, J., Shenoy, K., 2019. Hand Knob Area of Motor Cortex in People with Tetraplegia Represents the Whole Body in a Modular Way. bioRxiv 659839. https://doi.org/10.1101/659839

Wong, A.L., Haith, A.M., Krakauer, J.W., 2015. Motor planning. Neuroscientist. https://doi.org/10.1177/1073858414541484
Highlights

• Recently, new TMS tools have emerged in the field of action preparation.
• Directional TMS enables investigating different subsets of M1 neurons.
• Paired-pulse TMS has been used to study the influence of the cerebellum on M1.
• Double-coil TMS facilitates the study of bilateral changes in M1 excitability.
• Discuss their bearings for the field compared to classic techniques.