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Dual-site TMS as a tool to probe effective interactions within the motor network: a review

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Abstract: Dual-site transcranial magnetic stimulation (ds-TMS) is well suited to investigate the causal effect of distant brain regions on the primary motor cortex, both at rest and during motor performance and learning. However, given the broad set of stimulation parameters, clarity about which parameters are most effective for identifying particular interactions is lacking. Here, evidence describing inter- and intra-hemispheric interactions during rest and in the context of motor tasks is reviewed. Our aims are threefold: (1) provide a detailed overview of ds-TMS literature regarding inter- and intra-hemispheric connectivity; (2) describe the applicability and contributions of these interactions to motor control, and; (3) discuss the practical implications and future directions. Of the 3659 studies screened, 109 were included and discussed. Overall, there is remarkable variability in the experimental context for assessing ds-TMS interactions, as well as in the use and reporting of stimulation parameters, hindering a quantitative comparison of results across studies. Further studies examining ds-TMS interactions in a systematic manner, and in which all critical parameters are carefully reported, are needed.

Keywords: connectivity; interhemispheric interactions; intrahemispheric interactions; motor network; transcranial magnetic stimulation.

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Introduction

Daily life activities require an enormous variety of coordinated movements involving both lower and upper limbs. It has been established that movement coordination relies on an interconnected network of brain areas (Debaere et al. 2001; Swinnen 2002), in which the primary motor cortex (M1) plays a pivotal role. More specifically, M1 is responsible for voluntary motor control by means of a complex integration of multiregional influences, e.g., from the motor areas, parietal cortex, supplementary motor area, cerebellum and primary somatosensory cortex of both the ipsi- and contra-lateral hemisphere, among other regions. The nature of these connections with M1 is state-dependent as interactions involved in motor control are modified during the preparation and/or execution of a motor task (Reis et al. 2008). Which brain regions of the network are activated and how they are interconnected varies as a function of task requirements (e.g., Debaere et al. 2003; Diedrichsen et al. 2006; Reis et al. 2008; Theorin and Johansson 2007).

Recent developments of a variety of neuroimaging techniques have extensively contributed to the emerging understanding of these inter-regional connectivity patterns. While brain imaging techniques such as functional magnetic resonance imaging (fMRI) and ^{15}O-O_2 or ^{18}F-FDG positron emission tomography (PET) (Watabe and Hatazawa 2019) can be employed to evaluate the temporal correlation between spatially remote neurophysiological events, i.e., functional connectivity (Friston et al. 1993), they are restricted by a rather low temporal resolution (Bortoletto et al. 2015; Calhoun et al. 2014; Valchev et al. 2015). In contrast, electroencephalography (EEG) and transcranial magnetic stimulation (TMS) have a higher temporal resolution. However, unlike EEG, TMS can be

used to unravel causal relationships (Ruohonen and Karhu 2010). More specifically, TMS can be applied to investigate the direct and indirect influence of one neural system on another, i.e., the effective connectivity (Seghier and Friston 2013). In addition, TMS can be used to examine the relative timing of this contribution of neural systems during the preparation and/or performance of a specific motor task, i.e., the chronometry (de Graaf et al. 2009; Pascual-Leone et al. 2000). This allows us to determine both *'what'* the specific effect of a particular region on another region is and *'when'* this influence is exerted. Therefore, TMS appears to be particularly well suited to directly probe specific cortico–cortical interactions over time (Koch and Rothwell 2009), providing a unique possibility to identify the nature, the strength, and modulations of connectivity between specific brain areas (Rothwell 2011) to eventually gain insight into the organization and dynamics of global brain networks (Dayan et al. 2016).

To study effective connectivity, TMS can be used in two ways. First, TMS can be combined with other neuroimaging techniques (Friston et al. 1997), where a conditioning TMS pulse is applied over a certain brain area, and EEG, PET or fMRI are used to measure its effect on a target region. Second, TMS can be incorporated in a dual-site TMS (ds-TMS) paradigm, in which, e.g., the influence of an M1-modulating brain region on M1 is assessed by stimulating both regions in rapid succession. Using such paradigms, interactions between homologous M1s (Ferbert et al. 1992) as well as interactions between M1 and various other brain regions, both within and across hemispheres (Bäumer et al. 2006; Chen 2004; Civardi et al. 2001; Fiori et al. 2017; Koch et al. 2007), can be examined. Within the scope of this review, only ds-TMS will be discussed.

During single-pulse TMS solitary pulses (i.e., test stimuli, TS) are applied to M1 to elicit a motor evoked potential (MEP) in a specified target muscle, as assessed by means of electromyography (EMG). During a ds-TMS paradigm the TS over M1 is preceded by a conditioning stimulus (CS) over a motor-related, remote site, administered by a second coil. By comparing the average MEP amplitudes between the CS + TS condition and the TS only condition, a quantification of the influence of a specific motor-related brain region on corticospinal excitability, as measured by the TS, is provided. Depending on the conditioned brain region, the inter-stimulus interval (ISI), and the intensities of both CS and TS, either a facilitatory, inhibitory, or no interaction—corresponding to a respectively larger, reduced, or unchanged MEP amplitude in the CS + TS condition as compared to TS only—between the targeted brain regions can be established at rest (visualized in Figure 1, panel A). However, when a ds-TMS paradigm is applied during specific motor tasks, this modulatory interaction between brain regions can differ from the interaction at rest, as it depends on the excitability of the pathway at the time of stimulus delivery. For a more comprehensive description on the motor circuitry involved in goal-directed actions we refer to Culham and Valyear (2006), Reis et al. (2008), Koch and Rothwell (2009), Cisek and Kalaska (2010), Davare et al. (2011), Vesia and Crawford (2012), Shenoy et al. (2013), Aron et al. (2014), Turella and Lingnau (2014), Mirabella (2014), and Neige et al. (2021).

Over the past decades, research aimed at identifying intra- and inter-hemispheric interactions using ds-TMS has emerged [e.g., Fiori et al. (2017); Groppa et al. (2012b); Vesia et al. (2018)], also referring to this paradigm as twin coil design [e.g., Hasan et al. (2013); Torriero et al. (2011)], paired coil TMS [e.g., Arai et al. (2012)], dual-coil paired-pulse TMS [e.g., Byblow et al. (2007); Koch et al. (2006)], double-coil TMS [e.g., Picazio et al. (2014)], double-pulse TMS [e.g., Liuzzi et al. (2010), (2011)] and dual-coil TMS [e.g., Green et al. (2018)]. Confusingly, some authors also use the term paired-pulse TMS in this context [e.g., Buch et al. (2010); De Gennaro et al. (2004); O'Shea et al. (2007)], which originally refers to paradigms where two successive pulses are administered to the same location via the same coil [for review, see Hallett (2007)].

It has been suggested that the transcallosal connections between homologous motor areas are excitatory in nature as has been demonstrated in cats (Asanuma and Okuda 1962). However, these facilitatory transcallosal pathways synapse over local inhibitory (i.e., GABAergic) interneurons in the contralateral homologue (Somogyi et al. 1998). The same applies to the excitatory cerebello–thalamo–cortical pathway, which is inhibited by the surrounding Purkinje cells in the cerebellar hemispheres (Grimaldi et al. 2014; Groiss and Ugawa 2013; Na et al. 1997; Stoodley and Schmahmann 2010). For most interactions between different brain regions and M1, facilitation could only be elicited under specific conditions (i.e., low CS intensity, often only with pre-activation of the target muscle), and was often very inconsistent [i.e., Ferbert et al. (1992); Hanajima et al. (2001); Koch et al. (2009)]. Because of the widespread distribution of the induced electric field, an accurate stimulation of specific neural populations is exceedingly difficult. Hence, surround inhibition outweighs facilitation in most cases. Subtle changes in stimulation parameters [i.e., TMS intensity (Fiori et al. 2017), direction of the induced current flow and waveform of the magnetic pulses (Casula et al. 2018; Di Lazzaro et al. 2001; Di Lazzaro and Rothwell 2014; Spampinato et al. 2020b) and ISI (Ghosh et al. 2013)] may recruit (partially) distinct

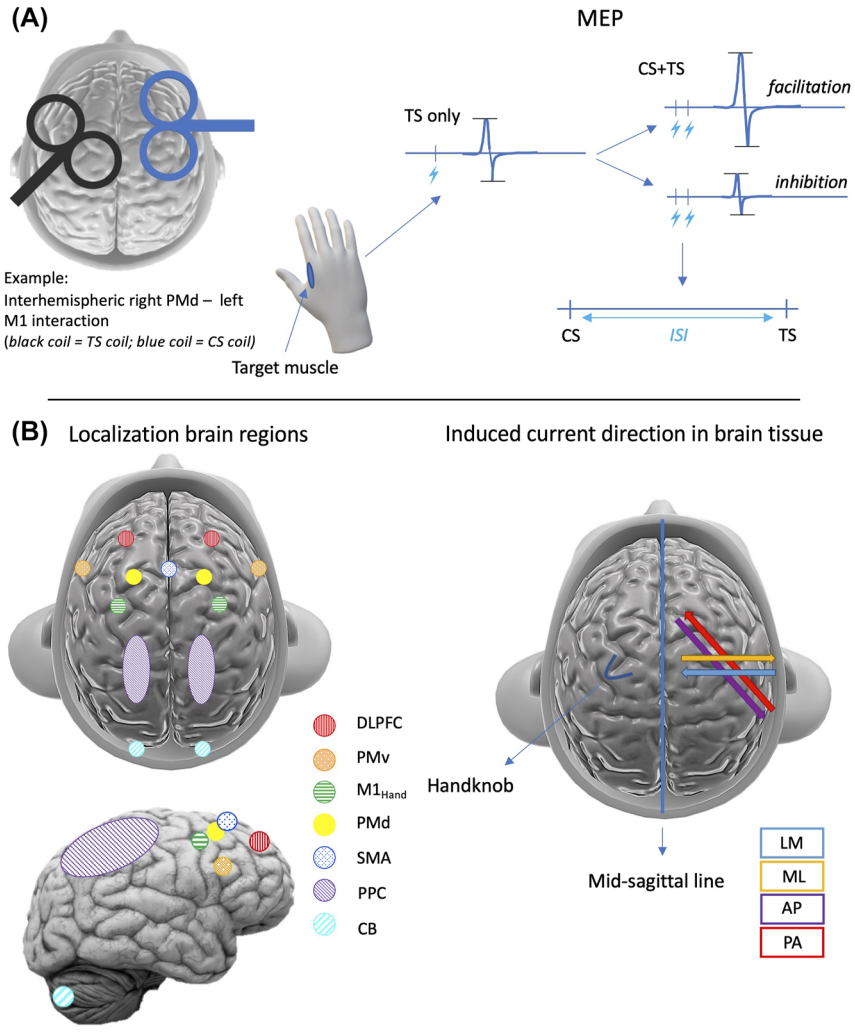

Figure 1: Overview of the basic principle of ds-TMS, the targeted brain regions and the induced current directions. (A) Principle of ds-TMS paradigms: The test stimulus (TS) over the primary motor cortex (M1) is preceded by a conditioning stimulus (CS) over a motor-related, remote site [e.g., the premotor dorsal (PMd)], at a certain interstimulus interval (ISI), i.e., the time between CS and TS application. By comparing the motor evoked potential (MEP) amplitudes between the CS + TS condition and the TS only condition, a quantification of the influence of a specific motor-related brain region on corticospinal excitability, as measured by the TS, is provided. Here, larger MEPs in the "CS + TS" relative to the "TS only" condition can be interpreted as facilitation, whereas smaller MEPs represent inhibition. (B) Location of the targeted brain regions, handknob and mid-sagittal line, and the different induced current directions used to stimulate these brain regions. AP, anterior-to-posterior-directed current; CB, cerebellum; CS, conditioning stimulus; DLPFC, dorsolateral prefrontal cortex; ISI, interstimulus interval; LM, lateral-to-medial-directed current; $M1_{Hand}$, hand representation of the primary motor cortex (also known as handknob); MEP, motor evoked potential; ML, medial-to-lateral-directed current; PA, posterior-to-anterior-directed current; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PPC, posterior parietal cortex; SMA, supplementary motor cortex; TS, test stimulus.

neurological populations/pathways and may differently interact with the direct (D-) and indirect (I-) waves that are sent downwards through the spinal cord (Di Lazzaro and Rothwell 2014). Wich might subsequently affect interregional connectivity. However, not only the characteristics of the applied pulse but also the internal state of the brain determine its neuronal impact (Silvanto et al. 2007; Silvanto and Pascual-Leone 2008). This state-dependency of TMS highlights the importance of evaluating cortico–cortical interactions both at rest and in the context of task-related conditions.

Ds-TMS studies have provided insight into the interactions of motor-related brain regions at rest and during the preparation and performance of motor tasks, while investigating the effective connectivity between both M1s as well as between M1 and other motor-related brain areas, including the dorsal (PMd) and ventral (PMv) premotor cortex, the supplementary motor area (SMA), the

dorsolateral prefrontal cortex (DLPFC), the posterior parietal cortex (PPC) and the cerebellum (CB), both within and between hemispheres (their respective position is indicated in Figure 1, panel B).

Altogether, ds-TMS is a valuable technique to investigate the causal influence of various motor-related brain regions on respectively contra- and ipsi-lateral M1. However, given the broad set of stimulation parameter possibilities (e.g., stimulus intensities, ISI, induced current direction, etc.), there is a lack of clarity as to which parameters are most effective for identifying certain interactions, e.g., facilitation or inhibition. Furthermore, a complete overview of the evidence regarding the application of ds-TMS to study a variety of motor-related cortico–cortical interactions seems to be lacking. Over the past 10 years, multiple efforts were made to review ds-TMS literature, with a specific focus on resting-state effective connectivity (Lafleur et al. 2016), specific task-related processing (Neige et al. 2021), clinical applications (Valero-Cabre et al. 2017), pathological conditions (Takeuchi et al. 2017), or multimodal approaches, e.g., using TMS concurrently with EEG or fMRI (Hallet et al. 2017). In a recent narrative review by Koch (2020), most important features of ds-TMS protocols are briefly discussed. However, a complete overview of ds-TMS work, including the mapping of effective connectivity between a broad set of motor-related brain regions and M1 during both resting-state and motor task-related conditions, is currently lacking.

To expand upon and extend previous reviews, the aims of the current review are threefold: (1) to provide a comprehensive, complete and up-to-date overview of ds-TMS literature investigating inter- and/or intra-hemispheric connectivity between motor-related brain regions at rest, and how these interactions are modulated prior to and during the execution of motor tasks; (2) to describe the applicability and unique contribution of this technique in the context of motor control; and (3) to discuss methodological implications, limitations in terms of application and interpretation of the results, as well as future directions.

Methods

A computer-based search on PUBMED was conducted using the keywords [(M1 OR primary motor cortex AND ("transcranial magnetic stimulation") AND (interactions)] OR [(M1 OR primary motor cortex) AND ("transcranial magnetic stimulation") AND (connectivity)] for the M1. The same approach was used for PMd, PMv, DLPFC, SMA and PPC. For the cerebellum, an additional search term 'cerebellar brain inhibition' was added based on keywords identified in relevant literature.

The selection procedure for identifying eligible articles was conducted in compliance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009) and is summarized in Figure 2. First, duplicates were removed. Second, titles and abstracts of the articles were screened for the inclusion and exclusion criteria. Last, full texts of the remaining articles were screened for eligibility. Original research studies on healthy human subjects, written in English, and published before July 2021 were included. Furthermore, as the objective of this review was to provide an overview of ds-TMS paradigms used for the examination of motor-related intra- and inter-hemispheric interactions in healthy adults, only studies using two coils on separate brain areas to investigate the interactions between these brain areas either between both hemispheres, i.e., interhemispheric, or within one hemisphere, i.e., intrahemispheric, were included. Moreover, in order to limit the scope of this report, studies employing repetitive TMS, triple-pulse TMS, quadri-pulse TMS, transcranial direct current stimulation (tDCS) or examining interactions in the pathological or animal brain were excluded. Additionally, all studies specifically targeting older adults or examining brain connectivity in the context of aging were excluded. Studies regarding non-motor-related interventions (e.g., sleep, alcohol and drugs) or during which only non-motor-related tasks were used (e.g., cognitive tasks) were also excluded. Finally, the bibliographies of previously included articles were screened for eligible studies.

Of all screened papers, 109 studies were deemed eligible and were subsequently included in this review. From the included studies, information about the study design (e.g., rest vs. motor task and number of participants), stimulation parameters (e.g., stimulus intensity and ISI) and the results were extracted. This information was then summarized per interaction pair of two brain regions both intra- and inter-hemispherically and listed in Tables 1–12. Additionally, findings have been categorized for rest and specific motor tasks. To assist a selective reading of this manuscript, a brief summary of the general findings and remarks for each region discussed in this study is provided at the end of each chapter.

Please note that the results discussed in this review always refer to right-handed participants, unless differently specified in the text.

Results

M1–M1 interactions

The primary motor cortex (M1) is located on the anterior wall of the central sulcus and the posterior part of the precentral gyrus, within the frontal lobe of the human brain (Brodmann 1909; Fulton 1935; Meier et al. 2008). It contains upper motor neurons, known as Betz cells, which project onto interneurons and lower (peripheral) motor neurons at the level of the spinal cord, through the corticospinal tract. In turn, these lower motor neurons exit the spine and synapse with the motor unit of their target muscle. Hence, M1 plays a crucial role in generating voluntary movements (Pearson 2000). Furthermore, it integrates input from several motor-related brain regions and the midbrain (e.g., Bhattacharjee et al. 2020; Lemon 1993;

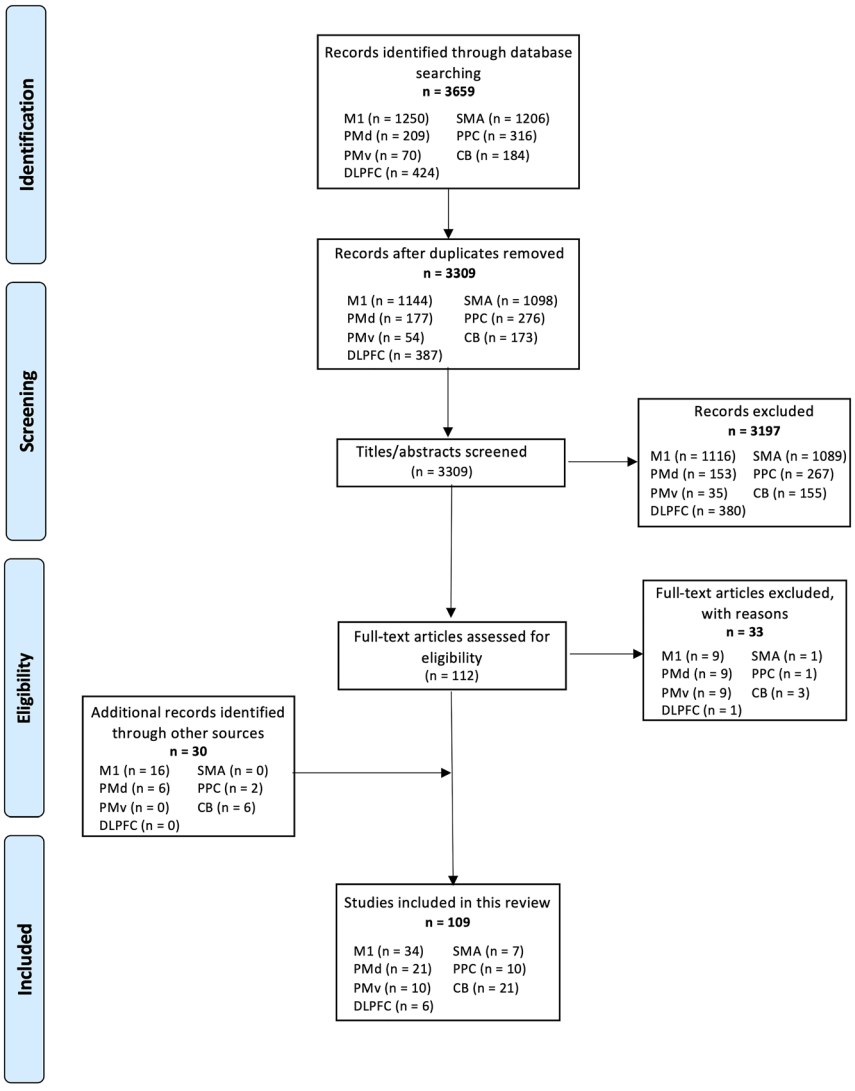

Figure 2: Flowchart according to the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher et al. 2009). CB, cerebellum; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PPC, posterior parietal cortex; SMA, supplementary motor cortex.

Sanes and Donoghue 2000). Additionally, M1 plays a role in motor learning, and its neural circuit demonstrates plastic changes as a result of brain insults, repeated motor activity, and brain stimulation (e.g., Ogawa et al. 2019; Sanes and Donoghue 2000).

Homologous M1s are linked by pathways passing through the corpus callosum (Gooijers and Swinnen 2014; Hanajima et al. 2001; Jenny 1979). Consequently, interhemispheric interactions between homologous M1s are found to be predominantly mediated via these transcallosal pathways (Bloom and Hynd 2005; Chen 2004; Daskalakis et al. 2002; Di Lazzaro et al. 1999; Ferbert et al. 1992). However, some subcortical mechanisms are assumed to be contributing to the M1–M1 connectivity as well (Gerloff et al. 1998). Indeed, combined TMS/fMRI studies yielded blood-oxygen-level-dependent (BOLD) imaging changes after applying TMS to M1 at rest, both in cortical and subcortical motor regions functionally linked to M1 (Bestmann et al. 2003; Bestmann et al. 2004; Bohning et al. 1999, 2000; Denslow et al. 2005; Jung et al. 2020). Table 1 provides an overview of the studies examining M1–M1 interactions using ds-TMS.

In TMS studies, the target location for stimulating M1 (i.e., the 'hotspot') is usually defined as the site wherein the target muscle yields MEPs of maximal amplitude. In more recent studies this technique was complemented by individual magnetic resonance imaging (MRI) scans in combination with stereotactic neuronavigation to guide TMS over M1, allowing to keep coil position/orientation over M1 stable over time (Cunningham et al. 2017; Fiori et al. 2017; Fujiyama et al. 2016a; Sharples and Kalmar 2012). The most frequently used coil orientations are visualized in Figure 4. An exact description of the different orientations can be found in the appendix.

At rest

Ferbert et al. (1992) examined interhemispheric left M1–right M1 interactions using ds-TMS. They reported inhibition of the TS-induced MEP, when using CS and TS intensities of approximately 55% of the maximal stimulator output (MSO) at ISIs of 6–15 ms, referred to as interhemispheric inhibition (IHI). Further, the amount of inhibition was positively associated with the CS intensity but negatively with the TS intensity. Most of the subsequent studies investigating M1–M1 connectivity demonstrated predominantly inhibitory interactions both confirming and extending the results of Ferbert et al. (1992) (Bäumer et al. 2007; Calvert et al. 2020; Chen et al. 2003; Daskalakis et al. 2002; De Gennaro et al. 2004; Di Lazzaro et al. 1999; Fujiyama et al. 2016a; Gerloff et al. 1998; Harris-Love et al. 2007; Kobayashi et al. 2003; Liuzzi et al. 2010; Mochizuki et al. 2004b; Nelson et al. 2009; Ridding et al. 2000; Sattler et al. 2012; Tazoe and Perez 2013). Moreover, comparable results were reported regardless of the direction of the measured interaction (i.e., from the dominant to the non-dominant hemisphere or vice versa) (Fujiyama et al. 2016a; Kobayashi et al. 2003; Nelson et al. 2009; Ridding et al. 2000; Sattler et al. 2012). Additionally, these interactions have been demonstrated at a wide range of ISIs, ranging from 6 to 150 ms, with maximal IHI both at short (ISI = 8–15 ms) (Gerloff et al. 1998; Mochizuki et al. 2004a; Ni et al. 2009) and longer (ISI ≥ 40 ms) (Chen et al. 2003; Fiori et al. 2017; Ni et al. 2009; Tazoe and Perez 2013) latencies, referred to as short (i.e., SIHI) and long interval/latency interhemispheric inhibition (i.e., LIHI), respectively. Moreover, Fiori et al. (2017) even demonstrated IHI at an ISI of 150 ms. Ni et al. (2020) demonstrated SIHI from 8–15 ms with maximal inhibition at around 10 ms. Further, in line with the results of Ferbert et al. (1992), IHI was found to decrease with increasing TS intensity (Daskalakis et al. 2002), and conversely, increase with increasing CS intensity. While various studies were able to elicit both SIHI and LIHI using the same CS intensities (e.g., Chen et al. 2003; Gerloff et al. 1998; Nelson et al. 2010), Ni et al. (2009) investigated CS intensity recruitment curves and showed that LIHI could be elicited at lower CS intensities as compared to SIHI. Yet, Fiori et al. (2017) could only elicit LIHI at 150 ms using 110% rMT CS intensity in contrast to LIHI at 40 ms which could be elicited using either a 90 or 110% rMT CS intensity.

Similar to short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI), SIHI and LIHI have been suggested to be mediated by different mechanisms (e.g., Chen 2004; Daskalakis et al. 2002). While pharmacological research suggested that $GABA_B$-ergic neurons mediate LIHI, the mechanisms underlying SIHI remain largely unknown (Florian et al. 2008; Irlbacher et al. 2007). Perhaps, SIHI might be mediated by a $GABA_A$-ergic transmitter system as has been demonstrated in rats (Kawaguchi 1992). Mechanisms underlying LIHI at 150 ms, however, have not yet been investigated. While the mediating neurons remain unclear, it might be presumed that indirect cortico–subcortical pathways are involved (Fiori et al. 2017; Neubert et al. 2010). It should be noted that, in contrast to SICI and LICI (Di Lazzaro et al. 2007, 2005; Florian et al. 2008; McDonnell et al. 2006; Werhahn et al. 1999), only few pharmacological studies investigated the mechanism underlying SIHI and LIHI (Florian et al. 2008; Irlbacher et al. 2007).

Inhibitory interhemispheric M1–M1 interactions have not only been demonstrated in hand muscles [i.e., the first dorsal interosseus (FDI) and abductor digiti minimi (ADM)] but also in forearm [i.e., the extensor carpi radialis (ECR) and flexor carpi radialis (FCR)] (Sattler et al. 2012) and upper arm muscles [i.e., the biceps brachii (BB) and triceps brachii (TB)] (Harris-Love et al. 2007; Tazoe and Perez 2013). Furthermore, Harris-Love et al. (2007) found that the magnitude of IHI was greater in the FDI and BB as compared to the TB. Additionally, the TB also required a higher CS intensity to elicit IHI (~60% MSO) as compared to the FDI and BB (30–39% and 40–49% MSO, respectively) (Harris-Love et al. 2007). Additionally, SIHI could also be elicited in the upper trapezius (but not in the lower trapezius and serratus anterior) with a CS intensity of 120% active motor threshold (i.e., during active contraction of the target muscle; aMT) and an 8 ms ISI during tonic contraction of the target muscle [30% maximal voluntary contraction (MVC)] (Matthews et al. 2013). Furthermore, although most authors used an anterior–posterior (AP)-directed CS, it appears that interhemispheric M1–M1 interactions were not influenced by the CS current direction (Chen et al. 2003; Mochizuki et al. 2004a; Ni et al. 2009). Lastly, it was reported that IHI was diminished in musicians as compared to non-musicians (Ridding et al. 2000) and was greater in women as compared to men (De Gennaro et al. 2004). As suggested by the authors, the latter might be due to gender differences in the size of the anterior half of the body of the corpus callosum (Davatzikos and Resnick 1998; De Gennaro et al. 2004).

Although inhibition was their most significant finding, Ferbert et al. (1992) could also elicit facilitation, later referred to as interhemispheric facilitation (IHF), at shorter ISIs (<5 ms), even though this was highly variable and poorly reproducible both within and between subjects (Ferbert et al. 1992). More recent studies demonstrated that IHF is most likely to be generated by low-intensity CS

[i.e., 110–130% aMT (Hanajima et al. 2001), 60–80% aMT (Bäumer et al. 2006), or at a TMS intensity evoking a MEP amplitude of ~0.05 mV (Ugawa et al. 1993)], with which Ni et al. (2020) demonstrated a maximal amount of IHF at around 4.5 ms. Whereas it was initially thought that IHF could only be provoked at very short latencies (ISI = 2–6 ms) (Ferbert et al. 1992; Hanajima et al. 2001; Ni et al. 2020), facilitation was also reported at slightly longer (ISI = 6–8 ms) (Bäumer et al. 2006; Ugawa et al. 1993) or even at long latencies (ISI = 80 ms) (Fiori et al. 2017). Lastly, it remains unclear which CS and TS current directions are optimal for eliciting facilitatory M1–M1 interactions. More specific, Hanajima et al. (2001) demonstrated IHF with a CS inducing a medially directed current flow and an AP-directed TS in the brain, whereas Bäumer et al. (2006) elicited a facilitatory right M1–left M1 interaction with a posterior–anterior (PA)-directed CS combined with either a PA- or AP-directed TS current.

Finally, it has been suggested that the existing protocol for investigating interhemispheric interactions could be further optimized (Corp et al. 2021). Interactions between brain areas, as investigated by ds-TMS, are typically expressed as a percentage of the amplitude of conditioned MEPs (CS + TS) divided by the amplitude of single-pulse MEPs (TS only) [i.e., $(MEP_{CS+TS}/MEP_{TS}) * 100$]. However, the authors argue that MEPs elicited by a suprathreshold CS, i.e., measured at the hand contralateral to the target muscle, can also be used for this ratio [i.e., $(MEP_{CS+TS}/MEP_{CS\ measured\ in\ contralateral\ hand}) * 100$]. In support of this notion, MEPs elicited by TS alone were similar to those elicited in the contralateral hand by the CS pulse, when using an intensity of 130% resting motor threshold (i.e., motor threshold obtained with the target muscle at rest; rMT) for both CS and TS. Moreover, the magnitude of IHI computed as the classical ratio between conditioned and non-conditioned MEPs was identical to the IHI, as calculated by the conditioned MEP divided by the CS-evoked MEP for both R M1–L M1 and L M1–R M1 interactions at short and long latencies (ISI = 10 or 40 ms). Using the CS MEPs as a baseline implies that no additional TS-only condition would be required, which significantly shortens the protocol, and is therefore referred to as 'expedited interhemispheric inhibition'. It is important to note that the intensity of TS and CS were identical in this study, and each was applied to the respective M1 (Corp et al. 2021). Hence, this approach could be interesting for resting-state studies using the same suprathreshold stimulation intensity for both TS and CS but is probably less ideal for motor task paradigms since the corticospinal excitability in each M1 might change independently depending on the task, rendering the CS MEP no longer a valid control (denominator of the ratio). Along the same line, corticospinal excitability in both M1's can also be impacted in a different manner in the context of neurological conditions [e.g., stroke (Murase et al. 2004) and amputation (Kilteni et al. 2016)]. While this more time-efficient method could be particularly relevant for clinical populations where time with patients may be extremely limited, using the same intensity for both hemispheres and interchanging MEPs elicited by the TS with MEPs elicited by the CS (on the contralateral hemisphere) may introduce a confound.

Task-related interactions

Task-related interactions with active target muscle

Distal upper limb muscles

Tonic contraction of the distal target muscle. The results of studies investigating the influence of a tonic target muscle contraction on M1–M1 interactions are highly inconsistent. While some authors found an increase of M1–M1 SIHI (Ferbert et al. 1992; Mochizuki et al. 2004a; Uehara et al. 2013), others demonstrated a decrease in SIHI (Chen et al. 2003; Nelson et al. 2009; Ridding et al. 2000) or even no modulation at all (Sharples and Kalmar 2012). It should be emphasized that these studies used slightly different parameters (for details see Table 1). Along the same lines, LIHI between homologous M1s was not influenced by tonic contraction of the target muscle (Chen et al. 2003), yet another study demonstrated disinhibition during tonic contraction (Nelson et al. 2009). The effect of a tonic contraction on the IHI is suggested to be the same for uni- and bi-manual contractions as Cunningham et al. (2017) could not demonstrate a significant difference when examining changes in SIHI from the left to the right hemisphere during either a unilateral or bimanual [with symmetric (30/30% MVC) or asymmetric force (L, 30/R, 10 and L, 30/R, 70% MVC)] tonic contraction of the FDIs (abduction index finger) (Cunningham et al. 2017).

Regarding IHF, it is important to take into account that both Hanajima et al. (2001) and Ugawa et al. (1993) could only demonstrate facilitation between both M1s when using low CS intensities during a tonic contraction of the target muscle, but not at rest. Interestingly, the facilitation of right M1 elicited by a PA-directed TS current and preceded by a 60% aMT CS at a 6 ms ISI over left M1 demonstrated by Bäumer et al. (2006) was abolished during tonic contraction of the target muscle (10% MVC). Facilitatory right M1–left M1 interactions elicited by an AP-directed TS current at an 8 ms ISI using a CS intensity of 80% aMT, however, were not influenced during tonic contraction (Bäumer et al. 2006), in

line with the findings of Ugawa et al. (1993) and Hanajima et al. (2001).

Rhythmic contraction of the target muscle. The inhibitory influence from the resting (right) M1 to the active (left) M1 was found to increase prior (500 ms) to rhythmic contractions of the target muscle, relative to rest and during contraction (Sharples and Kalmar 2012). The authors suggested that this increase in SIHI from the resting to the active hemisphere, prior to a contraction, might counterbalance the increased corticospinal excitability observed during the preparatory period of motor tasks, thereby impeding premature movement execution to secure (spatio-)temporal accuracy of movements (Sharples and Kalmar 2012).

Self-paced and ballistic movements of the target muscle. Tazoe and Perez (2013) studied long-latency interhemispheric M1–M1 interactions during both the preparatory period and execution of self-paced and ballistic finger movements. Ballistic movements are actions performed with maximal velocity and acceleration (Zehr and Sale 1994), while self-paced movements were defined as movements performed at a slower and more comfortable speed (Tazoe and Perez 2013). A CS was applied over the resting (left) M1 prior to a TS applied over the active (right) M1 at a 40 ms ISI. The results showed that LIHI from left to right M1 decreased during the preparatory period of both self-paced and ballistic movements relative to rest. Moreover, the LIHI decrease was more pronounced for ballistic as compared to self-paced movements. In contrast, the inhibitory influence from left to right M1 increased during movement execution for ballistic relative to self-paced movements (Tazoe and Perez 2013).

Proximal upper limb muscles

Tonic contraction of the proximal upper limb target muscle. The results of tonic contractions of a distal upper limb target muscle do not seem to apply to proximal muscles as the IHI during tonic contraction appears to be selective for unilateral muscle contractions in proximal upper limb muscles. Specifically, Matthews et al. (2013) could only elicit SIHI from left to right M1 (CS intensity of 120% aMT, ISI of 8 ms) during a tonic contraction of the left upper trapezius (30% MVC, held in 45° elevated scaption, i.e., raising the arms from the side and slightly forward in the scapular plane) but neither during a tonic bilateral upper trapezius contraction nor during contraction of the lower trapezius or serratus anterior muscle, targeting their respective hotspots (Matthews et al. 2013).

Self-paced and ballistic movements of the target muscle. In addition to finger movements, Tazoe and Perez (2013) studied long-latency (40 ms ISI) interhemispheric M1–M1 interactions during both the preparatory period and execution of self-paced and ballistic elbow movements (measured in m. Biceps Brachii, an upper arm muscle). As with finger movements, left-to-right M1 LIHI decreased during the preparatory period of both self-paced and ballistic movements relative to rest with the decrease being more pronounced for ballistic movements than for self-paced movements. In turn, the inhibitory influence of left to right M1 increased during the performance of ballistic movements compared to self-paced movements, in line with the results of finger movements (Tazoe and Perez 2013).

Task-related interactions in the non-active target muscle during activity in the contralateral homologous muscle

Distal upper limb muscles

Tonic contraction of a distal muscle contralateral to the target muscle. Several authors investigated the effective connectivity between the active M1 and the (target) non-active M1, by measuring the MEPs in the resting homologous muscle (i.e., ipsilateral to the active M1). For instance, Ferbert et al. (1992) an increase in the amount of SIHI during a 10% MVC tonic contraction, while investigating the influence of a tonic contraction of the left FDI on interhemispheric interactions from the active right to the non-active left M1. Along the same line, Uehara et al. (2013) examined the influence of a tonic abduction (10% MVC) of the left index finger on the M1–M1 interaction and reported an increase of the amount in inhibition exerted by the active (right) M1 over the resting (left) M1 at an ISI of 10 ms, as measured in the right FDI. In contrast to the above-mentioned studies, Morishita et al. (2012) did not detect a decrease in SIHI from the active (right) to the non-active (left) M1 during tonic contraction (10% MVC) of the left FDI. According to the authors, this might be caused by significant intersubject variability as the effects of isotonic contractions from the active over the "non-active" M1 have been demonstrated to be fluctuating. Finally, as opposed to the increase of SIHI, LIHI was not modulated during a tonic contraction of the left index finger (Uehara et al. 2013).

Rhythmic contraction contralateral to the target muscle. Uehara et al. (2013) examined interactions between both M1s during an auditory paced rhythmic contraction contralateral to the target muscle. In particular, participants were required to rhythmically abduct their left index finger (at 10% MVC). During task performance, a CS was

applied over the active (right) M1 prior to a TS applied over the non-active (left) M1, measuring MEPs in the right FDI. In line with studies that investigated IHI during a sustained contraction of the muscle contralateral to the target muscle, their results overall demonstrated an increase of the amount of SIHI exerted by the right over the left M1, relative to rest. The authors argued that this increase in inhibition exerted by the active hemisphere over the contralateral, resting M1 could serve to suppress (undesirable) mirror movements in the right FDI during rhythmic contraction of the left FDI. In contrast to SIHI, LIHI was not influenced by rhythmic contraction of the left index finger (Uehara et al. 2013).

Unilateral fine motor manipulation contralateral to the target muscle. The inhibitory influence from the active (right) M1 to the resting (left) M1 was found to increase in the context of unilateral fine motor manipulation contralateral to the target muscle (Morishita et al. 2012). Here, participants were required to repetitively grip and lift, transport and release glass balls from one box to another and vice versa, using wooden chopsticks. While this task was performed with their left hand, a CS was applied over right M1 followed by a TS over left M1 10 ms later. Similar to Uehara et al. (2013), the increase in SIHI during this task was interpreted as a reduction of excessive excitability in the resting M1, preventing involuntary mirror movements to occur (Morishita et al. 2012).

Reaction time task (target or the contralateral muscle)

The amount of SIHI decreased during the preparation period of a simple reaction time (RT) task, during which participants had to make a rapid movement towards a goal, relative to rest (Duque et al. 2007; Liuzzi et al. 2010). More specific, the inhibitory right M1–left M1 interaction demonstrated at rest was disinhibited in the late phase of movement preparation (80–100% of the RT), when participants were instructed to abduct their right index finger (target muscle) as fast as possible (Liuzzi et al. 2010). Duque et al. (2007) reported similar results and demonstrated a stronger modulation for the right (i.e., right M1–left M1 interactions) as compared to the left (i.e., left M1–right M1 interactions) target muscle. This finding supports the results of behavioural studies indicating a dominant (right-)hand advantage in the performance of motor control tasks, especially when these tasks need to be performed quickly and/or very precisely (Bryden and Roy 2005; Noguchi et al. 2006; Roy et al. 2003; Triggs et al. 2000; Wang et al. 2011). Hence, the general left hemisphere dominance for planning and execution of future movements might explain this asymmetry in interhemispheric interactions (Mutha et al. 2012). As opposed to the active target muscles, contralateral muscles at the inactive side were inhibited (i.e., inhibition right M1–left M1 and left M1–right M1 during the preparatory period of left and right finger movements, respectively) (Duque et al. 2007). Along the same line, Hinder et al. (2018) showed that left M1–right M1 inhibition also selectively decreased in the responding hand during the preparatory period of a choice RT task when an informative warning signal indicated which hand should be used in the next trial. When the warning signal was uninformative (i.e., 50/50% chance that left/right hand should be used), however, the amount of SIHI was reduced in both hands. LIHI decreased in both the responding and non-responding hand irrespective of whether an informative or non-informative warning signal was used (Hinder et al. 2018).

Bimanual motor tasks

Bimanual tracking task. Fujiyama et al. (2016a) examined M1–M1 interactions, from the dominant (left) to the non-dominant (right) hemisphere and vice versa, in the context of a bimanual tracking task, in which the participants had to track a moving dot on the computer screen by simultaneously rotating two dials (one with each index finger). The results indicated facilitation of long-latency (ISI = 40 ms), at rest inhibitory, M1–M1 interactions during the preparatory period of a trial, regardless of the required inter-hand movement frequency. In contrast, short-latency (ISI = 10 ms) interactions remained unchanged. As modulation of LIHI was not task-specific the authors suggest that it might reflect a general decrease of inhibition in preparation for motor execution (Fujiyama et al. 2016a).

Bimanual response inhibition task. Interhemispheric M1–M1 interactions are assumed to play a role in response inhibition, i.e., abrupt cessation of a prepared movement, and were therefore examined during complete and partial cancellation of bimanual movements (MacDonald et al. 2021). During the task at hand, participants had to press a switch with each index finger, causing two corresponding bars on the screen in front of them to 'fill' at a constant speed. Releasing a switch (by an index finger abduction) caused the corresponding bar to stop filling. The majority of trials required simultaneous bimanual abduction of both index fingers to stop the bar from filling at a predefined goal line ('Go' bimanual trials). However, in some trials the filling of one bar (unimanual trials; partial cancellation) or both bars (bimanual trials; bimanual cancellation) stopped before reaching the goal line, requiring the participant to cancel the planned action and keeping the corresponding finger(s) on the switch.

The authors demonstrated a release of inhibition for both M1–M1 interactions during the preparatory period of bimanual movement ('Go' bimanual trials). In the context of bimanual cancellation, the amount of SIHI increased for both directions. During unimanual stop trials requiring a partial cancellation, however, the inhibitory influence on the M1 corresponding to the canceled movement increased, while the inhibitory influence on the M1 corresponding to the reacting hand decreased. The foregoing occurred later in trials in which the left-hand response had to be inhibited in contrast to trials in which the right-hand response had to be inhibited (MacDonald et al. 2021).

Proximal upper limb muscles

Tonic contraction of a proximal muscle contralateral to the target muscle. Similar to tonic contraction of distal upper limb muscles, Vercauteren et al. (2008) demonstrated an increase in the amount of SIHI during a 5% MVC tonic contraction, while investigating the influence of right tonic wrist flexion and extension on interhemispheric interactions from the active left to the non-active right M1. This increase in inhibition was greater in FCR as compared to the ECR. Furthermore, SIHI measured in the FCR increased during both flexion and extension relative to rest, whereas SIHI measured in the ECR only increased during flexion as compared to rest (Vercauteren et al. 2008). The authors suggested that the smaller ECR effects were likely due to the fact that the parameters were set in favor of the FCR. Lastly, the modulation of SIHI was found to be larger in men as compared to women (Vercauteren et al. 2008). In contrast, Perez and Cohen (2008) examined the influence of stronger tonic contraction (either 10, 30, or 70% MVC) of the right FCR (i.e., a wrist flexor) on SIHI from the left (i.e., active) to the right (i.e., non-active/resting) hemisphere (measuring left FCR MEPs). The inhibitory influence exerted at rest was diminished and even completely attenuated at an ISI of 10 ms during 30 and 70% MVC of the right wrist, respectively (Perez and Cohen 2008). This study does not necessarily contradict the previous ones as it examines the influence of higher forces (i.e., 30 and 70% MVC vs. 5–10% MVC). Hence, it might be possible that the inhibitory influence from the active to the inactive M1 reaches its maximum capacity at relatively low forces, decreasing again and even reversing to facilitation as the applied force increases, rendering the suppressing mirror movements no longer possible. This is in agreement with the finding that mirror EMG activity is more prevalent during strong unimanual contractions compared to smaller efforts (Zijdewind et al. 2006).

As compared to the results for the intrinsic hand and wrist muscles, SIHI could not be elicited in shoulder stabilizing muscles such as the upper and lower trapezius, and the serratus anterior during neither a tonic contraction of the muscle contralateral to the target muscle nor a bilateral contraction of both the target muscle and its contralateral homologue (Matthews et al. 2013).

Bimanual rhythmic flexion and extension in proximal upper limb muscles. Jordan et al. (2021) examined the difference in SIHI and LIHI from right to left M1 for bimanual rhythmic symmetric versus asymmetric wrist flexion and extension movements, holding either a dumbbell in each hand or holding with both hands two connected handles that could rotate independently. Since for the latter both hands interact with the same object, these task variants are considered cooperative, whereas the task variants with the dumbbell are deemed independent. With each object, participants had to either extend both wrists simultaneously (symmetrical) or extend one wrist while the other was flexed out of phase (asymmetrical). While the authors hypothesized a greater reduction of SIHI and LIHI during symmetrical cooperative tasks as compared to asymmetrical and independent tasks, indicating a stronger coupling between bilateral M1 during symmetrical cooperative tasks, both SIHI and LIHI remained unmodulated (Jordan et al. 2021). This is in line with the lack of difference in SIHI during a static bilateral symmetric versus an asymmetric contraction (Cunningham et al. 2017).

Summary and discussion M1–M1 interactions

To summarize, robust findings were demonstrated for interhemispheric M1–M1 interactions at rest, demonstrating a strong inhibition over a wide range of ISIs (i.e., 10, 40 and 150 ms). Inhibition can be elicited both at short and long latencies (mostly 10 and 40 ms, respectively) at a wide range of CS intensities. Nevertheless, it has been demonstrated that LIHI can be elicited using lower CS intensities as opposed to SIHI. Yet, LIHI with 150 ms ISI could only be elicited using 110% but not 90% rMT CS intensity. Further, the amount of inhibition was found to increase with increasing CS intensities (i.e., a higher CS intensity results in stronger inhibition) and, conversely, decrease with increasing TS intensity (i.e., a higher TS intensity results in reduced inhibition). Comparable results were reported regardless of the direction of the measured interaction (i.e., from the dominant to the non-dominant hemisphere or vice versa) (Fujiyama et al. 2016a; Kobayashi et al. 2003; Nelson et al. 2009; Ridding et al. 2000; Sattler et al. 2012). Along the same line, interhemispheric M1–M1 interactions do not seem to be influenced by the CS

current direction (Chen et al. 2003; Mochizuki et al. 2004a, b; Ni et al. 2009). Specifically, while some of the studies examining the influence of CS current direction (eliciting an AP, PA, LM and ML directed current in the brain) reported a tendency for anteriorly directed CS intensities to produce stronger IHI as compared to AP, LM and ML directed currents (Chen et al. 2003; Mochizuki et al. 2004a,b), none of these studies were able to demonstrate any significant directional effects on IHI (Chen et al. 2003; Mochizuki et al. 2004a,b; Ni et al. 2009). Nevertheless, it might be possible that both the optimal latencies of IHI and its optimal stimulation intensity may differ between different flow directions. Therefore, studies using a fixed latency and CS intensity might have missed IHI's directional specificity. Conversely, it might be that neurons of the transhemispheric pathway underlying IHI specifically have no directional preference. As for the TS current direction, previous research points to a directional preference of the neurons within M1 (i.e., corticospinal excitability) for AP-directed current directions (Brasil-Neto et al. 1992; Mills et al. 1992).

Lastly, IHI could reliably be demonstrated in hand, forearm, and shoulder muscles, however, not always to the same extent. Besides inhibition, facilitatory M1–M1 interactions have also been demonstrated. Yet, facilitatory interactions between homologous M1s were more variable and less reproducible compared to IHI (Ferbert et al. 1992). Predominantly low CS intensities were found to be more successful in eliciting IHF (e.g., Hanajima et al. 2001). Please note that authors mostly report %MSO to discuss the effect of CS intensity for inhibition, while % of the motor threshold is mostly used when referring to the CS intensity for facilitation. One possible rationale for using % of (active) motor threshold instead of %MSO could be based on the need to use the lowest possible intensity to ensure that the subtle IHF is not masked by the stronger IHI (Bäumer et al. 2006).

M1–M1 interactions were investigated in the context of a broad range of motor tasks. Overall, the above-mentioned studies demonstrate that the results for M1–M1 effective connectivity during tonic contraction of the target muscle are equivocal, with some studies indicating a reduction of SIHI (Chen et al. 2003; Nelson et al. 2009; Ridding et al. 2000), while others demonstrate SIHI to increase (Ferbert et al. 1992; Matthews et al. 2013; Mochizuki et al. 2004a; Uehara et al. 2013), or even no modulation at all (Sharples and Kalmar 2012). It should be emphasized that these studies used slightly different methodological parameters (for details see Table 1), which might explain the differences in their results. Furthermore, these results appear to be selective for unilateral muscle contractions (Matthews et al. 2013). Similar to the findings of studies investigating a tonic contraction of the target muscle, the results of studies examining a tonic contraction of the contralateral homologue also seem contradictory. That is, while most studies demonstrated an increase of inhibition from the active to the non-active M1 during a tonic contraction (e.g., Ferbert et al. 1992; Uehara et al. 2013; Vercauteren et al. 2008), Perez and Cohen (2008) demonstrated a reduction and even a complete attenuation of inhibition at higher forces. Yet, this reduction might reflect the influence of higher muscle force (i.e., 30 and 70% MVC vs.5–10% MVC), rather than it contradicts previous findings. This finding is also in line with the prevalence of mirror EMG activity during strong unimanual contractions as compared to smaller efforts (Zijdewind et al. 2006).

In the context of a motor task, interactions from the resting to the active M1 were mostly disinhibited/facilitated, while interactions from the active to the resting M1 became inhibitory presumably in order to inhibit involuntary mirror movements in the non-active hand (Duque et al. 2007). More specifically, it was shown that the amount of IHI decreased during the preparatory period of both slow and fast movements, as well as during the preparatory period of simple RT tasks with the target muscle (Liuzzi et al. 2010; Tazoe and Perez 2013). However, Duque et al. (2007) could only demonstrate this for the right M1–left M1 interaction during the preparatory period of right finger movements but not for the left M1–right M1 interaction during the preparatory period of left finger movements. This is in line with the dominant (right) hand advantage when performing motor control tasks (Bryden and Roy 2005; Noguchi et al. 2006; Roy et al. 2003; Triggs et al. 2000; Wang et al. 2011) and might be explained by the general dominance of the left hemisphere for planning and executing future movements (Mutha et al. 2012). An increase in inhibition rather than disinhibition or facilitation from the resting to the active hemisphere has been observed prior to rhythmic contraction (Sharples and Kalmar 2012). While a disinhibitory or facilitatory influence of the resting M1 towards the active M1 enables movement, this inhibitory influence prior to movement onset might counterbalance the increased corticospinal excitability observed during the preparatory period of motor tasks, thereby impeding premature movement execution to secure spatio-temporal accuracy of movements (Sharples and Kalmar 2012).

For bimanual movements, SIHI is not altered, whereas modulation of interhemispheric interactions (i.e., from inhibition at rest towards facilitation during movement preparation) is demonstrated at long latencies during a bimanual tracking task (Fujiyama et al. 2016a). In contrast,

a release of SIHI (both from left M1 to right M1 and vice versa) arises during the preparatory period of a bimanual movement. The sudden cancellation of prepared bimanual movements, in turn, resulted in an increase of bilateral SIHI, whereas a unimanual cancellation of a planned bimanual response led to a site-specific modulation in inhibition. More specifically, a decrease in inhibitory influence on the M1 corresponding to the responding hand and an increase in inhibitory influence on the M1 corresponding to the annulled movement occurred, allowing the selective initiation of the required unimanual movement (MacDonald et al. 2021).

In the context of bimanual rhythmic wrist flexion and extension, no difference between symmetric and asymmetric movements has been demonstrated in short and long-latency right M1–left M1 interactions. While the bimanual response inhibition task is considered a discrete and non-repetitive bimanual task, both the bimanual tracking task and the bimanual rhythmic flexion and extension task can be categorized as continuous bimanual tasks. However, the bimanual tracking task differs from the bimanual rhythmic flexion and extension task in that it is more complex (i.e., different inter-hand frequencies) and visually guided (i.e., externally generated). Since these tasks differ in task requirements and complexity one might suspect that brain regions, other than contralateral M1, and their interplay may be of relevance. For example, externally generated movements rely more on regions such as the visual cortex, the superior parietal cortex, PMd and PMv (Debaere et al. 2003; Diedrichsen et al. 2001; Swinnen and Wenderoth 2004). In contrast, the SMA and the inferior parietal cortex, among others, are assumed to underly internally driven movements (Debaere et al. 2003; Goldberg 1985; Swinnen and Wenderoth 2004). Given that motor tasks with varying task demands differ in the involvement and interaction of motor-related brain regions, this could explain why M1–M1 interactions are also modulated in a different manner.

Lastly, the inhibitory influence from the active to the resting M1 was found to increase in the context of a unilateral fine motor manipulation task (Morishita et al. 2014) and during the preparatory period of a voluntary contraction, which might be responsible for suppressing involuntary mirror movements of the contralateral homologue not involved in this task, enhancing the independent functioning of each hemisphere, as suggested by neuroimaging (Newton et al. 2005) and neurophysiological evidence (Giovannelli et al. 2009; Perez and Cohen 2008). Yet, recent research suggests that subcortical regions may also play some role in mirror movements. Specifically, while one would expect primarily specific activation of the homologous muscle due to cortical contributions to mirror movements, the wide distribution of mirrored forces across different muscles, which include both homologous and non-homologous muscles, argues for the involvement of subcortical pathways (Ejaz et al. 2017, 2018). Furthermore, recent literature has argued that these inhibitory interactions account for surround inhibition that subsequently shapes the net output of M1 rather than a generalized and undifferentiated inhibition of the contralateral hemisphere (Carson 2020; Derosiere and Duque 2020).

PMd–M1 interactions

The dorsal premotor cortex (PMd) is part of the premotor cortex and lies anterior to the M1, on the superior frontal gyrus within the frontal lobe of the brain (Geyer et al. 2000b; Picard and Strick 2001).

The PMd plays a crucial part in movement selection, preparation and execution of unimanual as well as coordinated bimanual movements (Cisek and Kalaska 2005; Duque et al. 2005; Fujiyama et al. 2016a; Kiyama et al. 2014; Perez et al. 2007; Wise 1985). Whereas right PMd performs a principal role in the selection and implementation of action plans of unimanual movements carried out with the left hand, left PMd appears to be involved in movements of both the left and right hand (Cisek et al. 2002; Kantak et al. 2012; Schluter et al. 2001). This is consistent with the leading role of the left hemisphere in motor control of right-handed individuals (Schluter et al. 1998). As part of the dorsomedial circuit, receiving input from the parietal subregions (Superior parieto–occipital cortex (SPOC) and the posterior part of the intraparietal sulcus (pIPS)), it underlies reaching (Vingerhoets 2014). Specficially it encodes the coordination of the reaching and grasping components as they need to be synchronized to achieve successful movement (Cavina-Pratesi et al. 2010; Stark et al. 2007). Moreover, the PMd controls movements based on sensory information, is critical during externally guided movement, and plays an important role in the planning of complex motor responses to visual and auditory arbitrary cues (e.g., RT tasks) (e.g., Chouinard et al. 2005; Debaere et al. 2003; Kurata and Wise 1988; Rice and Stocco 2019), for a review see (Chouinard and Paus 2006).

Anatomical studies in non-human primates have revealed interhemispheric pathways not only between bilateral M1s but also between bilateral PMd. Additionally, a dense connection between bilateral PMd and both ipsilateral (Ghosh and Porter 1988) and contralateral M1 exists (Boussaoud et al. 2005; Marconi et al. 2003). These interhemispheric connections between the PMd and both its

Table 1: Overview of studies investigating M1–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Bäumer et al. (2006) [*N* = 20]	– At rest – During tonic contraction (10% MVC)	L M1	R M1	60/80% aMT	1 mV	3–8/10 ms	TS + CS: fig8 (70 mm outer diameter)	PA	– PA – AP	L FDI	At rest: IHF for – CS = 80% aMT, ISI = 6 or 8 ms, TS current direction = AP – CS = 60% aMT, ISI = 6 ms, TS current direction = PA During tonic contraction: IHF – At 6 ms ISI abolished – At 8 ms ISI unchanged
Bäumer et al. (2007) [*N* = 25; right-handed *N* = 12, left-handed *N* = 13]	At rest	– R M1 – L M1	– L M1 – R M1	120% rMT	1 mV	6–8/10 ms	TS + CS: fig8 (70 mm outer diameter)	PA	PA	– R FDI – L FDI	– IHI present in right- and left-handed participants (ISI = 7–10 ms, for 6 ms only for dominant–non-dominant interaction)
Calvert et al. (2020) [*N* = 32]	At rest	L M1	R M1	110/120/130% rMT	0.2 mV	10/20 ms	TS + CS: fig8 (55 mm)	LM	– PA – AP	– L FDI – R & L ECR	– IHI with TS of both PA- and AP-directed current flow (ISI 10 or 20 ms; CS = 110, 120 or 130% rMT) – CS intensity ↑ = IHI ↑ (only with TS = PA but not AP)
Chen et al. (2003) [*N* = 19]	– At rest – During tonic contraction (50% MVC)	R M1	L M1	– 1.5 mV – 45/60/75/90% MSO	– 1 mV (at rest) – 1.5 mV (tonic contraction)	2/5/6/8/10/20/50/80 ms	TS + CS: fig8 (70 mm)	– LM – ML – PA – AP	Towards AM	R FDI	At rest: – IHI at ISI = 8–50 ms, irrespective of CS current direction – CS intensity ↑ (45–75% MSO) = IHI ↑ (for ISI = 8 or 40 ms) During tonic contraction: – SIHI ↓ during isometric contraction of target muscle (ISI = 8 ms) as compared to rest – LIHI was not influenced during isometric contraction (ISI = 40 ms) as compared to rest

Table 1: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Corp et al. (2021) [*N* = 14]	At rest	– R M1 – L M1	– L M1 – R M1	130% rMT	130% rMT	10/40 ms	TS + CS: fig8 (70 mm, ns)	ns	ns	– R FDI – L FDI	– TS-elicited MEP amplitude = CS-elicited MEP amplitude – Magnitude IHI as conditioned MEP/non-conditioned MEP = magnitude IHI as conditioned MEP/CS-evoked MEP, for both ISI and bilateral M1–M1 interactions
Cunningham et al. (2017) [*N* = 14]	During tonic contraction [unilateral (L, 30% MVC); bilateral symmetric (30/30% MVC); bilateral asymmetric (L, 30/R, 10 and L, 30/R, 70% MVC)]	L M1	R M1	Intensity that evokes 50% IHI	1.5–2.5 mV	12 ms	TS + CS: fig8 (70 mm, ns)	ns	ns	L FDI	– Similar amount of IHI for unimanual and bimanual, symmetric and asymmetric conditions – Greater IHI was associated with smaller MEP amplitudes in the right hand – Stronger IHI was correlated with poorer force accuracy of the target muscle
Daskalakis et al. (2002) [*N* = 11]	At rest	L M1	R M1	70% rMT	0.2/1/4 mV	10 ms	TS + CS: fig8 (70 mm, ns)	PA	ns (coil handle 45°AL)	L FDI	IHI ↓ with increasing TS intensity (0.2–4 mV)
De Gennaro et al. (2004) [*N* = 7]	At rest	– R M1 – L M1	– L M1 – R M1	80/120% rMT	120% rMT	2–20 ms*	TS + CS: fig8 (90 mm outer diameter)	PA	PA	R & L ADM	– IHI (data of both hemispheres pooled) with a CS = 120%, but not 80% rMT, at ISI = 8–20 ms – SIHI (ISI = 12 ms) females > males – IHI can be elicited over a different range of ISIs in females (10/12/14/16 ms) as compared to males (8/10/14 ms)
Di Lazzaro et al. (1999) [*N* = 3]	At rest	L M1	R M1	0.2 mV	0.2 mV	5–11 ms	TS + CS: fig8 (90 mm outer diameter)	PA	PA	L FDI	IHI at ISI = 6–11 ms (maximal for ISI = 7–11 ms)

Table 1: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Duque et al. (2007) [*N* = 13]	During simple RT task	– R M1 – L M1	– L M1 – R M1	Intensity that evokes 50% IHI	0.5–1.5 mV	10 ms	CS: fig8 (35 mm inner diameter) TS: fig8 (70 mm, ns)	ns	ns	– R FDI – L FDI	– IHI of inactive side: R M1–L M1 and L M1–R M1 during preparatory period of L and R finger movements, respectively – R finger movement: During preparatory period (close to movement onset) the R M1–L M1 IHI turned into IHF – L finger movement: During preparatory period the L M1–R M1 IHI remained unchanged
Ferbert et al. (1992) [*N* = 15]	– At rest – During tonic contraction (5–10% MVC)	L M1	R M1	55% MSO	55% MSO	3–11; 15/20/25/30 ms	CS: fig8 (70 mm*) TS: – fig8 (ns) – Circular coil (140 mm*) * outer diameter	ns	ns	L FDI	At rest: – IHI at ISI = 6–30 ms – CS intensity ↑ = IHI ↑; TS intensity ↑ = IHI ↓ During tonic contraction: IHI ↑ during contraction of L FDI
Fiori et al. (2017) [*N* = 15]	At rest	R M1	L M1	90/110% rMT	1 mV	40–120■/150 ms	TS + CS: fig8 (50 mm, ns)	ns	PA	R FDI	– IHI at ISI = 40 ms, CS intensity = 90 or 110% – IHI at ISI = 150 ms, CS intensity = 110% (but not 90%) rMT – IHF at ISI = 80 ms, CS intensity = 110% rMT
Fujiyama et al. (2016a) [*N* = 15]	– At rest – During bimanual tracking task	– R M1 – L M1	– L M1 – R M1	110% rMT	1 mV	10/40 ms	TS + CS: fig8 (50 mm outer diameter)	PA	PA	– R FDI – L FDI	At rest: IHI M1–M1 (both directions) at ISI = 10 and 40 ms During bimanual tracking task: – IHF during movement preparation (at the onset of the auditory imperative signal) at ISI = 40 ms irrespective of specific task demands – IHI remained unchanged during movement preparation at ISI = 10 ms

Table 1: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Gerloff et al. (1998) [*N* = 16]	– At rest – During tonic contraction (5% MVC)	R M1	L M1	Slightly higher than TS intensity	1.5 mV (at rest) 2.5 (tonic contraction)	2–100 ms	TS + CS: fig8 (45 mm, ns)	ns	ns	R FDI	At rest: – IHI at ISI = 10/20/30/40/50 ms (maximal IHI for ISI = 10 ms) – CS intensity ↓ = IHI↓ During tonic contraction: – IHI at ISI = 6–20 ms – No comparison to IHI at rest
Hanajima et al. (2001) [*N* = 11]	During tonic contraction (5–10% MVC)	L M1	R M1	aMT + 5/10/20/30% MSO	0.2–0.4 mV	3–15 ms	TS + CS: fig8 (70 mm outer diameter)	– LM – AP	– PA – AP	L FDI	– IHF at ISI = 4–5 ms, when TS directed AP and CS directed LM, CS intensity = 5% MSO above aMT – IHI at ISIs ≥ 11 ms, both with AP directed TS current, and with LM or PA directed CS current, CS intensity = 10/20/30% MSO above aMT – CS intensity ↑ = IHI ↑ – aMT at CS location is for AP.-directed current 19% MSO higher than for LM-directed current
Harris-Love et al. (2007) [*N* = 17]	At rest	L M1	R M1	110–150% rMT	0.3 mV	3/5/6/8/10/40 ms	ns	ns	ns	L FDI, TB and BB	– IHI in FDI/TB/BB could be elicited with CS intensities ≥ 120% rMT – IHI FDI > IHI TB – IHI BB > IHI TB – Minimum CS intensity to elicit IHI: 30–39% MSO for FDI, 40–49% MSO for BB, ≥ 60% MSO for TB – Strongest IHI for FDI at ISI = 8 and 10 ms, for BB and TB at ISI = 10 ms

Table 1: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Hinder et al. (2018) [*N* = 18/21 for un-/informative warning signal variant, respectively]	Choice RT task	L M1	R M1	130% rMT	130% rMT	10/40 ms	TS + CS: fig8 (70 mm, outer diameter)	PA	PA	L FDI	SIHI: – *Non-informative warning signal:* IHI ↓ in both hands at an ISI of 10 ms – *Informative warning signal:* Selective IHI ↓ in the responding hand at an ISI of 10 ms during movement preparation LIHI: – IHI ↓ in both hands at an ISI of 40 ms during movement preparation, for both the un-/informative warning signal variants
Jordan et al. (2021) [*N* = 20]	Bimanual rhythmic wrist flexion/extension ([a]symmetric; independent vs. cooperative)	R M1	L M1	– 120/140% aMT*	Intensity to elicit 50% of the maximal unconditioned MEP amplitude	10/40 ms	TS + CS: fig8 (50 mm, ns)	PA	PA	R Extensor carpi ulnaris	No difference in SIHI and LIHI between different task variants (symmetric vs. asymmetric; cooperative vs. independent)
Kobayashi et al. (2003) [*N* = 10]	At rest	– R M1 – L M1	– L M1 – R M1	110% rMT	1 mV	5/7/8/9/10/12/15/20 ms	TS + CS: fig8 (70 mm, ns)	ns	ns	– R FDI – L FDI	– IHI L M1–R M1 at ISI = 7–12 ms – IHI R M1–L M1 occurred only in subjects with L M1 activation (fMRI; *N* = 5) during L finger movements (ISI = 9–13 ms)
Liuzzi et al. (2010) [*N* = 10]	– At rest – During simple RT task	R M1	L M1	30–50% inhibition (0.5–0.7 mV)	1 mV	10 ms	TS + CS: fig8 (70 mm, ns)	ns	ns	R FDI	At rest: IHI During simple RT task: disinhibition in late phase of movement preparation (80–100% of RT)

Table 1: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
MacDonald et al. (2021) [*Sub-experiment 1: N* = 10 for each, R → L M1 and L → R M1 interaction *Sub-experiment 2:* *N* = 20]	– During bimanual response inhibition task	– R M1 – L M1	– L M1 – R M1	50% inhibition	1 mV	10 ms	TS + CS: fig8 (70 mm, ns)	LM	PA	– R FDI – L FDI	*'Go bimanual' trials:* – IHI ↓ (for both M1 → M1 directions) at 175 and 125 ms before movement onset *'Stop' trials*: – IHI R M1 → L M1 ↓ but IHI L M1 → R M1 ↑ in unimanual trials of L- and R-hand action withholding as compared to bimanual cancellation at 175 and 250 ms after stop cue, respectively
Matthews et al. (2013) [*N* = 15]	– During tonic contraction [bilateral and unilateral (30% MVC, arm(s) at ±45° elevation in scaption)]	L M1	R M1	80/120% aMT	1 mV	4–8 ms*	TS + CS: fig8 (90 mm, ns)	Towards AM (overlapping CS coil)	Towards AM	L Upper trapezius, lower trapezius and serratus anterior	– IHI in upper trapezius with CS intensity = 120% aMT and ISI = 8 ms when target muscle was unilaterally activated, but not during contralateral or bilateral activation – IHI could not be demonstrated in both the lower trapezius and the serratus anterior
Mochizuki et al. (2004a) [*N* = 10]	– At rest – During tonic contraction (20–30% MVC)	R M1	L M1	90/110% rMT	1 mV	4–12*/16/20 ms	CS: fig8 (55 mm*) TS: fig8 (90 mm*) *Outer diameter	LM subexperiment: – LM – ML – PA – AP	LM	R FDI	At rest: – IHI at ISI = 8 and 10 ms and CS intensity = 90 and 120% rMT – No significant effect of CS current direction During tonic contraction: IHI ↑ during tonic contraction of L FDI
Morishita et al. (2012) [*N* = 10]	– During tonic contraction (L, 10% MVC) – During fine-motor manipulation (unilateral L)	R M1	L M1	60–140% rMT	1 mV	10 ms	TS + CS: fig8 (90 mm outer diameter)	ns	ns	R FDI	During tonic contraction contralateral to target muscle: No modulation of IHI during L hand contraction During fine motor manipulation: IHI ↑ during fine motor manipulation with L hand relative to rest or tonic contraction

Table 1: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Nelson et al. (2009) [*N* = 15]	– At rest – During tonic contraction (20% MVC) – During holding a pen (20% MVC)	– R M1 – L M1	– L M1 – R M1	1 mV	1 mV	6–12*/30/40/50 ms	TS + CS: fig8 (50 mm)	ns	ns	– R FDI – L FDI	At rest: IHI M1–M1 (both directions) at ISI = 8–10 and 30–40 ms During tonic contraction: IHI ↓ (both directions) during tonic contraction with and without holding a pen (both ipsi- or contralaterally) at ISI = 8–10 and 30–40 ms
Ni et al. (2020) [*N* = 12]	At rest	R M1	L M1	0.5 mV	0.5 mV	1–15 ms, individually adapted in steps of 0.1 ms for maximal IHI/IHF	TS + CS: fig8 (50 mm outer diameter)	PA	PA	R FDI	– IHF at ISI of 2–6 ms (maximum: 4.5 ± 0.4 ms, mean ± SD) – IHI at ISI of 8–15 ms (maximum: 9.6 ± 0.6 m, mean ± SD) – IHF and IHI ↑ with ISI ↑ until their respective maximum is reached – IHF and IHI ↓ with further ISI ↑ after their maximum was reached
Perez and Cohen (2008) [*N* = 10]	During tonic contraction (R wrist, 10/30/70% MVC)	L M1	R M1	– Intensity that evokes 50% IHI at rest – 1 mV	0.3–0.5 mV	10 ms	TS + CS: fig8 (80 mm, ns)	ns	ns	L FCR	IHI ↓ during tonic contraction of R wrist at 30 and 70% MVC as compared to rest and 10% MVC
Ridding et al. (2000) [*N* = 12]	– At rest – During tonic contraction (1N)	– R M1 – L M1	– L M1 – R M1	1 mV	1 mV	4–12*/16 ms	TS + CS: fig8 (90 mm outer diameter)	ns	ns	– R FDI – L FDI	– L M1–R M1 and R M1–L M1 SIHI were comparable – SIHI in musicians < non-musicians both at rest (–29%) and during tonic contraction (–63%) At rest: – SIHI at ISI = 6–16 ms in non-musicians and at ISI = 10–16 ms in musicians During tonic contraction: SIHI, only in non-musicians at ISI = 10 ms

Table 1: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Sattler et al. (2012) [*N* = 9]	– At rest – During tonic contraction (unimanual, holding a pen, 10–20% MVC)	– R M1 – L M1	– L M1 – R M1	0.8–1.5 mV	0.8–1.5 mV	10/40 ms	TS + CS: fig8 (95 mm outer diameter)	ns	ns	– R FCR and ECR – L FCR and ECR	At rest: – IHI M1–M1 (both directions) at ISI = 10 and 40 ms in both FCR and ECR – IHI measured in wrist muscles is comparable to IHI measured in FDI During tonic contraction: – IHI ↓ relative to rest at ISI = 10 ms (SIHI) in both FCR and ECR – IHI ↓ in ECR > FCR during tonic contraction
Sharples and Kalmar (2012) [*N* = 10]	– At rest – Prior to rhythmic contractions (5% MVC) – During rhythmic contraction (5% MVC)	R M1	L M1	1 mV	1 mV	10 ms	TS + CS: fig8 (90 mm, ns)	ns	PA	R FDI	Prior to rhythmic contraction: – IHI ↑ as compared to rest and to ongoing contraction During rhythmic contractions: – IHI did not change as compared to rest
Tazoe and Perez (2013) [*N* = 24]	– At rest – During self-paced or ballistic movements (finger and elbow, preparation and execution period)	L M1	R M1	Intensity that evokes 50% IHI at rest	Intensity required to evoke 50% of the maximal MEP amplitude at rest	40 ms	TS + CS: fig8 (70 mm, ns)	AP	AP	L FDI and BB	At rest: IHI During ballistic/self-paced movement preparation: IHI ↓ L during movement preparation of L finger and elbow movements for ballistic movements > self-paced movements During movement execution: IHI ↑ during ballistic movements relative to self-paced movements of both the finger and elbow when adjusting test MEPs during ballistic movements to the size of those during self-paced movements

Table 1: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Uehara et al. (2013) [*N* = 28]	– During tonic contraction (L, 10% MVC) – During rhythmic contraction (L, 10% MVC, 1/2/3 Hz)	R M1	L M1	100/120/140% rMT	1 mV	10/40 ms	TS + CS: fig8 (90 mm outer diameter)	ns	PA	R FDI	– SIHI (ISI = 10 ms) ↑ during both tonic and rhythmic contraction at 1 and 3 Hz of L hand relative to rest – LIHI (ISI = 40 ms) was not influenced during both tonic and rhythmic contraction
Ugawa et al. (1993) [*N* = 6]	During tonic contraction (ns)	R M1	L M1	0.05/0.2 mV	Just above aMT	7–12 ms	TS + CS: fig8 (70 mm outer diameter)	ns	ns	R FDI	– IHF only with low intensity CS (evoking 0.05 mV MEP amplitude in active L FDI), at ISI = 8 ms – IHI with a higher CS intensity (evoking 0.2 mV MEP in active L FDI), at all examined ISIs
Vercauteren et al. (2008) [*N* = 13]	During tonic contraction (R, 5% MVC)	L M1	R M1	110% rMT (of the FCR)	110% rMT (of the FCR)	10 ms	CS: fig8 (50 mm, ns) TS: fig8 (70 mm, ns)	ns	ns	L ECR and FCR	– IHI ↑ during tonic contraction as compared to rest for FCR > ECR – IHI in FCR ↑ during both flexion and extension relative to rest – IHI in the ECR ↑ during flexion relative to rest – IHI males > females

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range. The following characters were used to indicate which increment size was used within a range: "*" indicates 2 ms steps, "■" indicates 20 ms steps, while 1 ms increments were considered default and therefore were not indicated by a character. ADM, abductor digiti minimi muscle; aMT, active motor threshold; AP, anterior-to-posterior-directed current; BB, biceps brachii muscle; CS, conditioning stimulus; ECR, extensor carpi radialis muscle; FCR, flexor carpi radialis muscle; FDI, first dorsal interosseus muscle; fig8, figure-of-eight coil; fMRI, functional magnetic resonance imaging; IHI, interhemispheric inhibition; ISI, interstimulus interval; L, left; LIHI, long latency interhemispheric inhibition; LM, lateral-to-medial-directed current; M1, primary motor cortex; ms, milliseconds; ML, medial-to-lateral-directed current; MSO, maximum stimulator output; mV, millivolt; MVC, maximal voluntary contraction; *N*, Newton; ns, not specified; PA, posterior-to-anterior-directed current; rMT, resting motor threshold; RT, reaction time; SD, standard deviation; SIHI, short latency interhemispheric inhibition; TB, triceps brachii muscle.

contralateral homologue and M1 have also been demonstrated in humans (Ruddy et al. 2017). However, the pathways mediating interhemispheric PMd–M1 interactions are not yet fully understood. Presumably, SIHI is mediated by direct transcallosal fibers between PMd and contralateral M1 (Ni et al. 2009; Zarei et al. 2006). The neural population mediating LIHI, on the other hand, might be less straightforward and several pathways can be considered. Firstly, there is evidence for a slow but direct transcallosal PMd–M1 connection, comparable to the M1–M1 LIHI (Ni et al. 2009). Secondly, long-latency interhemispheric PMd–M1 interactions may pass through the inhibitory transcallosal M1–M1 fibers via a relay in the ipsilateral M1 ($PMd–M1_{ipsilateral}–M1_{contralateral}$) as facilitatory intrahemispheric interactions between PMd and M1 are likely activated by a CS delivered to PMd (Civardi et al. 2001) (see below). Indeed, Ni et al. (2009) found that the ISIs at which LIHI emerged were somewhat longer for PMd in comparison with those for M1, supporting this hypothesis. Lastly, a reciprocal functional connection between both homologous premotor areas has been verified by Mochizuki et al. (2007) making use of a combined near-infrared spectroscopy (NIRS)–ds-TMS paradigm. Apart from the established M1–M1 connection, these findings imply the presence of transcallosal fibers between homologous PMds (e.g., right PMd–left PMd–left M1). As it is not yet clear which of the above pathways is responsible for long-latency interactions between PMd and contralateral M1, more research regarding the pathways mediating LIHI is warranted. In addition to interhemispheric PMd–M1 connections, direct cortico–cortical connections exist between PMd and ipsilateral M1 in non-human primates (Dum 2005; Dum and Strick 2002). By analogy, comparable intrahemispheric PMd–M1 connections are hypothesized in humans (Groppa et al. 2012b).

Functional imaging studies indicated that the distance between PMd and ipsilateral M1 is approximately 1.5–2 cm in adult humans (Amiez et al. 2006; Fink et al. 1997) or 0.8–2.3 cm in monkeys (Picard and Strick 2001). Since standard coils are relatively large, placement of both coils on their optimal stimulation point is hindered, which makes the usage of a ds-TMS paradigm to investigate PMd–M1 interactions quite challenging. Nevertheless, several studies attempted to investigate this interaction by means of ds-TMS. An overview of studies investigating inter- and intrahemispheric PMd–M1 interactions can be found in Tables 2 and 3, respectively. In the included studies, the target location for the PMd was most often defined craniometrically relative to the ipsilateral M1 (i.e., motor hotspot). Particularly, to stimulate PMd, either a point located anterior and medial relative to M1 was determined [i.e., 2 cm anterior and 0.5 cm medial (Liuzzi et al. 2010, 2011), 2 cm anterior and 1 cm medial (O'Shea et al. 2007) or 2.5 cm anterior and 1 cm medial (Calvert et al. 2020; Fiori et al. 2017; Mochizuki et al. 2004a; Ni et al. 2009; Uehara et al. 2013; Vesia et al. 2018)], or a point anterior to the M1 hand region ($M1_{hand}$) at a fixed distance of 3–5 cm anterior (Bäumer et al. 2009; Byblow et al. 2007; Civardi et al. 2001), or alternatively, at a distance defined as 8% of the distance between the nasion and the inion (usually about 3 cm) was used. Authors employed this method with the aim to avoid M1 activation during PMd stimulation (Bäumer et al. 2006, 2009; Koch et al. 2006; Kroeger et al. 2010). In contrast, Fujiyama et al. (2016a) used anatomical landmarks (anterior to the precentral sulcus and adjacent to the dorsal bank of the superior frontal sulcus), based on individual T1-weighted anatomical images to identify and target PMd using a neuro-navigation system (Fujiyama et al. 2016a).

Specifically for intrahemispheric PMd–M1 interactions, Bäumer et al. (2009) moved the CS coil as close as technically possible towards the ipsilateral M1; thereby overlapping both coils (Bäumer et al. 2009). Along the same lines, Groppa and colleagues (Groppa et al. 2012a,b) used custom-made figure-of-eight coils with a handle perpendicular to the plane of the coil windings (also known as 'branding iron style'). These coils had asymmetric wiring so that the point of maximal stimulation was shifted towards one long edge of the coil, allowing for stimulation in close proximity when placing the CS coil over left PMd directly anterior and in a mirrored fashion to the TS coil over left M1. Hence, this coil configuration and orientation allowed them to put two coils next to each other on the participant's head and stimulate both the M1 hotspot and a point 3–4 cm anterior to the hotspot. Alternatively, to overcome the difficulty of placing one coil over $M1_{hand}$ and the other over PMd at the same time, Parmigiani et al. (2015) and (2018) applied a TS over the M1 orofacial region ($M1_{lip}$), defined as the point where the largest MEPs could be evoked in the orbicularis oris muscle. The CS was applied over three different points within the putative PMd region, established on MRI-based anatomical landmarks. Specifically, (1) a point that corresponded to the junction between the superior frontal sulcus and the superior precentral sulcus, (2) 1.5 cm (Parmigiani et al. 2018), and (3) 3 cm anterior to this point (Parmigiani et al. 2015), where ipsilateral PMd–M1 interactions were only modulated following a CS applied over the second point. Changing the TS target location to the orofacial motor cortex allowed placing both coils on their optimal stimulation point, as $M1_{lip}$ is located laterally in relation to the hand and elbow region (Lotze et al. 2000). It should be noted that the distance between the stimulation location of the PMd and M1, as determined by the different researchers, varies greatly across

studies and was mostly larger than the 1.5–2 cm identified by human imaging studies (Amiez et al. 2006; Fink et al. 1997). Hence, it might be expected that pre-PMd rather than PMd proper was stimulated. In contrast to the PMd proper, the pre-PMd demonstrates projections to prefrontal regions rather than to the PMd and M1 (Dum 2005; Geyer et al. 2000a; Lu et al. 1994; Picard and Strick 2001) and is thus assumed to be more strongly involved in cognitive as compared to motor processes, rendering the comparability between these studies limited.

To ensure optimal stimulation of both PMd and M1, while allowing both coils to be placed on the subject's head at the same time, coils were oriented in a specific manner so that both coils could be placed as close to each other as possible or even overlap. A detailed description of these coil orientations is provided in the appendix, while Figures 4 and 5 provide a general overview of the coil orientations used for inter- and intrahemispheric PMd–M1 interactions, respectively.

Interhemispheric

At rest

Similar to M1–M1 interactions, interhemispheric PMd–M1 interactions can be elicited at rest at both short and long latencies (Bäumer et al. 2006; Calvert et al. 2020; Fiori et al. 2017; Koch et al. 2006; Kroeger et al. 2010; Mochizuki et al. 2004a; Ni et al. 2009). Whether these interactions are inhibitory or facilitatory appears to be dependent on the stimulation parameters. Particularly, facilitatory interhemispheric PMd–M1 interactions have only been elicited using subthreshold CS intensities (short interval = 80% aMT; long interval = 90% rMT) (Bäumer et al. 2006; Fiori et al. 2017; Koch et al. 2006), whereas suprathreshold CS intensities elicited inhibitory interhemispheric PMd–M1 interactions (inhibition at short latencies = 110–200% aMT or 110–130% rMT; inhibition at long latencies = 140–200% aMT) (Calvert et al. 2020; Fujiyama et al. 2016a; Koch et al. 2006; Liuzzi et al. 2010; Mochizuki et al. 2004a; Ni et al. 2009). In addition, inhibitory PMd–M1 interactions seem to be analogous for both hemispheres, i.e., left PMd–right M1 interactions did not differ from right PMd–left M1 interactions (Fujiyama et al. 2016a; Koch et al. 2006). In contrast, facilitatory interactions were shown to be reliant on the conditioned hemisphere. More specifically, while Koch et al. (2006) demonstrated a facilitatory left PMd–right M1 interaction when applying a low-intensity CS (80% aMT) over PMd, Bäumer et al. (2006) could not confirm this modulatory effect for the right PMd–left M1 interaction using the same parameters. Regarding the optimal time interval, ISIs of 8–10 ms were identified to be optimal for short latency interhemispheric inhibitory or facilitatory interactions, and ISIs of 40–50 and 80 ms to elicit inhibitory or facilitatory long-latency interactions, respectively. Finally, the influence exerted by PMd on contralateral M1 was neither affected by the studied CS (Mochizuki et al. 2004a; Ni et al. 2009) nor TS (Bäumer et al. 2006) current directions.

It is important to note that there are many contradictory results regarding the above-mentioned findings. Namely, although the majority of studies indicated that inhibitory effects could be elicited with a suprathreshold CS applied over PMd, other studies did not confirm this using an identical intensity (Fiori et al. 2017; Kroeger et al. 2010). The same applies to facilitatory interactions, assumed to be elicited by a subthreshold CS intensity. That is, authors using parameters equal to earlier studies (90% rMT subthreshold CS intensity) revealed inhibitory rather than facilitatory PMd–M1 interactions (Calvert et al. 2020; Mochizuki et al. 2004a). In addition to these ambiguities regarding the CS intensity, there was also inconsistency regarding the influence of the TS current direction. Namely, while Bäumer et al. (2006) did not find any difference between PA- and AP-directed TS currents in the cortical tissue, Calvert et al. (2020) demonstrated an inhibitory right PMd–left M1 interaction only for a PA-, but not an AP-, directed TS current.

Task-related interactions

Tonic contraction of the target muscle. As opposed to M1–M1 interactions, interhemispheric PMd–M1 interactions, both from left PMd to right M1 and from the right PMd to the left M1, were not modulated during a tonic contraction of the target muscle (Bäumer et al. 2006; Mochizuki et al. 2004a).

Tonic and rhythmic contraction of the muscle contralateral to the target muscle. Similar to a tonic contraction of the target muscle, a tonic contraction of the muscle contralateral to the target muscle did not influence interhemispheric PMd–M1 interactions (i.e., interactions from the resting to the active hemisphere) (Mochizuki et al. 2004a). Specifically, right PMd–left M1 interactions were not modulated during a tonic contraction of the left FDI. Along the same lines, Uehara et al. (2013) examined the effect of both sustained and rhythmic (1, 2, and 3 Hz) tonic contraction of the left FDI on right PMd–left M1 interactions. Their results demonstrated a stronger inhibition during the rhythmic contraction, for a CS intensity of 120% but not 140% (Uehara et al. 2013).

Simple reaction time task. A study by Liuzzi et al. (2010) demonstrated that the inhibitory right PMd–left M1

interaction identified at rest was facilitated during both the early and late premovement phase (i.e., at 20 and 85% of the RT) of a simple, right-hand visuomotor RT task. In contrast with studies investigating a choice RT task or Go/NoGo task (see corresponding sections), this task does not require decision making-processes. This facilitation early in the pre-movement phase was abolished when the CS intensity was increased to values above the right M1 threshold (i.e., when the CS applied over right PMd provoked an MEP in the left FDI) (Liuzzi et al. 2010).

Choice reaction time task. Koch et al. (2006) demonstrated a task- and time-specific modulation of interhemispheric left PMd–right M1 interactions during the preparatory period of an auditory cued choice RT task, facilitating the moving (left) hand and inhibiting the non-moving (right) hand after the auditory stimulus onset. More specifically, right M1 excitability was selectively enhanced (i.e., facilitation of the left PMd–right M1 interaction) 75 ms after an auditory stimulus indicating left (i.e., the target muscle) hand movements when a subthreshold CS (80% aMT) was applied over left PMd, but not in case of right-hand movements. In contrast, inhibition of right PMd–left M1 predominated at 100 ms after the stimulus indicating left-hand movements, with a suprathreshold (110% rMT) CS, similar to left PMd–right M1 interactions, but no facilitatory influence of left PMd could be demonstrated. Hence, left-hand movements that are about to be executed may be facilitated by left PMd, whereas movements that are planned but will not be executed are inhibited by the left or right PMd, for left and right-hand movements, respectively (Koch et al. 2006). This finding might be attributable to the dominant role of left PMd in action selection (Rushworth et al. 2003; Schluter et al. 2001). Lastly, these interhemispheric PMd–M1 interactions were found to be muscle-specific, as solely connections with muscle representations of potential effectors were modulated (Koch et al. 2006).

The timing of PMd–M1 modulations during response selection (i.e., 75 and 100 ms after the stimulus onset) described by Koch et al. (2006) was confirmed by O'Shea et al. (2007) combining ds-TMS with a visuomotor choice RT task. They demonstrated PMd–M1 facilitation (CS = 110% rMT) at 75 ms after the stimulus onset, independent from whether the target muscle or its contralateral homologue had to move. In addition, conditioning left, but not right, PMd at 100 ms following the stimulus onset, delayed the RT of the left (i.e., the target muscle), but not the right hand (O'Shea et al. 2007).

Note that, despite the similar timing in the two studies (i.e., facilitation 75 ms after the start cue), different results were obtained. While Koch et al. (2006) found a facilitatory modulation only when probing the left PMd–right M1 interaction at 75 ms after the stimulus indicating a left-hand movement (contralateral to the stimulated M1), O'Shea et al. (2007) reported facilitation of both (i.e., left to right and right to left) interhemispheric PMd–M1 interactions independent of the hand required to perform the upcoming movement. Accordingly, in contrast to the behavioural data (i.e., delayed RT in the target hand after stimulating the left but not the right PMd), the suggested dominance of the left hemispheres is not reflected in the interhemispheric interactions. The authors argue that the interhemispheric nature of a ds-TMS protocol renders it suboptimal for the detection of hemispheric asymmetries. In addition, both authors used different CS intensities [80% aMT (Koch et al. 2006) and 110% rMT (O'Shea et al. 2007), respectively], which might also explain the difference in results.

Go/NoGo task. Kroeger et al. (2010) examined how interhemispheric PMd –M1 interactions were modified in the context of a delayed Go/NoGo task, i.e., with a first cue indicating to select either the right or the left hand and a second cue indicating to react ('Go') or not ('NoGo'). Their results showed that left PMd–right M1 interactions are context-dependent. Specifically, inhibition was found 300 ms after the first cue when the left (i.e., the target muscle), but not the right, index finger had to press the response button. This inhibitory left PMd–right M1 interaction turned into facilitation 150 ms after the second cue, but only if this second cue was a 'Go' cue. In 'NoGo' trials the interaction remained unchanged. Lastly, conditioning left PMd resulted in a faster RT during trials requiring left-hand movements. The authors suggested that this result is in line with the assumed dominance of left PMd in releasing a preselected movement (Kroeger et al. 2010).

Bimanual tracking task. Task-related changes in the interhemispheric PMd–M1 interaction were also established during the preparation of coordinated bimanual movements, underscoring the importance of particularly the left PMd during bimanual movement preparation (Fujiyama et al. 2016a). More specifically, participants turned two dials simultaneously at different frequencies and ds-TMS was applied during the movement preparation phase. As compared to rest, the left PMd–right M1 interaction became facilitatory in trials during which the left hand had to move faster than the right hand, while an inhibitory left PMd–right M1 interaction was reported for trials in which the right hand had to move faster. Additionally, left PMd–right M1 interactions were not modulated when both hands had to move at the same speed. In contrast to left PMd–right M1 interactions, right PMd–left M1 interactions were not

modulated during any task variant. Notably, the ability to modulate interhemispheric PMd–M1 interactions during movement preparation was positively correlated with better motor performance, at least the first seconds following movement initiation. The authors interpreted this as the "gating" function of left PMd, i.e., gating right M1 output for non-dominant hand movement in addition to the assumed gating of left M1 output for dominant hand movement, depending on the task condition (Fujiyama et al. 2016a).

Bimanual rhythmic finger tapping task. Liuzzi et al. (2011) examined right PMd–left M1 interactions in the context of a bimanual, rhythmic finger tapping task. More specifically, the role of interhemispheric interactions between right PMd and left M1 were compared between unimanual finger tapping, bimanual antiphase (asymmetric) tapping, and bimanual in-phase (symmetric) tapping. The results indicated a facilitatory modulation of right PMd–left M1 interactions early in the preparatory period (20% of RT) of anti-phase tapping. Remarkably, a stronger facilitatory modulation was positively associated with higher performance on the bimanual anti-phase task, but not the in-phase or unimanual tasks (Liuzzi et al. 2011). Since the mode (i.e., inhibition or facilitation) of interhemispheric interactions varies depending on the specific requirements of a motor task, the more demanding anti-phase bimanual movements might therefore rely on a facilitatory exchange of information (Yazgan et al. 1995), as suggested by the authors. Additionally, this finding is in line with the role of the right PMd during bimanual coordination of anti-phase movements (Aramaki et al. 2006; Meister et al. 2010; Meyer-Lindenberg et al. 2002).

Summary and discussion interhemispheric PMd–M1 interactions

Interhemispheric PMd–M1 interactions could be elicited at rest using both short and long latencies (Bäumer et al. 2006; Calvert et al. 2020; Fiori et al. 2017; Koch et al. 2006; Kroeger et al. 2010; Mochizuki et al. 2004a; Ni et al. 2009), resulting in either an inhibitory or facilitatory influence on M1, depending on the stimulation parameters. Despite the presence of some ambiguities, conditioning of the PMd with suprathreshold CS intensity seems to inhibit the contralateral M1 while conditioning of the dominant (left) PMd with a subthreshold CS intensity seems to facilitate the contralateral M1. Due to the close proximity of PMd to M1, the fact that the spatial resolution of TMS is rather limited (Brasil-Neto et al. 1992; Sliwinska et al. 2014), and the variability of induced E-fields (Van Hoornweder et al. 2021), the induced current may unintentionally spread, resulting in a stimulation of regions other than PMd (such as M1 or PMv). This might particularly be the case when higher (suprathreshold) CS intensities are used. Especially since the CS intensities and intervals at which inhibition is observed are similar to those of interhemispheric M1–M1 and PMv–M1 interactions. The use of a craniometric method (e.g., a fixed distance) for determining the PMd stimulation location may also contribute to inaccurate targeting (e.g., Calvert et al. 2020). This unintentional stimulation of regions in the vicinity of the PMd may contribute to the conflicting findings regarding interhemispheric interactions between PMd and M1. Yet, it is difficult or impossible to control for using TMS.

Similar to IHF between homologous M1s, IHF between PMd and contralateral M1 is thought to be subtle and very volatile in healthy people, while IHI is a consistent phenomenon that can be easily elicited at a wide range of intensities above the individual rMT (Bäumer et al. 2006; De Gennaro et al. 2004; Di Lazzaro et al. 1999; Ferbert et al. 1992; Hanajima et al. 2001; Ugawa et al. 1993). In a study by Asanuma and Okuda (1962), it has been shown that inhibitory interneurons are abundant while facilitating interneurons are scarce. This implies that IHF is indeed subtle and focal and can only be elicited under very specific circumstances. Outside this specific window, stronger inhibition predominates and cancels out facilitatory effects. As with M1, such low intensity pulses lead to IHF in PMd conditioning. This might also be the reason why the weak IHF was missed in studies that only used higher CS intensities. Lastly, these PMd–M1 interactions are potentially influenced by the current direction of the TS, but not the CS (Calvert et al. 2020; Mochizuki et al. 2004a).

During a tonic contraction of the target muscle interhemispheric PMd–M1 interactions, both from left PMd to right M1 and from the right PMd to the left M1, are not modulated (Bäumer et al. 2006; Mochizuki et al. 2004a), as opposed to M1–M1 interactions. PMd–M1 interactions were also unaffected during a tonic contraction of target muscles' contralateral homologue (Mochizuki et al. 2004a). This may be consistent with the role of PMd in more complex movements requiring preparation, selection and (bimanual) coordination (Cisek and Kalaska 2005; Duque et al. 2005; Fujiyama et al. 2016a; Mochizuki et al. 2004a; Perez et al. 2007; Wise 1985).

Most often, interactions from the inactive to the active hemisphere were, similar to M1, disinhibited/facilitated in the context of a motor task (Kroeger et al. 2010; Liuzzi et al. 2010). However, the PMd's function is generally more lateralized (Verstraelen et al. 2021). More specifically, as opposed to M1–M1 interactions, the studies described in this review demonstrated a context-dependent modulation during

different uni- and bi-manual tasks, in which the left PMd plays a dominant role. For example, while unwanted mirror movements of the inactive hand are suppressed by the corresponding left and right PMd during unimanual movements, only left PMd is involved in the action selection of both the left and right hand by exerting a facilitatory influence during movement preparation (Koch et al. 2006; O'Shea et al. 2007). Additionally, this left PMd dominance has also been demonstrated in a bimanual coordination task, where the left PMd–M1 interaction was modulated in a task-specific manner. More specifically, while connectivity between right PMd and left M1 remained unchanged, the interaction became facilitatory or inhibitory in trials during which the left hand, respectively, had to move faster or slower than the right hand. This might be interpreted as, respectively, an increase and decrease of output gating from the left PMd to the right M1 (Fujiyama et al. 2016a). It should be noted that, despite the laterality in favor of the left PMd (in right-handed individuals), only four of the 12 studies examined PMd–M1 interactions in both directions Furthermore, there are also studies that did not fully support this dominant role of the left PMd, reporting an equivalent facilitatory role for both PMd's (O'Shea et al. 2007) or for the right PMd (Liuzzi et al. 2010). Accordingly, it might be argued that the interhemispheric nature of these ds-TMS protocols makes the technique less suitable to detect hemispheric asymmetries.

Intrahemispheric

At rest

Civardi et al. (2001) found decreased MEP amplitude elicited by TS applied over left M1 when it was preceded by a CS applied to a point corresponding with the premotor cortex (left PMd), inducing an AP-directed current in the brain. This inhibitory PMd–M1 interaction was established at ISIs of both 4 and 6 ms when a CS intensity of 90% aMT (measured at the hotspot) was used. With increasing CS intensity this inhibition diminished and even resulted in facilitation when using 6 ms ISI and a higher-intensity CS of 120% aMT. In contrast, Bäumer et al. (2009) were not able to elicit PMd–M1 interactions when using the same parameters and target location. However, inhibition could be elicited with CS intensities of 90% aMT (ISI = 8 ms) and 110% rMT (ISI = 2 and 4 ms), when placing the CS coil as close as possible to M1 within the left hemisphere (Bäumer et al. 2009). In other studies, Groppa and colleagues (Groppa et al. 2012a,b) demonstrated PMd–M1 facilitation rather than inhibition when using specifically designed coils and reversing the sequence of stimuli, meaning that the CS over PMd was applied after (instead of prior to) the TS over M1. More specific, facilitatory left PMd–left M1 interactions were found with a TS over M1, followed by a CS (50/70/90% of TS intensity) over left PMd applied 2.4, 2.8 or 4.4 ms later (Groppa et al. 2012a), and with a CS at intensities of 70 and 90% rMT applied 1.2 ms after the TS (Groppa et al. 2012b).

In contrast, Van Hoornweder et al. (2021), demonstrated an inhibitory left PMd–left M1 interaction in males but not females with a lateral–medial-directed CS using a similar sequence of stimuli (TS prior to CS) and stimulation parameters (i.e., ISI = 2.8 ms; CS intensity = 75% rMT). It should be noted, however, that despite the similarities, there are marked differences between the two protocols that may explain these contradictory results. As suggested by the authors, we can infer from these results that the late I-waves of the TS applied over left M1 may still be influenced by the CS over the ipsilateral PMd 2.8 ms earlier. Finally, these results indicate the sensitivity of PMd to the induced current direction and its dependency on sex (Van Hoornweder et al. 2021), as only lateral–medial-, but not medial–lateral-, directed CS pulses could elicit an inhibitory left PMd–left M1 interaction in males, but not females.

Differences in stimulation parameters, coils and target location render comparison of the results described above difficult.

Task-related interactions

During tonic contraction of the target muscle. During tonic contraction of the target muscle, the magnitude of intrahemispheric PMd–M1 inhibitory/facilitatory interactions seems to decrease, as compared to rest. More specifically, the amount of inhibition, elicited with a CS of 90% aMT at 6 ms ISI, was found to decrease as compared to rest (Civardi et al. 2001). Likewise, Groppa et al. (2012b) demonstrated that also the facilitatory left PMd–left M1 interaction found at rest was abolished during tonic contraction of the target muscle. The lack of intrahemispheric PMd-M1 interactions during tonic contraction could be due to the fact that the M1 receives both inhibitory and excitatory input from a variety of motor-related areas, possibly overshadowing the selective impact of the ipsilateral PMd (Groppa et al. 2012b).

As mentioned above (section "PMd–M1 interactions"), Parmigiani et al. (2015) and (2018) applied a TS over the left $M1_{lip}$ rather than the $M1_{hand}$. The MEPs within the orbicularis oris muscle were measured during a tonic contraction, as eliciting MEPs in the facial region at rest is difficult due to the high stimulation threshold of the orofacial motor cortex. In a first study, they demonstrated an inhibitory left PMd–left $M1_{lip}$ interaction at 6 ms ISI when the CS was applied to a point 1.5 cm rostral to the junction between the superior frontal sulcus and superior precentral sulcus (Parmigiani et al. 2015).

Table 2: Overview of studies investigating interhemispheric PMd–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Bäumer et al. (2006) [*N* = 20]	– At rest – During tonic contraction (10% MVC)	L PMd	R M1	60/80% aMT	1 mV	3–8/10 ms	TS + CS: fig8 (70 mm outer diameter)	PA	– PA – AP	L FDI	At rest: facilitation with CS intensity = 80% aMT, ISI = 8 ms, irrespective of TS current direction During tonic contraction: No modulation of R PMd–L M1 interactions during tonic contraction
Calvert et al. (2020) [*N* = 32]	At rest	R PMd	L M1	90/110/130% rMT	0.2 mV	8/10/40 ms	TS + CS: fig8 (55 mm)	LM	– AP – PA	L FDI; R & L ECR	– Inhibition with PA-, but not AP-, directed TS, irrespective of ISI – Inhibition ↑ with CS intensity ↑ (inhibition for CS intensity = 130% rMT > 90% rMT)
Fiori et al. (2017) [*N* = 15]	At rest	R PMd	L M1	90/110% rMT	1 mV	40–120■/ 150 ms	TS + CS: fig8 (40 mm, ns)	LM	PA	R FDI	– No inhibition R PMd–L M1 with ISIs = 40–150 ms, irrespective of CS intensity – Facilitation with CS intensity = 90% rMT at ISI = 80 ms
Fujiyama et al. (2016a) [*N* = 15]	– At rest – During a bimanual tracking task	– L PMd – R PMd	– R M1 – L M1	110% rMT	1 mV	8/40 ms	TS + CS: fig8 (50 mm outer diameter)	ns	PA	R & L FDI	At rest: – Inhibition L PMd–R M1 and R PMd–L M1 at ISI = 8 or 40 ms During bimanual tracking task: in preparation period: – Facilitation L PMd–R M1 ↑ when speed L hand > R hand – Facilitation L PMd–R M1 abolished when speed R hand > L hand

Table 2: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
											– L PMd–R M1 interactions not influenced when speed R hand = L hand – More L PMd–R M1 modulation was associated with better task performance – No modulation of R PMd–L M1 interactions (all movement ratios)
Koch et al. (2006) [*N* = 15]	– At rest – During simple RT task	– L PMd – R PMd	– R M1 – L M1	– 80% aMT – 110% rMT	1 mV	8 ms	TS: fig8 (70 mm*) CS: fig8 (55 mm*) * outer diameter	LM	PA	R & L FDI; L ADM	At rest: *L PMd–R M1:* – Facilitation with CS intensity = 80% aMT – Inhibition with CS intensity = 110% rMT *R PMd–L M1:* – No modulation with CS intensity = 80% aMT – Inhibition with CS intensity = 110% rMT – No IHF nor IHI in the (non- involved) ADM muscle During simple RT task: *CS intensity = 80% aMT, at 75 ms after cue indicating a L hand movement:* – Facilitation L PMd–R M1 – No modulation of R PMd–L M1 interactions *CS intensity = 110% rMT, at 100 ms after cue indicating R hand movement:* – Inhibition L PMd–R M1 and R PMd–L M1

Table 2: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Kroeger et al. (2010) [*N* = 19]	– At rest: – During delayed Go/NoGo task	L PMd	R M1	110% rMT	1 mV	8 ms	TS + CS: fig8 (70 mm outer diameter)	ns	PA	L FDI	At rest: no L PMd–R M1 interactions During delayed Go/NoGo task (1st cue: which hand to move, 2nd cue: "Go" signal): – Inhibition at 300 ms after 1st cue – Facilitation at 150 ms after 2nd cue, only when L hand movement was required (MEP "Go" > "NoGo" trials) – CS applied over L PMd = faster RT in trials requiring L hand movement
Liuzzi et al. (2010) [*N* = 10]	– At rest – During simple RT task	R PMd	L M1	– Intensity that evokes 30–50% inhibition – Intensity experiment: 110/120% M1 rMT; PMd rMT −2%/+3%/+10% MSO	1 mV	10 ms	TS + CS: fig8 (70 mm, ns)	ns	ns	R FDI	At rest: Inhibition R PMd–L M1 During simple RT task: – Facilitation at 20 and 95% of RT – Facilitation abolished when CS intensity = PMd rMT −2% MSO – IHI when CS intensity = PMd rMT +3 and 10% MSO
Liuzzi et al. (2011) [*N* = 14]	During bimanual rhythmic finger tapping task	R PMd	L M1	Intensity that evokes 30–50% inhibition	1 mV	10 ms	TS + CS: fig8 (70 mm, ns)	ns	ns	R FDI	Facilitation during preparatory period of anti-phase movements, positively associated with task performance
Mochizuki et al. (2004a) [*N* = 10]	– At rest – During tonic contraction	– R PMd – L PMd	– L M1 – R M1	90/110% rMT	1 mV	4–12*/16/20 ms	TS: fig8 (90 mm*) CS: fig8	– LM – ML – PA	LM	R & L FDI	At rest: *R PMd–L M1:*

Table 2: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
	(20–30% MVC; only R PMd → L M1 examined)						(55 mm*) *Outer diameter	– AP			– Inhibition with CS intensity = 90% rMT and ISI = 8 ms – Inhibition with CS intensity = 110% rMT and ISI = 8/10 ms – Not influenced by CS current direction *L PMd–R M1:* Inhibition equal to R PMd–L M1 for CS intensity = 90% rMT During tonic contraction: No modulation of R PMd–L M1 interaction, during tonic contraction of the left FDI
Ni et al. (2009) [*N* = 12]	At rest	R PMd	L M1	– 1 mV – 60–200% aMT	1 mV	4–12*/16/ 20–60▼/80/ 100 ms	TS: fig8 (95 mm*) CS: fig8 (80 mm*) * outer diameter	– LM – ML – PA – AP	PA	R FDI	– Maximal inhibition at ISIs = ±10 ms and ±50 ms – Inhibition at short latencies only for CS intensity = 160–200% aMT – Inhibition at long latencies only for CS intensities = 140–200% aMT
O'Shea et al. (2007) [*N* = 8/11 for simple/choice RT task, respectively]	– During simple RT task – During choice RT task	– L PMd – R PMd	– R M1 – L M1	110% rMT	1 mV	8 ms	TS: fig8 (70 mm, ns) CS: fig8 (50 mm, ns)	ns	ns	R & L FDI	R PMd–L M1 and L PMd–R M1 interactions did not differ during either of these tasks During choice RT task: – Facilitation at 75 ms after stimulus onset, irrespective of the selected hand

Table 2: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
											– CS applied over L PMd, but not R PMd, at 100 ms after stimulus onset delayed RT of L hand (contralateral to M1) During simple RT task: facilitation at 50 ms after stimulus onset
Uehara et al. (2013) [*N* = 28]	– During tonic contraction (L, 10% MVC) – During rhythmic contraction (L, 10% MVC, 1/2/3 Hz)	R PMd	L M1	120/140% rMT	1 mV	10 ms	TS + CS: fig8 (90 mm outer diameter)	ns	ns	R FDI	Inhibition with CS intensity = 120% rMT at 2 Hz > 3 Hz or tonic contraction condition

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range. The following characters were used to indicate which increment size was used within a range: "*" indicates 2 ms increments, "■" indicates 20 ms steps, and "▼" indicates 10 ms increments, while 1 ms increments were considered default and therefore were not indicated by a character. ADM, abductor digiti minimi muscle; aMT, active motor threshold; ant., anterior; AP, anterior-to-posterior-directed current; CS, conditioning stimulus; ECR, extensor carpi radialis muscle; FDI, first dorsal interosseus muscle; fig8, figure-of-eight coil; ISI, interstimulus interval; L, left; LIHI, long latency interhemispheric inhibition; LM, lateral-to-medial-directed current; M1, primary motor cortex; MEP, motor evoked potential; ML, medial-to-lateral-directed current; ms, milliseconds; MSO, maximal stimulator output; mV, millivolt; MVC, maximal voluntary contraction; ns, not specified; PA, posterior-to-anterior-directed current; PMd, dorsal premotor cortex; post., posterior; R, right; rMT, resting motor threshold; RT, reaction time; SIHI, short latency interhemispheric inhibition; TS, test stimulus. Note that the study of Boorman et al. (2007) was not included in this table as the ds-TMS data used in their study come from the studies of Koch et al. (2006) and O'Shea et al. (2007).

These results were confirmed in a second study, using the same stimulation parameters (Parmigiani et al. 2018).

Tonic contraction of a muscle other than the target muscle. Byblow et al. (2007) examined the effect of tonic right ankle dorsiflexion and plantar flexion on the interaction between left PMd and the ipsilateral M1 ECR (i.e., wrist extensor) hotspot 6 ms later. The forearm remained inactive in a pronated position. Their results indicated a facilitatory intrahemispheric PMd–M1 interaction with a CS intensity of 90 and 130% aMT during dorsiflexion as compared to rest, but no modulation of this interaction during plantar flexion. The authors suggested that this intrahemispheric PMd–M1 pathway facilitates the ECR muscle only during dorsiflexion as this is the 'preferred' (iso-directional) coordination pattern.

Choice reaction time task. Groppa et al. (2012b) examined PMd–M1 interactions in the context of a choice RT task. During this task, participants had to press a button as quickly as possible either with their right or left index finger upon the presentation of, respectively, a circle or square on a screen located in front of them. A facilitatory interaction between left PMd and left M1 was established at a 125 ms interval following the stimulus onset only when subjects were required to respond with their right (i.e., contralateral) but not left hand (Groppa et al. 2012b).

Delayed simple reaction time task. In an alternative ds-TMS protocol (extensively described in section 'During tonic contraction of the target muscle') Parmigiani et al. (2018) probed the interaction between left PMd and ipsilateral $M1_{lip}$ during the delay period of a simple reaction task. More specifically, a warning signal was presented for a fixed and predictable interval of 900 ms prior to the presentation of an imperative 'Go' signal, to which participants had to react with a lip movement. During the delay period between the two signals, ds-TMS was applied at several time points. The results indicated an inhibitory left PMd–left $M1_{lip}$ interaction (ISI = 6 ms) at 600 ms after the presentation of the warning signal. This inhibition was abolished when approaching the 'Go' signal. Moreover, when varying the duration of the delay period, PMd–$M1_{lip}$ inhibition was found to take place about halfway through the action-withholding phase, irrespective of the duration of this period (Parmigiani et al. 2018).

Reach and grasp preparation. Vesia et al. (2018) investigated intrahemispheric PMd–M1 interactions in the left hemisphere in the context of reach and grasp preparation. In their experiment, participants made reaching and grasping movements with their right hand to a cylinder located in front of them. The cylinder had to be grasped using either a pinch grip (i.e., engaging the FDI muscle) or a whole-handgrip (i.e., engaging both the FDI and ADM muscles). Alternatively, the cylinder needed to be touched with their index finger knuckle without forming a grip. An illumination of this cylinder indicated the grip type required for the upcoming trial, whereas extinction of the light represented the 'Go' signal. Their results indicated the involvement of the left PMd–left M1 pathway in encoding handgrip during reaching and grasping preparation. In particular, facilitatory left PMd–left M1 interactions were found for the FDI both during precision grip (all studied ISIs) and whole handgrip (ISI = 6 ms) as compared to touch. In contrast, MEP amplitudes in the ADM increased at an ISI of 6 ms during whole handgrip but not during precision grip (Vesia et al. 2018).

Summary and discussion intrahemispheric PMd–M1 interactions

To summarize, the demonstration of intrahemispheric PMd–M1 interactions employing a ds-TMS paradigm is complicated due to the technical difficulty of placing two coils in such close spatial proximity. The use of different strategies to overcome this problem, as well as the use of a broad spectrum of stimulation parameters and paradigms renders a comparison of the results difficult. When the distance between both coils is larger than the 1.5–2 cm identified by human imaging studies (Amiez et al. 2006; Fink et al. 1997) one presumably stimulates the pre-PMd or even DLPFC rather than the PMd proper. Since these regions serve different functions and exhibit different connectivity patterns than PMd, the outcome is likely to differ from that of stimulation of the PMd proper.

At rest, both facilitatory and inhibitory PMd–M1 pathways could be elicited depending on the specific target location within PMd and the stimulation parameters used.

Studies investigating how these interactions are modulated during contraction of the target muscle fail to provide unambiguous results. However, an overall facilitatory modulation of the PMd–ipsilateral M1 pathway seems to exist in the context of motor tasks. This facilitatory modulation has been suggested to promote preferred coordination modes (i.e., isodirectional; both limbs move in the same direction) between upper and lower limbs (Byblow et al. 2007), govern movement of the target muscle during choice RT tasks (Groppa et al. 2012b) and encode hand and grip selection (Vesia et al. 2018). In contrast, inhibitory rather than facilitatory PMd–M1 interactions

were found in the context of action withholding, hypothesized as the neural correlate of the ability to suppress a planned movement. This inhibitory influence was released during "GO"-trials. Hence, the coaction between inhibition and facilitation in PMd does not only support choices between competing actions, but single actions that must be withheld too (Parmigiani et al. 2018). Yet, these interactions were only examined in the dominant (left) and not in the non-dominant hemisphere.

PMv–M1 interactions

The ventral premotor cortex (PMv) is a premotor region located on the lateral surface of the premotor area within the frontal cortex, laterally to the PMd (Grezes and Decety 2001; Tomassini et al. 2007). Given its connection to motor, sensory and high-level cognitive areas involved in controlling motor actions and decision variables, the PMv has been suggested to be part of a supervisory network responsible for shaping future behaviour (specifically arm movements (Kakei et al. 2001)) and motor learning (Pardo-Vazquez et al. 2008), similar to the PMd. However, while the PMd is more engaged in movement based on arbitrary visual signals (Deiber et al. 1997; Mitz et al. 1991), the PMv is primarily involved in processing visuospatial information, incorporating visuospatial object properties for grasping movements and controlling the movement mechanisms for appropriate hand-object interaction for the manipulation of objects (Chouinard and Paus 2006; Kakei et al. 2001; Majdandzic et al. 2009). More specifically, it plays a crucial role in sensory integration [i.e., the integration of information from multiple sensory modalities with different reference frames to simplify movement planning such as reaching, (Engel et al. 2002)] for visually guided actions and perception-based decisions. Furthermore, PMv is involved in the observation of motor actions (Bonini 2017; Bonini et al. 2010; Kostorz et al. 2020), as supported by the significant amount of mirror neurons in this region (Kilner and Lemon 2013; Rizzolatti and Luppino 2001).

Concerning its anatomical pathway, the PMv is anatomically interconnected not only to ipsilateral (Dum and Strick 1991; Godschalk et al. 1984; Jeannerod et al. 1995; Lu et al. 1994; Matelli et al. 1986; Muakkassa and Strick 1979; Picard and Strick 2001) but also to contralateral M1 (Ghosh et al. 1987; Muakkassa and Strick 1979), as indicated by studies investigating non-human primates.

Various techniques were used to determine the target location for stimulating PMv. Precisely, either (1) anatomical landmarks [caudal part of the pars opercularis within the inferior frontal gyrus (BA44) (Davare et al. 2008, 2009; Koch et al. 2010b; Lago et al. 2010); or the anterior aspect of the precentral gyrus, at the border with the posterior part of the inferior frontal gyrus (Buch et al. 2010; Fiori et al. 2017)] were identified based on individual T1-weighted anatomical, or (2) MNI (Montreal Neurological Institute) coordinates from several MRI and TMS studies identifying the PMv location were averaged (de Beukelaar et al. 2016), or (3) a point measured on the scalp at a position 3 cm anterior and 2.5 cm lateral (Bäumer et al. 2009), or 2.5 cm anterior to M1 (Mochizuki et al. 2004b) relative to the motor hotspot was determined. Given the limited distance between PMv and ipsilateral M1 (Bäumer et al. 2009), simultaneous stimulation without coil overlap is technically challenging. Thus, small custom-made figure-of-eight coils (e.g., 50 mm outer wing diameter) were used for applying the CS (Bäumer et al. 2009; de Beukelaar et al. 2016), TS (Lago et al. 2010), or both (Byblow et al. 2007; Koch et al. 2010b). Despite the use of small custom-made coils, there was still overlap between TS and CS coil in two studies (Bäumer et al. 2009; de Beukelaar et al. 2016). An exact description of the different orientations can be found in the appendix and a general overview is presented in Figures 4 and 5 for inter- and intrahemispheric interactions, respectively. Effective inter- and intra-hemispheric PMv–M1 connectivity has been examined in multiple studies using ds-TMS, of which an overview can be found in Tables 4 and 5, respectively.

Interhemispheric

At rest

Mochizuki et al. (2004b) demonstrated a reduction of left M1 excitability at rest after a CS was applied to right PMv 50–150 ms earlier. Likewise, Fiori et al. (2017) also investigated long-latency interhemispheric right PMv–left M1 interactions and found a robust influence of PMv on M1 with a slightly shorter ISI. In particular, a strong inhibitory influence on contralateral M1 excitability was identified at a 40 ms ISI after conditioning right PMv, with both a sub- (90% rMT) and supra-threshold (110% rMT) CS intensity. This finding was in line with other motor-related areas such as M1, SMA and DLPFC (Fiori et al. 2016; Ni et al. 2009). Moreover, interhemispheric inhibition appeared to be even more pronounced for right PMv–left M1 as compared to right M1–left M1 and right SMA–left M1 interactions. Further, in accordance with Mochizuki et al. (2004b), a later inhibitory episode was found when a suprathreshold CS (110% rMT) was applied over the right PMv at an ISI of 150 ms (Fiori et al. 2017). It should be noted that short-latency interhemispheric PMv–M1 interactions have not been investigated at rest. In addition, these interhemispheric interactions have only

Table 3: Overview of studies investigating intrahemispheric PMd–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Bäumer et al. (2009) [*N* = 11]	At rest	L PMd – P1: Point located at 8% of nasion–inion distance – P2: 5 cm anterior to motor hotspot and 6 cm lateral to the vertex (EEG 10–20 system) – P3: Coil as close to M1 as technically possible	L M1	– 80/90% aMT – 90/110% rMT	1 mV	2–10∗ ms	TS: fig8 (90 mm outer diameter) CS: fig8 (55 mm, ns) overlap between coils	AP	PA	R FDI	CS at P1 or P2: No L PMd–L M1 interaction CS at P3: – Inhibition L PMd–L M1 with CS intensity = 90% aMT (ISI = 8 ms) and CS intensity = 110% rMT (ISI = 2/4 ms) – No L PMd–L M1 interaction at 80% aMT and 90% rMT
Byblow et al. (2007) [*N* = 8]	– At rest – During tonic contraction of another limb (R ankle dorsiflexion/ plantar flexion)	L PMd	L M1	70–140% aMT	1 mV	6 ms	TS + CS: fig8 (50 mm outer wing diameter)	AP	PA	R ECR	– MEP amplitudes during dorsiflexion > during plantar flexion with CS intensity = 130% but not 90% aMT Iso-directional tonic ankle contraction: – Facilitatory L PMd–L M1 interaction with CS intensity = 90 or 130% aMT during dorsiflexion as compared to rest Non-iso-directional tonic ankle contraction: – No modulation of L PMd–L M1 interactions during plantarflexion as compared to rest

Table 3: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Civardi et al. (2001) [*N* = 16]	– At rest – During tonic contraction (10% MVC)	L Premotor area	L M1	– 90% aMT – 80–120% aMT	120% rMT	2–10∗/ 15 ms	TS + CS: fig8 (40 mm inner diameter)	– AP – PA	PA	R FDI	At rest: – Inhibitory L PMd–L M1 interaction with CS intensity = 90% aMT at ISI = 4 or 6 ms when CS current direction = AP (in brain) – Facilitatory L PMd–L M1 interaction with CS intensity = 120% aMT at ISI = 6 ms During tonic contraction: – Inhibition ↓ as compared to rest for CS intensity = 90% with ISI = 6 ms
Groppa et al. (2012a) [*N* = 18, only males]	At rest	L PMd	L M1	50/70/90% of TS intensity	0.5 mV	TS → CS: – 0.5/2.0–5.2‡ ms	TS + CS: fig8 (ns, custom-made, asymmetric wiring)	PA	PA	R FDI	– Facilitation L PMd–L M1 at ISI = 2.4, 2.8 or 4.4 ms, irrespective of CS intensity – The precise ISI to elicit facilitation differed across subjects
Groppa et al. (2012b) [*N* = 33]	– At rest – During tonic contraction (20% MVC) – During choice RT task	L PMd	L M1	– 70% rMT – 90% rMT	0.5 mV	TS → CS: 0.8–2.0‡ ms	TS + CS: fig8 (ns, custom-made, asymmetric wiring)	PA	PA	R FDI	At rest: facilitation L PMd–L M1 at ISI = 1.2 ms with CS intensity = 70 or 90% rMT During tonic contraction: No L PMd–L M1 interaction at any ISI During choice RT task: facilitation L PMd–L M1

Table 3: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
											following a 125 ms interval after stimulus onset when subject was required to respond with R but not L hand
Parmigiani et al. (2015) [*N* = 16]	During tonic contraction (lips)	L PMd – P1: Junction between superior precentral and superior frontal sulcus – P2: 1.5 cm ant. To P1 – P3: 3 cm ant. To P1	L $M1_{lip}$	120% aMT (orbicularis oris muscle)	120% aMT (orbicularis oris muscle)	CS → TS: 2/4/6/8 ms TS → CS: 1 ms	TS: fig8 (55 mm outer diameter) CS: fig8 (35 mm, ns)	ns	ns	R Orbicularis oris muscle	Inhibition L PMd–L M1 at ISI = 6 ms with CS applied over P2 but not P1 or P3
Parmigiani et al. (2018) [*N* = 16]	– During tonic contraction (lips) – During delayed simple RT task	L PMd	L $M1_{lip}$	120% aMT (orbicularis oris muscle)	120% aMT (orbicularis oris muscle)	CS → TS: 2/4/6/8 ms TS → CS: 1 ms	TS: fig8 (55 mm outer diameter) CS: fig8 (35 mm, ns)	ML	ns	R Orbicularis oris muscle	During tonic contraction: Inhibition L PMd–L $M1_{lip}$ with an ISI of 6 ms During delayed simple RT task: – Inhibition at 600 ms after start of action-withholding phase (for ISI = 6 ms) – Inhibition occurred at ±50% of action-withholding period, irrespective of its duration
Van Hoornweder et al. (2021) [*N* = 28]	At rest	L PMd	L M1	CS → TS: 75% rMT (or 60% MSO if rMT > 80% MSO) TS → CS: 90% TS	1 mV	CS → TS: 6 ms TS → CS: 2.8 ms	TS: fig8 (35 mm, ns; cooled coil) CS: Butterfly fig8 coil, ns	– LM – ML	PA	R FDI	*Males:* – Inhibition when TS → CS (ISI = 2.8 ms) with a LM- but not ML-directed CS current *Females:* – No interaction

Table 3: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Vesia et al. (2018) [*N* = 10]	During reaching and grasping (precision vs. whole-handgrip vs. touch only)	L PMd	L M1	90% aMT	1.5 mV (FDI) 1 mV (ADM)	4/6/8 ms	TS + CS: fig8 (ns) overlap between coils	ns	ns	R FDI & ADM	– Facilitation for FDI during the preparatory period of precision grip (all intervals) and whole-handgrip (ISI = 6 ms) relative to touch and rest – Facilitation for ADM only during whole-handgrip (ISI = 6 ms) relative to touch, precision grip and rest

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range. The following characters were used to indicate which increment size was used within a range: "∗" indicates 2 ms steps, "‡" indicates 0,4 ms steps, while 1 ms increments were considered default and therefore were not indicated by a character. ADM, abductor digiti minimi muscle; aMT, active motor threshold; ant., anterior; CS → TS, conditioning stimulus applied before test stimulus; CS, conditioning stimulus; FDI, first dorsal interosseus muscle; fig8, figure-of-eight coil; ISI, interstimulus interval; M1, primary motor cortex; M1lip, orofacial region of the primary motor cortex; ML, medial-to-lateral-directed current; ns, not specified; L, left; LM, lateral-to-medial-directed current; P, position; PMd, dorsal premotor cortex; R, right; rMT, resting motor threshold; RT, reaction time; TS → CS, conditioning stimulus applied after test stimulus; TS, test stimulus.

been examined from the non-dominant hemisphere to the dominant hemisphere (i.e., from right PMv to left M1) but not *vice versa*.

Task-related interactions

Response selection and adaptation task. Short interval interhemispheric PMv–M1 interactions (ISI = 8 ms) seem to be altered as a function of the behavioural context (Buch et al. 2010). More specifically, the right PMv exerted a facilitatory influence on left M1 during movement preparation and execution of reaching and grasping movements. However, when the intended motion needed to be adapted to an alternative movement, the right PMv inhibited contralateral M1 at 75 ms after the change of movement goal was announced (Buch et al. 2010).

Summary and discussion interhemispheric PMv–M1 interactions

In summary, the PMv has been demonstrated to exert an inhibitory influence over contralateral M1 at long latencies ranging from 40–150 ms (Fiori et al. 2017; Mochizuki et al. 2004a), using both subthreshold and suprathreshold CS intensities. To date, short latency interhemispheric PMv–M1 interactions have not been investigated in the resting brain. In addition, these interhemispheric interactions have only been examined from the non-dominant to the dominant hemisphere (i.e., from right PMv to left M1), but not vice versa. In the context of response selection and adaptation, however, respectively facilitation and inhibition can be observed at a short ISI depending on whether a planned movement must be performed or adjustment of movement is required (Buch et al. 2010). This inhibitory influence during reprogramming of a motor action was interpreted as a selective inhibition, decreasing the activity in the corticospinal neurons associated with the planned movement within M1, which minimizes the movement tendency of the intended action and subsequently has a beneficial effect on the proposed alternative movement (Buch et al. 2010). Furthermore, this modulatory influence of right PMv might be driven by the right hemisphere dominance in (stimulus-driven) spatial response selection (Schumacher et al. 2003; Serrien et al. 2006).

Intrahemispheric

At rest

In humans, the PMv–ipsilateral M1 pathway can be probed using short latencies, i.e., ISIs of 2–10 ms (Bäumer et al. 2009; Byblow et al. 2007; Davare et al. 2008, 2009; de Beukelaar et al. 2016; Koch et al. 2010b; Lago et al. 2010), with an ISI of 6 ms most frequently found to be effective at rest as well as during tonic muscle contraction and motor task preparation. However, no interactions for long-latency ISIs have been established for the intrahemispheric PMv–M1 pathway.

Besides the ISI duration, intrahemispheric PMv–M1 interactions seem to be dependent on the CS intensity. That is, stimulating the left PMv at low intensity (80–90% aMT) facilitates ipsilateral M1 (Bäumer et al. 2009; Lago et al. 2010) while stimulating PMv at higher intensities (80, 90 and 120% rMT) has an inhibitory effect on M1 (Bäumer et al. 2009; Davare et al. 2008; de Beukelaar et al. 2016). Hence, the influence of the CS intensity seems to be contrary to the ipsilateral PMd–M1 interaction, implying a functional segregation of efferent pathways originating, respectively, from PMv and PMd towards ipsilateral M1, in which the threshold for activating the facilitatory or inhibitory circuitry differs. Note that the parameters stated above might be specific for examining interactions related to the M1 representation of intrinsic hand muscles such as the FDI and ADM. In contrast, Byblow et al. (2007) did not report ipsilateral PMv–M1 interactions at rest while examining the right ECR, a forearm muscle.

Task-related interactions

Tonic contraction of the target muscle. Davare et al. (2008) investigated whether intrahemispheric PMv–M1 interactions were modulated by the execution of different types of tonic grasps, i.e., a sustained precision or power grip at 10% MVC. Their results indicated that the inhibitory influence from left PMv to left M1 was indeed selectively modulated by different types of grasps. More specifically, the inhibitory PMv–M1 interactions at rest were abolished during the performance of a power grip and even facilitated when participants performed a precision grip (Davare et al. 2008).

Tonic contraction of a muscle other than the target muscle. During a tonic contraction of the right ankle, Byblow et al. (2007) reported no modulation of the left PMv–M1 interaction in the right ECR. However, this study did not show any PMv–M1 modulation of the ECR at rest either, which might be due to different stimulation parameters of forearm muscles as compared to intrinsic hand muscles (Byblow et al. 2007).

Grasping movements. Davare et al. (2009) used a ds-TMS paradigm to probe PMv–M1 connectivity during grasping preparation. To do so, participants had to grasp either a pen or a disc requiring a precision grip or a whole handgrip respectively. During movement preparation, a CS was applied to left PMv followed by a TS over left M1 with an ISIs of 6 or 8 ms. When preparing for a precision grip, this

Table 4: Overview of studies investigating interhemispheric PMv–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (%)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Buch et al. (2010) [*N* = 14]	During response selection and adaptation (reaching and grasping movement)	R PMv	L M1	110% rMT	1 mV	8 ms	TS: fig8 (70 mm, ns) CS: fig8 (50 mm, ns)	ns	ns	R FDI & APB	– Facilitation during reaching and grasping preparation and execution after response selection – Inhibition when intended and initiated motion needed to be adapted to alternative movement (at 75 ms after change of target) – CS over PMv = delay in movement adaptation ↑
Fiori et al. (2017) [*N* = 15]	At rest	R PMv	L M1	– 90% rMT – 110% rMT	ns	40–120■/ 150	TS + CS: fig8 (50 mm, ns)	PA	PA	R FDI	– Inhibition at ISI = 40 ms with CS intensity = 90 or 110% rMT – Inhibition at ISI = 150 ms with CS intensity = 110% rMT
Mochizuki et al. (2004b) [*N* = 11]	At rest	R PMv	L M1	110% aMT	0.2–0.5 mV	50/100/ 150/200/ 300/ 400 ms	TS + CS: fig8 (70 mm outer diameter)	LM	PA	R FDI	Inhibition at ISI = 50–150 ms

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range. "■" was used to indicate an increment size of 20 ms. aMT, active motor threshold; ant., anterior; APB, abductor pollicis brevis muscle; CS, conditioning stimulus; FDI, first dorsal interosseus muscle; fig8, figure-of-eight coil; ISI, interstimulus interval; L, left; LM, lateral-to-medial-directed current; M1, primary motor cortex; MVC, maximal voluntary contraction; ns, not specified; PA, posterior-to-anterior-directed current; PMv, ventral premotor cortex; R, right; rMT, resting motor threshold; TS, test stimulus.

resulted in increased MEP amplitude in the FDI (i.e., a muscle playing a major role during precision grip) as compared to rest, whereas an augmented MEP amplitude in the ADM (i.e., a muscle engaged in whole handgrip), but not the FDI, was reporting when preparing for a whole handgrip. Hence, these modulations of M1 excitability during movement preparation indicate the role of PMv in the initial goal-encoding of upcoming actions. Moreover, the authors state that this facilitatory influence seems to be action- and muscle-specific as only MEPs of the hand muscles engaged in the upcoming grasp were modulated (Davare et al. 2008, 2009).

Observation of reaching and grasping movements. In a study by Koch et al. (2010b), intrahemispheric PMv–M1 interactions (CS = 90% rMT, ISI = 6 ms) within the left hemisphere were investigated during the observation of reaching and grasping movements. Participants watched three different clips of either a successful goal-directed grasping movement (i.e., the grasping posture did fit to the target object), an unsuccessful goal-directed grasping movement (i.e., the grasping posture did not fit the target object), or a neutral condition in which the object was shown but no grasping action was performed. As compared to rest, a facilitatory modulation of the left PMv–M1 interaction during the observation of 'successful' goal-directed reaching and grasping movements for the FDI and ADM during, respectively, pinch and whole hand grasping movement was shown, that was absent during the presentation of 'unsuccessful' movements (Koch et al. 2010b). Along the same line, de Beukelaar et al. (2016) confirmed that modulations in M1 excitability are specific to the type of grasp observed. More specifically, left PMv–M1 interactions (CS = 80% rMT, ISI = 7 ms) for ADM, but not FDI, were facilitated during the observation of a whole hand, as compared to precision, grip. Additionally, they even demonstrated anticipatory muscle-specific facilitation following a cue indicating whether participants were to observe a pinch or whole handgrip (de Beukelaar et al. 2016). In contrast, another study found that facilitatory PMv–M1 interactions within the left hemisphere at rest (CS intensity = 90% aMT, ISI = 6 ms) were modulated towards inhibition when observing naturalistic (i.e., closely imitating real-life movements) grasping movements (Lago et al. 2010).

The authors argue that, despite demonstrating the reverse phenomenon, their results still point to a specific modulation of PMv–M1 interactions occurring during the observation of a comparable action. Thus, in line with previous research, it might be suggested that the observation of naturalistic movement is mediated by the samecortical circuits as those involved in actual movement performance (Gangitano et al. 2001; Rizzolatti and Luppino 2001). These modulations did not occur during the observation of noxious grasping (i.e., a video showing a person reaching towards and preparing to grasp the end of a hot soldering iron) or during neutral videos (i.e., the table was demonstrated without the object or the reaching arm) (Lago et al. 2010). Such results imply a different modulation depending on the interpretation of an action and are in agreement with behavioural research showing a top–down regulation of internal motor representations in observers based on their interpretation of the observed action (Liepelt et al. 2008).

Summary and discussion intrahemispheric PMv–M1 interactions

Intrahemispheric PMv–M1 interactions can be probed at short latencies, with an ISI of 6 ms most frequently proven to be effective at rest as well as during tonic muscle contraction and motor task preparation. At rest, both inhibitory and facilitatory interactions can be elicited at short latencies, depending on the CS intensity. In contrast to intrahemisperic PMd–M1 interactions, stimulating the left PMv at low intensity (80–90% aMT) facilitates ipsilateral M1 (Bäumer et al. 2009; Lago et al. 2010), while stimulating PMv at higher intensities (80, 90 and 120% rMT) has an inhibitory effect on M1 (Bäumer et al. 2009; Davare et al. 2008; de Beukelaar et al. 2016). This might indicate a functional segregation between efferent pathways originating from, respectively, PMv and PMd towards ipsilateral M1. In contrast, Byblow et al. (2007) did not report ipsilateral PMv–M1 interactions at rest while examining the right ECR, a forearm muscle. PMv–M1 interactions as evoked by higher CS intensities (80–120% rMT), which were inhibitory at rest, turned into facilitation during the preparation, execution, or observation of grasping movements. In contrast, facilitatory PMv–M1 interactions as evoked by lower CS intensities (80–90% aMT), were reported to be facilitatory at rest and turned into inhibition during the observation of grasping movements. Furthermore, these modulations appear to be muscle-specific.

Lastly, it should be noted that, up to now, intrahemispheric PMv–M1 interactions have to date exclusively been examined in the dominant, left hemisphere at short but not long latencies.

DLPFC–M1 interactions

The dorsolateral prefrontal cortex (DLPFC) is located in the lateral part of Brodmann area (BA) 9 and 46, within the

Table 5: Overview of studies investigating intrahemispheric PMv–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Bäumer et al. (2009) [*N* = 24]	At rest	L PMv	L M1	– 80/90% aMT – 90/110% rMT	1 mV	2–10∗ ms	TS: fig8 (90 mm outer diameter) CS: fig8 (55 mm, ns) overlap between coils	AP	PA	R FDI	– Facilitatory L PMv–L M1 interaction with CS intensity = 80% aMT at ISI = 4, 6 or 8 ms (strongest at 6 ms) – No L PMv–L M1 interaction at CS intensity = 90% aMT – Inhibitory L PMv–L M1 interaction with CS intensity = 90% rMT at ISI = 2, 4 or 6 ms (strongest at 4 ms) – Inhibitory L PMv–L M1 interaction with CS intensity = 110% rMT at ISI = 2, 4 or 10 ms
Byblow et al. (2007) [*N* = 8]	– At rest – During tonic contraction of a muscle other than the target muscle (R ankle dorsiflexion/plantar flexion)	L PMv	L M1	70–140% aMT	1 mV	6 ms	TS + CS: fig8 (50 mm outer diameter)	AP	PA	R ECR	No L PMv–L M1 interaction at rest or tonic contraction of a muscle other than the target muscle (ankle)
Davare et al. (2008) [*N* = 7]	– At rest – During tonic contraction (precision and power grip, 10% MVC)	L PMv	L M1	80% rMT	120% rMT	1/2/4/6/8/10/15 ms	TS + CS: fig8 (70 mm outer diameter)	AP	PA	R FDI	At rest: inhibitory L PMv–L M1 interaction at ISI = 6 or 8 ms During tonic contraction (grip): – Facilitatory L PMv–L M1 interaction during precision grip at ISI = 6 or 8 ms – Disinhibition L PMv–L M1 during power grip at ISI = 6 or 8 ms
Davare et al. (2009) [*N* = 11]	During grasping preparation (precision and power grip)	L PMv	L M1	80% rMT	120% rMT	1/2/4/6/8/10/15 ms	TS + CS: fig8 (70 mm outer diameter)	AP	PA	R FDI R ADM	Facilitatory L PMv–L M1 interaction at ISI = 6 or 8 ms ISI: – For FDI during preparation period of precision grip – For ADM during preparation period of whole handgrip
de Beukelaar et al.	– At rest	L PMv	L M1	80% rMT	– 120% rMT – 0.5–1 mV	7 ms	TS: fig8 (70 mm, ns) CS: fig8	ns	PA	R FDI R ADM	At rest: facilitatory L PMv–L M1 interaction with CS intensity = 80% rMT at ISI = 7 ms

Table 5: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
(2016) [*N* = 16]	– During movement observation (grasping movement)						(50 mm, ns) overlap between coils				During observation of grasping movement: Facilitation in ADM during grasping phase observation of whole hand, but not precision, grip
Koch et al. (2010b) [*N* = 16]	During movement observation (reaching and grasping movements)	L PMv	L M1	90% rMT	1 mV	6 ms	TS + CS: fig8 coil (50 mm outer diameter)	ns	PA	R FDI R ADM	– Facilitation only for FDI during observation of a pinch grip – Facilitation only for ADM during observation of a whole handgrip
Lago et al. (2010) [*N* = 11]	– At rest – During movement observation (naturalistic/noxious reaching and grasping movements)	L PMv	L M1	90% aMT	1 mV	6 ms	TS: fig8 coil (50 mm∗) CS: fig8 coil (70 mm∗) ∗ outer diameter	ns	PA	R FDI	At rest: facilitatory L PMv–L M1 interaction During observation of reaching and grasping movement: Inhibition at the end (last frame) relative to start of the video when observing of a naturalistic grasp, but not noxious grasp or neutral videos

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range: "∗" was used to indicate 2 ms increments. ADM, abductor digiti minimi muscle; aMT, active motor threshold; AP, anterior-to-posterior-directed current; CS, conditioning stimulus; FDI, first dorsal interosseus muscle; fig8, figure-of-eight coil; ISI, interstimulus interval; L, left; M1, primary motor cortex; MVC, maximum voluntary contraction; ns, not specified; PA, posterior-to-anterior-directed current; PMv, ventral premotor cortex; R, right; rMT, resting motor threshold; TS, test stimulus.

prefrontal cortex of the human brain (Brodmann 1909; Mylius et al. 2013). In addition to its role in cognition, the DLPFC is involved in various aspects of complex motor control mechanisms and fulfills a central integrative and executive role in motor regulation and behaviour (Miller 2000). More specifically, it plays an important role in higher-order control processes that, based on conditional actions, govern the selection between multiple competing movement alternatives and stimuli (Duque et al. 2012; Lucci et al. 2014; Petrides 2005; Rowe et al. 2000, 2005). Moreover, it is involved in the selection of information relevant to the upcoming task by integrating information from the working memory with the planning of upcoming motor actions (Brass and von Cramon 2004; Fuster 2001; Pochon et al. 2001) by transforming conceptual information into a specific motor plan (Duque et al. 2012; Miller and Cohen 2001). Furthermore, the DLPFC plays an essential role in both the planning and execution of complex bimanual tasks (e.g.,Beets et al. 2015; Fujiyama et al. 2016a; Remy et al. 2008) and has been demonstrated to be involved in proactive inhibitory control (e.g., Jahanshahi et al. 2015) and response reversal (Mitchell et al. 2008).

As regards the pathway mediating interhemispheric DLPFC–M1 interactions, transcallosal pathways via either ipsilateral M1 (e.g., $DLPFC_{left}$–$M1_{left}$–$M1_{right}$) or via its contralateral homologue (e.g., $DLPFC_{left}$–$DLPFC_{right}$–$M1_{right}$) are considered possible (Fujiyama et al. 2016b; Ni et al. 2009). However, there is only limited evidence for the presence of direct anatomical connections between DLPFC and ipsilateral M1 (Bates and Goldman-Rakic 1993; Xiao et al. 2009; Yeterian et al. 2012), while a transcallosal connection, at the rostrum level, between homologous DLPFCs was demonstrated in healthy humans (Sisti et al. 2012). Therefore, the 'DLPFC–$DLPFC_{contralateral}$–M1'-pathway may be more plausible. Similar to interhemispheric DLPFC–M1 interactions, structural (and physiological) evidence suggests that DLPFC and ipsilateral M1 are interconnected via several indirect pathways since anatomical studies in non-human primates provide limited evidence for direct connections between DLPFC and the ipsilateral M1 (Bates and Goldman-Rakic 1993; Xiao et al. 2009; Yeterian et al. 2012). More specifically, DLPFC might modulate M1 excitability via the rostral portions of the PMd, the (pre-)SMA, or other motor-related brain regions, each acting as a relay between M1 and DLPFC (Johansen-Berg et al. 2004; Miller and Cohen 2001; Picard and Strick 2001). In addition, the basal ganglia might act as a mediator for aspects of movement and cognitive function as there are parallel loops connecting the basal ganglia to both the (pre)motor and prefrontal cortex (Middleton and Strick 2000) with specifically dense structural interconnections between the DLPFC and the basal ganglia (Alexander 1986; Jahanshahi et al. 2015; Middleton and Strick 1994). Lastly, pathways connecting the DLPFC to different motor nuclei in the thalamus have been demonstrated (Guillery 2003; Strick 1985; Xiao et al. 2009; Zikopoulos and Barbas 2006). Hence, PMd, pre-SMA, basal ganglia and thalamus potentially act as relays, indirectly providing input for the DLPFC–M1 interaction.

In line with standard procedures of DLPFC targeting, the optimal position for DLPFC stimulation with TMS was based on (1) a fixed distance (i.e., 5 cm anterior) relative to M1 (Ni et al. 2009; Uehara et al. 2013; Wang et al. 2020). Nonetheless, this method has been shown to be inaccurate as the distance between the DLPFC and M1 is often underestimated and the technique does not take into account interindividual anatomical variability (Ahdab et al. 2010; Herwig et al. 2001). Alternatively (2) an anatomical MRI scan in combination with neuronavigation was used to target the DLPFC. Using MRI, DLPFC was either based on individual landmarks along the middle frontal gyrus (Brown et al. 2019; Fujiyama et al. 2016a; Mylius et al. 2013), or Talairach coordinates ([*x*, *y*, *z*]: –40, 28, 30) corresponding to BA 46 (Hasan et al. 2013). Coil orientations are visualized in Figures 4 and 5 for inter- and intra-hemispheric interactions, respectively. A detailed description of all different orientations can be found in the appendix.

To avoid coil overlapping when targeting DLPFC and M1 within one hemisphere simultaneously, small custom-made figure-of-eight CS coils were used (Hasan et al. 2013), sometimes combined with a TS coil of equal size (Brown et al. 2019; Wang et al. 2020). Furthermore, both Brown et al. (2019) and Wang et al. (2020) used 'branding iron' figure-of-eight coils (i.e., with the handle perpendicular to the plane of the coil) to better enable the placement of both coils on their optimal position within the same hemisphere.

Even though the DLPFC is often targeted during therapeutic (repetitive) TMS applications [e.g., (Mosimann et al. 2004)], to date, effective DLPFC–M1 connectivity has only been investigated to a limited extent using ds-TMS. An overview of all studies investigating interhemispheric interactions between DLPFC and contralateral M1 included in this review is provided in Table 6 and between DLPFC and ipsilateral M1 in Table 7.

Interhemispheric

At rest

Ni et al. (2009) examined interhemispheric connectivity between right DLPFC and left M1. Interestingly, interhemispheric DLPFC–M1 interactions could only be elicited at long latencies (ISIs = 30–60 ms) when a suprathreshold

CS (120–200% aMT) was used, regardless of the CS current direction (AP, PA, ML or LM). Further, stronger CS intensities seemed to increase inhibition (Ni et al. 2009). Accordingly, Fujiyama et al. (2016a,b) reported inhibitory interhemispheric DLPFC–M1 interactions at rest (CS intensity = 140% rMT, ISI = 60 ms), either when assessed from the left to the right hemisphere and vice versa. In contrast, Uehara et al. (2013) did not find a significant inhibitory/facilitatory right DLPFC–left M1 interaction at rest using the same stimulation parameters, however, coil orientations were slightly different.

Task-related interactions

Tonic and rhythmic contraction of the muscle contralateral to the target muscle. Interhemispheric interactions between right DLPFC and left M1 at long latencies were not modulated during sustained tonic contraction of the muscle contralateral to the target muscle. Similarly, rhythmic contractions with the left hand at different frequencies did not affect the right DLPFC–left M1 interaction (Uehara et al. 2013). Note that this study also failed to find any long-latency DLPFC–M1 interaction at rest.

Bimanual tracking task. Long- latency DLPFC–M1 interactions both from left DLPFC to right M1, and vice versa, were found to be facilitated during movement preparation of a bimanual tracking task relative to rest (Fujiyama et al. 2016a). Furthermore, the interaction became more facilitatory during complex (i.e., each hand moves at a different speed) but not during easier (i.e., both hands move at the same speed) task conditions. Interestingly, a greater relative facilitatory change of the DLPFC–M1 interaction throughout the preparatory period predicted better complex bimanual performance at movement initiation. Accordingly, these results reflect the vital role of DLPFC during the preparation period of complex bimanual movements (Fujiyama et al. 2016a). These findings might suggest that the DLPFC acts as a cognitive control mechanism for supporting complex motor actions.

Summary and discussion interhemispheric DLPFC–M1 interactions

At rest, inhibitory interhemispheric DLPFC–M1 interactions, from the left to the right hemisphere and vice versa, could only be elicited at long latencies (i.e., ISIs between 30 and 60 ms) when a suprathreshold CS was applied, regardless of the CS current direction (Fujiyama et al. 2016a; Ni et al. 2009). Moreover, stronger CS intensities seemed to increase IHI (Ni et al. 2009). Yet, Uehara et al. (2013) did not find a significant inhibitory/facilitatory right DLPFC–left M1 interaction at rest using approximately the same stimulation parameters. This difference in results might be attributed to the use of different coil orientations.

Regarding task-related DLPFC–M1 interactions both from the left to the right hemisphere and vice versa, a facilitatory modulation during the preparatory period is present in anticipation of complex, but not easy, bimanual movements and this is related to performance quality. In contrast, long-latency right DLPFC–left M1 interactions are not modulated during both tonic and rhythmic contraction of the target muscle. These results underscore the vital role of the DLPFC during the preparation phase of complex bimanual movements: while no DLPFC modulation could be noticed during tasks that do not require substantial movement planning, such as easy (isofrequency) task variants of a bimanual task as well as during tonic and rhythmic contractions, the interhemispheric DLPFC–M1 interaction was facilitated as a result of the need to prepare a more complex bimanual task with different movement speeds for each hand (Fujiyama et al. 2016a; Uehara et al. 2013).

Intrahemispheric

At rest

Brown et al. (2019) examined the connectivity between DLPFC and ipsilateral M1 within both the left and the right hemisphere. Their results indicated neither an inhibitory nor a facilitatory influence of DLPFC conditioning on ipsilateral M1 at rest, irrespective of the investigated hemisphere and ISI (i.e., 4–12, 15 and 20 ms) or CS intensity (i.e., 80 and 120% rMT) (Brown et al. 2019). In line with the results of Brown et al. (2019), Wang et al. (2020) found no DLPFC–M1 interaction for the right hemisphere. However, for the left hemisphere, an inhibitory DLPFC–M1 interaction was identified with slightly different stimulation parameters to those of Brown et al. (2019) (ISI = 2, 10–20 ms, CS intensity = 110% rMT) (Wang et al. 2020).

Task-related interactions

Tonic contraction of the target muscle. Consistent with their findings at rest, Brown et al. (2019) did not find any DLPFC–M1 interactions for either hemisphere during a tonic contraction of the target muscle, irrespective of ISI and CS intensity (Brown et al. 2019).

Choice reaction time task. In a ds-TMS study conducted by Hasan et al. (2013), functional left DLPFC–left M1 connectivity was probed during a choice RT task. During this task,

Table 6: Overview of studies investigating interhemispheric DLPFC–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coil (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Fujiyama et al. (2016a) [*N* = 15]	During bimanual coordination task	– R DLPFC – L DLPFC	– L M1 – R M1	140% rMT	1 mV	60	TS + CS: fig8 (50 mm outer diameter)	ns	PA	L & R FDI	– Facilitation DLPFC–M1 (both directions) only during preparatory period of complex (non-isofrequency) conditions – Magnitude of bilateral DLPFC–M1 modulations positively correlated with task performance during first 2 s
Ni et al. (2009) [*N* = 12]	At rest	R DLPFC	L M1	– 1 mV – 60–200% aMT	1 mV	4–12*/ 16/20–60▼/80/ 100 ms	TS: fig8 (95 mm*) CS: fig8 (80 mm*) *Outer diameter Overlap between coils in some subjects (ant. And post. Direction)	– LM – ML – PA – AP	PA	R FDI	Inhibition only at ISI = 30, 40, 50 or 60 ms but not at shorter or longer ISIs, irrespective of CS intensity and CS current direction
Uehara et al. (2013) [*N* = 8]	– During tonic contraction (L, 10% MVC) – During rhythmic contraction (L, 10% MVC, 1/2/3 Hz)	R DLPFC	L M1	120/140% rMT	1 mV	60	TS + CS: fig8 (90 mm outer diameter)	ns	ns	R FDI	During tonic contraction: No modulation of R DLPFC–L M1 relative to rest During rhythmic contraction: No modulation of R DLPFC–L M1 during rhythmic muscle contraction as compared to rest, irrespective of frequency

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range. The following characters were used to indicate which increment size was used within a range: "*" indicates 2 ms steps and "▼" indicates 10 ms increments. aMT, active motor threshold; ant., anterior; CS, conditioning stimulus; DLPFC, dorsolateral prefrontal cortex; FDI, first dorsal interosseous muscle; fig8, figure-of-eight coil; ISI, interstimulus interval; L, left; LM, lateral-to-medial-directed current; M1, primary motor cortex; ML, medial-to-lateral-directed current; MVC, maximum voluntary contraction; ns, not specified; PA, posterior-to-anterior-directed current; post., posterior; R, right; rMT, resting motor threshold; TS, test stimulus.

participants were asked to react, with their right hand, to a cue indicating either a specified finger movement (i.e., a button press with the index, middle, ring, or little finger) or a free choice trial. The MEP amplitude was measured for the FDI (i.e., a muscle involved in the task) and abductor pollicis brevis (APB) (i.e., a non-involved muscle). Their results indicated a timing- and muscle-specific facilitatory intrahemispheric DLPFC–M1 interaction at an ISI of 12 ms. More specifically, DLPFC–M1 interactions as measured in a non-involved muscle (i.e., APB) were facilitated for the specified choice task variant when the CS was applied at 75 ms after stimulus onset, while they were facilitated at 100 ms following stimulus onset during free choice task variants. In contrast, no difference between specified and free-choice tasks was observed for the FDI. More specifically, MEPs in the right FDI increased after conditioning left DLPFC in trials where the FDI was engaged as compared to other finger movements, independent of both condition (i.e., specified vs. free choice) and timing of the CS (75, 100, 125 ms after stimulus onset) (Hasan et al. 2013).

Summary and discussion intrahemispheric DLPFC–M1 interactions

Although intrahemispheric DLPFC–M1 interactions are suggested to be indirect, the precise pathway is still unclear. Studies that targeted this interaction with ds-TMS are scarce and there is still some ambiguity. While Wang et al. (2020) suggested hemispheric differences at rest, with the DLPFC exerting an inhibitory influence on M1 in the left hemisphere but no modulatory influence in the right hemisphere, Brown et al. (2019) could not demonstrate intrahemispheric interactions in either the left or right hemisphere. This might be explained by the slight difference in the CS intensity used or by the use of a craniometric method to define the target location, which did not allow for possible differences in the gyral pattern in the DLPFC to be taken into account.

Similar to interhemispheric interactions, it was suggested that the intrahemispheric DLPFC–M1 interaction is only modulated during complex movements that require higher cognitive control but not during a tonic contraction of the target muscle (Uehara et al. 2013). Indeed, DLPFC–M1 interaction was shown to be modulated in a muscle and task-specific manner during the preparation period of a choice RT task (Hasan et al. 2013). Further research is needed to gain more insight into the function of intrahemispheric DLPFC–M1 connectivity, as well as into the anatomical pathways that mediate these connectivity patterns.

SMA–M1 interactions

The (pre-)SMA is situated in the dorsomedial frontal cortex as part of the medial aspect of the human brain (Picard and Strick 1996). It appears to be a rather complex target for TMS as compared to the lateral premotor cortex for example (Reis et al. 2008). Even though stimulation of SMA is feasible, there is only a limited number of studies targeting interhemispheric SMA–M1 interactions in healthy participants. Remarkably, intrahemispheric interactions between (pre-)SMA and ipsilateral M1 were investigated more extensively.

Regarding its function, the supplementary motor complex is typically involved in motor tasks offering a wide range of possible actions that are ambiguously specified or determined by the external environment. Some examples are tasks, in which the response is either self-initiated or externally triggered, either learned or unlearned, or tasks where switching between different action possibilities is required (Nachev et al. 2008; Tanji 1996). Furthermore, the pre-SMA and SMA is known to play an important part in numerous motor functions such as movement preparation (Nachev et al. 2008), interlimb (including bimanual) coordination (Brinkman 1981; Debaere et al. 2001, 2004; Donchin et al. 1998; Heuninckx et al. 2004; Kermadi et al. 2000; Nakagawa et al. 2016), and in movement sequencing tasks (Debaere et al. 2001; Donchin et al. 2002; Duque et al. 2010; Immisch et al. 2001; Kermadi et al. 1998; Sadato et al. 1997; Stephan et al. 1999; Swinnen 2002; Toyokura et al. 1999; Ullén et al. 2003). Moreover, it plays a vital role, e.g., in response inhibition (Aron et al. 2007; Aron and Poldrack 2006; Coxon et al. 2012; Mostofsky et al. 2003; Simmonds et al. 2008), response selection (Carbonnell et al. 2004; Mars et al. 2009; Oliveri et al. 2003) and temporal organization of multiple motor actions including hand-foot coordination (Byblow et al. 2007; Debaere et al. 2001; Heuninckx et al. 2004; Nakagawa et al. 2016).

Studies in both humans and monkeys show a reciprocal connection between the SMA and both ipsi- and contralateral M1 (Dea et al. 2016; Dum 2005; Hamadjida et al. 2016; Luppino et al. 1993; Muakkassa and Strick 1979). However, the SMA has more intra- as compared to interhemispheric connections with M1, as demonstrated in non-human primates (Rouiller et al. 1994). Therefore, although both are possible, an indirect pathway via ipsilateral M1 (e.g., SMA_{right}–$M1_{right}$–$M1_{left}$) might be more plausible than a direct (e.g., SMA_{right}–$M1_{left}$) pathway in mediating interhemispheric SMA–M1 interactions. Alternatively, it was

Table 7: Overview of studies investigating intrahemispheric DLPFC–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	Intensity CS (% or MEP amplitude in mV)	Intensity TS (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction TS (in brain)	Current direction CS (in brain)	Target muscle	Main results
Brown et al. (2019) [*N* = 12]	– At rest – During voluntary contraction (20% MVC)	– L DLPFC – R DLPFC	– L M1 – R M1	– 80% rMT – 120% rMT	1 mV	4–12∗/ 15/20 ms	TS: fig8 (50 mm∗) CS: fig8 (40 mm∗) ∗Inner diameter	PA	AP	– R FDI – L FDI	No interaction L DLPFC–L M1 or R DLPFC–R M1 at any studied ISI or CS intensity, both at rest and during tonic contraction
Hasan et al. (2013) [*N* = 7–10 (subexperiments)]	During choice RT task (button press with 2nd–5th finger, instructed choice vs. free choice)	L DLPFC (= BA 46) (BA 9 as control region)	L M1	105% rMT	1 mV	6/8/ 12 ms	TS: fig8 (70mm∗) CS: fig8 (50 mm∗) ∗Outer diameter	ns	ns	R FDI R APB	Involved muscle (FDI): Facilitation during index, but not other, finger movements, independent of timing (75, 100, 125 ms after stimulus onset) or condition (instructed vs. free choice) Non-involved muscle (APB): Facilitation for APB, but not FDI, at all ISIs examined but most dominantly at ISI = 12 ms: – At 75 ms after stimulus onset during instructed choice tasks – At 100 ms after stimulus onset during free choice task – No BA 9–M1 interactions were found for the same experimental setup
Wang et al. (2020) [*N* = 14]	At rest	– L DLPFC – R DLPFC	– L M1 – R M1	110% rMT	1 mV	2–10∗/ 15–30△ ms	TS + CS: fig8 (40mm, ns)	PA	AP	– R FDI – L FDI	– Inhibition L DLPFC → L M1 at ISIs of 2, 10, 15 and 20 ms – No R DLPFC–L M1 interaction at any ISI

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range. A "∗" was used to indicate "∗" indicates 2 ms increments. AP, anterior-to-posterior-directed current; APB, abductor pollicis brevis muscle; BA, Brodmann area; CS, conditioning stimulus; DLPFC, dorsolateral prefrontal cortex; FDI, first dorsal interosseus muscle; fig8, figure-of-eight coil; ISI, interstimulus interval; L, left; M1, primary motor cortex; ns, not specified; PA, posterior-to-anterior-directed current; R, right; rMT, resting motor threshold; RT, reaction time; TS, test stimulus.

shown that the projections from the SMA to M1 are less substantial than its projections to PMd and PMv. Hence, the SMA's strongest influence on contralateral M1 might be exerted via other nodes such as PMd and/or PMv. It should be noted that evidence indicating that interhemispheric interactions between SMA and M1 are mediated by either one or more of these pathways is currently lacking. Concerning the anatomical connectivity of intrahemispheric interactions, however, a reciprocal connection between the SMA and ipsilateral M1 exists, both in human and non-human primates (Dum and Strick 1991; Geyer et al. 2000a; He et al. 1995; Johansen-Berg et al. 2004; Liu et al. 2002; Muakkassa and Strick 1979).

In order to determine the optimal target position, the SMA was defined as a point measured on the scalp at a specific position relative to the motor hotspot or the vertex, according to the 10–20 EEG system (Klem et al. 1999). In particular, the CS coil was placed anterior to the vertex on the mid-sagittal line in most studies included (Arai et al. 2012; Fiori et al. 2017; Mars et al. 2009; Oliveri et al. 2003), with the exception of three studies in which the coil was placed 6 cm anterior to M1 (Byblow et al. 2007) and 3 cm anterior to tibialis anterior (TA) hotspot on the mid-sagittal line (Shirota et al. 2012), or alternatively, the target location was based on anatomical landmarks obtained from an individual MRI scan, i.e., positioned over the dorso-medial frontal cortex near the paracentral sulcus and relatively in line with the vertical anterior commissure (Picazio et al. 2014). The distance between the coil and the vertex, however, did vary significantly between the different studies targeting either SMA proper or pre-SMA, i.e., 2–4 cm (Oliveri et al. 2003), 3 cm (Shirota et al. 2012), and 4 cm (Arai et al. 2012; Fiori et al. 2017; Mars et al. 2009), and authors used a different nomenclature (pre-SMA vs. SMA) although the same region was targeted (Arai et al. 2012; Mars et al. 2009). Coil orientations are visualized in Figures 4 and 5 for inter- and intrahemispheric interactions, respectively. A detailed description of all coil orientations is provided in the appendix.

It is argued that a discrete anatomical distinction between the different subregions of the supplementary motor complex (i.e., pre-SMA and SMA) might not exist (Nachev et al. 2008). In particular, there may be a rostro-caudal continuum, deriving from the SMA proper via the supplementary eye field (SEF), to the pre-SMA, forming an ordered modification in structure and function rather than distinct subregions (Nachev et al. 2008). For the sake of simplification and inconsistencies in nomenclature, we will summarize both SMA proper and pre-SMA under the term SMA. It should be noted, however, that while the SMA proper is anatomically connected to M1, the pre-SMA projects to prefrontal brain regions (Bates and Goldman-Rakic 1993; Lu et al. 1994; Luppino et al. 1993). Furthermore, both subregions demonstrate a differential activation pattern, suggesting the pre-SMA has a role similar to prefrontal areas rather than motor areas (Picard and Strick 2001). As such, the interpretation requires caution.

Regardless of the fact that the midline (i.e., a point anterior to the vertex) was stimulated, a distinction was made between both left and right SMA, and subsequently, between inter- and intra-hemispheric interactions. As the spatial resolution of TMS requires a distance of at least 10 mm between the two targets (Brasil-Neto et al. 1992; Sliwinska et al. 2014) to avoid involuntary stimulation, it may not be possible to stimulate both left and right SMA regions independently from each other since they border at the level of the vertex (Oliveri et al. 2003). Hence, there seems to be inconsistency about which specific region is stimulated. Therefore, results should be interpreted with care.

Tables 8 and 9 provide a summary of all studies investigating, respectively, inter- and intra-hemispheric interactions between SMA and M1 included in this review.

Interhemispheric

At rest

At rest, a CS of both subthreshold (90% rMT) and suprathreshold (110% rMT) intensity applied over the right SMA had an inhibitory effect on the contralateral M1 at an ISI of 40 ms. However, at an ISI of 150 ms, MEPs elicited following a CS of subthreshold intensity were smaller (tendency towards inhibition) as compared to MEPs elicited following a CS of suprathreshold intensity (tendency towards facilitation) (Fiori et al. 2017). It should be noted that short-latency interactions between SMA and contralateral M1 have not yet been investigated but might exist, comparable to those between other motor-related regions (e.g., PMd and PMv) and M1.

Task-related interactions

Go/NoGo task. Using a ds-TMS paradigm combined with a behavioural Go/NoGo task, Picazio et al. (2014) attempted to elucidate the underlying role of SMA–M1 interactions. Following the presentation of a fixation cross, participants pressed a key, using their right index finger, after the presentation of a triangle pointing either up or down ('Go' trial). When the presented triangle pointed left or right, however, subjects had to restrain their initial reaction ('NoGo' trial). The results indicated a facilitatory influence of right SMA on contralateral M1 only during the early preparatory period of 'NoGo' (i.e., 50, 100 and 150 ms after stimulus onset) but not 'Go' trials (Picazio et al. 2014).

Summary and discussion interhemispheric SMA–M1 interactions

In short, connectivity between SMA and contralateral M1 has to date only been examined to a limited extent using ds-TMS. Therefore, it is difficult to make general statements. At rest, the SMA was found to exert an inhibitory influence on contralateral M1 at a long-latency (i.e., 40 ms). At an even longer ISI of 150 ms, a significant difference between sub- and supra-CS intensities emerges (Fiori et al. 2017). It is likely that short-latency interactions between SMA and contralateral M1 exist as there is a direct anatomical connection between the two regions, but to date, these have not been investigated yet (Dea et al. 2016; Dum 2005; Hamadjida et al. 2016; Luppino et al. 1993; Muakkassa and Strick 1979).

In the context of motor tasks, the interhemispheric influence of SMA on contralateral M1 has only been examined in the preparatory period of a Go/No Go task, during which it appears to be modulated in the context of response inhibition, revealing a facilitatory interaction for 'NoGo' but not for 'Go' trials (Picazio et al. 2014).

Intrahemispheric

At rest

At rest, Shirota et al. (2012) used a ds-TMS paradigm for demonstrating the interaction between left SMA and left M1. In contrast to non-human primate studies, which demonstrated early excitatory responses in M1 following ipsilateral SMA conditioning (Aizawa and Tanji 1994; Tokuno and Nambu 2000), stimulating SMA did not influence M1 excitability in humans (Shirota et al. 2012). As a possible explanation for their findings, the authors stated that a CS intensity of 100% aMT, as measured in the TA muscle, may be inadequate to influence M1 excitability to a considerable degree (Shirota et al. 2012). This could indeed have been the case as Arai et al. (2012) found a facilitatory SMA–ipsilateral M1 interaction, within the dominant hemisphere, only with a CS intensity of 140% aMT but not 90% aMT, as measured in the FDI muscle. Furthermore, this SMA–M1 facilitatory effect occurred solely with an anterior–medial-directed TS current induced in M1 and a lateral-directed CS current induced in the SMA (Arai et al. 2012). However, earlier studies investigating left SMA–M1 intrahemispheric interactions demonstrated an inhibitory influence on left M1 following a CS with an intensity of 90% aMT as measured in the ECR (Byblow et al. 2007) but not with a CS of higher or lower intensity (Byblow et al. 2007). As different muscles have been used to investigate SMA–M1 connectivity, comparison and/or interpretation of the results is difficult. For example, there are several

Table 8: Overview of studies investigating interhemispheric SMA–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Fiori et al. (2017) [$N = 15$]	At rest	SMA	L M1	90/110% rMT	1 mV	40–120■/ 150 ms	TS + CS: fig8 (50 mm, ns)	AP	PA	R FDI	Inhibition at ISI = 40 ms, irrespective of CS intensity
Picazio et al. (2014) [$N = 15$]	During Go/ NoGo task	R SMA	L M1	90% rMT	1 mV	6 ms	TS + CS: fig8 (70 mm outer diameter)	LM	PA	R FDI	Facilitation at 50, 100, and 150 ms interval following stimulus onset 'NoGo' but not 'Go' trials, as compared to rest

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range. A "■" was used to indicate 20 ms increments within a range. AP, anterior-to-posterior-directed current; CS, conditioning stimulus; FDI, first dorsal interosseus muscle, PA, posterior-to-anterior-directed current; fig8, figure-of-eight; ISI, interstimulus interval; L, left; LM, lateral-to-medial-directed current; M1, primary motor cortex; R, right; rMT, resting motor threshold; SMA, supplementary motor area; TS, test stimulus.

challenges associated with stimulating muscles in the lower limb (e.g., TA) including the deeper location of lower limb muscle representations concerning the TMS coil and therefore requiring a higher stimulation intensity (Kesar et al. 2018), and dissimilarities between the orientation of corticospinal axons of upper and lower limb muscles within M1.

With regard to the ISI, all studies reviewed except for one (Shirota et al. 2012) showed that a 6 ms ISI was most optimal for measuring intrahemispheric SMA–M1 interactions both at rest and during a task (Arai et al. 2012; Byblow et al. 2007; Mars et al. 2009). In contrast, Oliveri et al. (2003) did not test a 6 ms ISI but selected an ISI of 4 ms, based on the time necessary for neuronal activation to spread from motor to premotor areas within the same hemisphere (Ilmoniemi et al. 1997).

Task-related interactions

Tonic contraction of the target muscle. Facilitatory ipsilateral SMA–M1 interactions demonstrated at rest were found to disappear during a tonic contraction of the target muscle (Arai et al. 2012).

Tonic contraction of a muscle other than the target muscle. Byblow et al. (2007) examined the distinct functional interactions between left SMA, left PMd, and left PMv on the one hand and ipsilateral M1 on the other hand, at rest and during tonic contractions of the ankle (plantarflexion or dorsiflexion). While, at rest, an inhibitory left SMA–left M1 interaction (CS intensity = 90% aMT) was found, MEPs, measured in the ECR, were facilitated during both ankle dorsiflexion and plantarflexion. This non-specific modulation of resting-state inhibition may be interpreted as relevant in the production of hand-foot coordination by maintaining posture, as suggested by the authors (Byblow et al. 2007). Furthermore, conditioning SMA at 130% aMT resulted in a higher MEP amplitude during plantarflexion as compared to MEPs obtained during dorsiflexion or rest. However, this difference in MEP amplitude was suggested to be due to a suppression of M1 excitability both at rest and during dorsiflexion rather than a facilitatory SMA–ipsilateral M1 interaction during plantarflexion (Byblow et al. 2007).

Response selection and adaptation task. The timing of the modulation of the left SMA–left M1 interaction in a response selection and adaptation task was probed in a study by Mars et al. (2009). Participants had to respond to a red or green colored cue with their left or right index finger. More specifically, for each trial, each index finger was randomly assigned the color red or green, which was presented together with a warning signal. This was followed by a red or green colored 'Go' signal, indicating a movement of the corresponding finger. As trials with the same 'Go' signal color were presented in blocks of variable length, participants could anticipate and prepare their response ('stay' trials). However, when the color of the 'Go' signal changed in between blocks ('switch' trials), an adaptation of the prepared response was required. Their results demonstrated a facilitatory left SMA–ipsilateral M1 modulation for 'switch' trials at 125 ms after the 'Go' signal as compared to single-pulse TMS to M1, but none for 'stay' trials. The authors concluded that SMA–M1 interactions are modulated during response selection tasks when adaptation is needed (Mars et al. 2009).

Action selection task (emotionally unpleasant stimuli). Based on the hypothesis of Goldberg (1985), which states that the SMA is mainly responsible for the control of internally triggered movements (Debaere et al. 2004; Swinnen and Wenderoth 2004), while movements triggered by external stimuli are processed by the premotor area, Oliveri et al. (2003) argued that the SMA may be more involved in movement triggered by visual cues (photographs) with strong emotional (unpleasant) content as compared to neutral cues. Their results indeed revealed a facilitatory SMA–M1 interaction following an emotionally unpleasant stimulus as compared to single-pulse TMS applied to M1 or ds-TMS during neutral visual cues. Finally, this interaction proved to be dependent on the conditioning stimulus intensity, whereby a facilitating SMA–M1 interaction could only be induced with CS intensities of 90 and 100% rMT but not 70 and 80% rMT. The authors hypothesize that specific brain areas of the limbic cortex might process these visual stimuli, i.e., either emotionally unpleasant or neutral, and subsequently, as an internal stimulus to movement, facilitate the SMA in preparation for this movement (Oliveri et al. 2003).

Summary and discussion intrahemispheric SMA–M1 interactions

Regarding intrahemispheric SMA–M1 interactions, there is still controversy. Indeed, there are studies that report a facilitatory SMA–M1 interaction at rest (Arai et al. 2012), while others demonstrate an inhibitory interaction (Byblow et al. 2007) or no influence (Shirota et al. 2012). This ambiguity could be explained by the fact that each of these studies used a different target muscle and stimulation parameters (i.e., CS location, coil orientation and, stimulation intensity), complicating the comparison of results. While interactions at rest can be both facilitatory and inhibitory, depending on the paradigm, task-based

interhemispheric SMA–M1 interactions were found to be facilitatory in nature during a variety of motor tasks. These motor tasks included a response selection and adaptation task (Mars et al. 2009), emotionally unpleasant stimuli indicating a movement (Oliveri et al. 2003), and ipsilateral foot-hand coordination (Byblow et al. 2007), of which the latter has also been supported by fMRI evidence (Nakagawa et al. 2016). Modulation was absent during a tonic contraction of the target muscle (Arai et al. 2012). Together with the findings of Picazio et al. (2014) who highlighted the role of interhemispheric SMA–M1 interactions in response inhibition, Mars and colleagues (Mars et al. 2009) confirm the SMA's role during cognitive control of actions that require rapid updating, inhibition or adaptation (Aron et al. 2007; Chevrier et al. 2007; Sharp et al. 2010). As the requirement to switch necessitates some degree of cognitive flexibility, its dissociative role in the adaptation of planned actions, in addition to pure inhibition, might be one of the (pre-)SMA's key features. Nevertheless, its specific contribution to changing motor behaviour is still largely unknown. As to the influence of emotions, this facilitatory SMA–M1 pathway might form an interface between limbic and motor systems as ds-TMS only resulted in facilitation during emotionally charged movement stimuli. In addition, these facilitatory interactions appear relevant during hand-foot coordination by maintaining posture as well as during action reprogramming/adaptation, when the initial response needs to be inhibited and another response needs to be selected.

Since there is no consensus regarding the optimal stimulation parameters and target location, and it remains unclear whether both the pre-SMA and SMA, as well as the left and right SMA region, can be stimulated independently, it is currently very difficult to draw general conclusions about the inter- and intrahemispheric SMA–M1 interactions studied with ds-TMS.

PPC–M1 interactions

The posterior parietal cortex (PPC), also referred to as the somatosensory association cortex, is located just posterior to the somatosensory cortex and anterior to the visual cortex at the occipital pole of the brain (Whitlock 2017). Therefore, the PPC is optimally located to integrate visual and somatosensory input (Jackson and Husain 2006), and through an interaction with the motor cortex and premotor areas, contribute to sensory planning and control of motor actions (Jax and Coslett 2009; Jeannerod et al. 1995; Tunik et al. 2007). Such as adjustment of the motor plan based on visual feedback (Desmurget et al. 1999), multisensory and

Table 9: Overview of studies investigating intrahemispheric SMA–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Arai et al. (2012) [N = 12 (10 R-, 2 L-handed)]	– At rest – During at tonic contraction (10% MVC)	Ipsilateral SMA	Dominant M1	140/90% aMT	1 mV	3/6 ms	TS: fig8 (70 mm, ns) CS: fig8 (25 mm, ns)	Towards – post. – Lat. – PL – Ant.	Towards – AM – PL	FDI (dominant hand)	At rest: facilitation only with PL. to AM directed TS, and lat.-directed CS with intensity = 140% aMT at ISI = 6 ms During tonic contraction: No modulation of SMA–M1 interactions
Byblow et al. (2007) [N = 8]	– At rest – During tonic contraction of another limb (R ankle dorsi-flexion/plantar flexion)	L SMA	L M1	70–140% aMT	1 mV	6 ms	CS + TS: fig8 (50 mm outer diameter)	AP	PA	R ECR	At rest: Inhibitory L SMA–L M1 interaction with CS intensity = 90% aMT During tonic ankle contraction:

Table 9: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
											– Facilitation only with CS intensity = 90% aMT (both ankle movements); for CS intensity = 130% aMT only during plantar flexion
Mars et al. (2009) [*N* = 6–11 (subexperiments)]	Response selection and adaptation task	SMA	L M1	120% rMT	1–1.5 mV	3/6/9/ 12/18 ms	CS: fig8 (ns) TS: fig8 (ns)	ns	ns	R FDI	Facilitation during action adaptation ('switch' trials), but not 'stay' trials, with ISI = 6 ms at 125 ms after 'Go' stimulus onset
Oliveri et al. (2003) [*N* = 14]	During response selection task, (neutral/emotionally unpleasant visual cues)	L SMA	L M1	110% rMT	70/80/90/ 100/110% rMT	4 ms	CS: fig8 (70 mm, ns) TS: Circular coil (90 Mm, ns)	AP	ns	R FDI	– Facilitation after emotionally unpleasant movement cues with CS intensity = 90, 100, or 110% rMT – On individual analysis: Inhibition with CS intensity = 110% rMT after neutral movement cues and when no movement is required
Shirota et al. (2012) [*N* = 14]	At rest	L SMA	L M1	100% aMT (for TA)	0.5 mV	2–6/9/ 12 ms	TS + CS: fig8 (90 mm outer diameter)	ns	FDI: Towards AM TA: LM	R FDI R TA	Conditioning SMA did not influence excitability in M1

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range with 1 ms increments. AM, anteromedial; aMT, active motor threshold; ant., anterior; AP, anterior-to-posterior-directed current; CS, conditioning stimulus; ECR, extensor carpi radialis muscle; FDI, first dorsal interosseus muscle; fig8, figure-of-eight coil; ISI, interstimulus interval; L, left; lat., lateral; LM, lateromedial; M1, primary motor cortex; med., medial; ns, not specified; PA, posterior-to-anterior-directed current; PL, posterolateral; post., posterior; R, right; rMT, resting motor threshold; SMA, supplementary motor area; SOL, soleus muscle; TA, tibialis anterior muscle; TS, test stimulus.

sensorimotor integration (Berlucchi and Vallar 2018), spatial attention and orientation (Berlucchi and Vallar 2018; Mountcastle 1995; Mountcastle et al. 1975), and reaching and grasping movements that typically require an integration visual and proprioceptive information of both the hand and target position (Vingerhoets 2014). The PPC covers the lobus parietalis superior (SPL) and lobus parietalis inferior (IPL), as well as the sulcus intraparietalis (IPS) situated between both lobes (Caspers and Zilles 2018). Due to its vast and diverse cortical and subcortical connections, distinct parts of the PPC participate in a wide range of behavioural and cognitive processes. The SPL demonstrates a strong interrelation with the occipital lobe, and hence, plays an important role in visuospatial perception, linking the own body perception to external space. More specifically, the superior parieto-occipital cortex (SPOC), located in the posterior part of the SPL just anterior to the parieto-occipital sulcus, is involved in arm actions implicated in reaching (Cavina-Pratesi et al. 2010; de Jong et al. 2001; Filimon et al. 2009; Quinlan and Culham 2007) and pointing (Connolly et al. 2003). Brodmann area 5 (BA5) on the other hand, situated at the most anterior part of the SPL, directly posterior to the primary somatosensory cortex, unsurprisingly has been associated with tactile discrimination (Nakashita et al. 2008; Stoeckel et al. 2004), the control of hand movements (Grafton et al. 1996; Kalaska et al. 1990), fine-motor control as well as movement imaging of finger actions (Hanakawa et al. 2003). Similar to BA5, the anterior part of the intraparietal sulcus (aIPS) is presumed to play a specialized role in handgrip, using an objects visual characteristics to guide hand movements, although it is involved in reaching too (Culham et al. 2003; Konen et al. 2013; Orban 2016; Rice et al. 2006; Verhagen et al. 2012). Projecting to the PMv, the aIPS forms the dorsolateral circuit, responsible for grasping (Vingerhoets 2014). The more dorsally located mid-sulcus region of the sulcus intra-parietalis (mIPS) and pIPS have been associated with reaching, linking visual and motor aspects of movement and are deemed to interact with the SPOC during reaching (Grefkes and Fink 2005; Grefkes et al. 2004; Vingerhoets 2014). Together with the PMd, these regions form the dorsomedial circuit that underlies reaching (Vingerhoets 2014). Hence, while dorsal–medial subregions of the PPC are mainly involved in the reaching or transport component, dependent on vision, ventral–lateral subregions are more involved in grasping movements, which are more dependent on the somatosensory system. Regions located in the middle of this gradient transition show activity during both reaching and grasping movements (Filimon 2010; Konen et al. 2013).

In contrast to the SPL and IPS region's role in movement execution, the IPL has a rather cognitive function and plays an important part in maintenance of attention (as measured by vigilance and non-spatial attention paradigms) (Adler et al. 2001; Pardo et al. 1991; Sturm et al. 1999) and action recognition, and understanding (Decroix et al. 2020; Fogassi et al. 2005; Rizzolatti et al. 2006). Similar to PMv and M1, mirror neurons were observed in the inferior parietal lobe (e.g., Bonini et al. 2010; Fogassi et al. 2005; Kilner and Lemon 2013) which argues for a strong role in action observation and motor imaging, specifically, during image manipulation (Newman-Norlund et al. 2010).

Mediated via transcallosal projections, a robust interconnection between various subregions of the PPC and the contralateral hemisphere were demonstrated by anatomical studies in human (Witelson 1989; Zarei et al. 2006) and non-human primates (Pandya et al. 1971). For example, direct connections between parietal areas and contralateral motor areas (e.g., PPC_{right}–$M1_{left}$) have been demonstrated (Jones et al. 1979; Pandya and Vignolo 1969). In addition, interhemispheric PPC–M1 interactions might also be mediated via the contralateral PPC (e.g., PPC_{right}–PPC_{left}–$M1_{left}$), as transcallosal connections exist between homologous PPC regions. On the other hand, studies in both monkeys (Fogassi et al. 2005; Petrides and Pandaya 1984) and humans (Koch and Rothwell 2009; Schmahmann et al. 2007) have revealed clear functional and anatomical connections between the PPC and motor areas in the same hemisphere, as mediated through the white matter fibers part of the superior longitudinal fasciculus (Karabanov et al. 2013). These connections are assumed to mediate interactions between different subregions of the PPC and ipsilateral M1. Alternatively, the influence exerted by the PPC on M1 may be mediated via the PMv (e.g., PPC_{left}–PMv_{left}–$M1_{left}$) (Koch et al. 2010a; Matelli et al. 1998; Shields et al. 2016). As compared to interhemispheric PPC–M1 connectivity, intrahemispheric PPC–M1 connectivity has been investigated more extensively at rest as well as during motor tasks.

Target locations within the PPC were determined based on either (1) the 10–20 EEG system (i.e., P3 and P4 for the left and right PPC, respectively, and 1 cm anterior and 1.5 cm lateral to the Pz position for the BA5 position) (Isayama et al. 2019; Koch et al. 2007, 2008; Koch and Rothwell 2009; Mackenzie et al. 2016; Schintu et al. 2016); (2) MNI coordinates obtained from probabilistic mapping (Choi et al. 2006) co-registered with anatomical T1-weighted MRI (Lebon et al. 2012); or (3) anatomical landmarks identified by individual anatomical MRI

(Isayama et al. 2019; Karabanov et al. 2012, 2013, 2017; Koch et al. 2009, 2010a,b; Vesia et al. 2013, 2017). In the latter, the anterior aspect of the IPS (aIPS) was defined as a point close to the intersection between the IPS and postcentral sulcus. The cIPS was defined as a part of the angular gyrus, situated close to the posterior part of the adjacent IPS (Koch et al. 2009).

An overview of all ds-TMS studies included in this review, investigating interhemispheric PPC–M1 connectivity can be found in Table 10, while an overview of all studies examining intrahemispheric PPC–M1 connectivity can be found in Table 11. A detailed description of all coil orientations can be found in the appendix, and a global overview of the coil orientations is provided in Figures 4 and 5, for inter- and intra-hemispheric interaction respectively.

Interhemispheric

At rest

Koch et al. (2009) targeted both the cIPS and aIPS at rest. They observed a facilitatory right cIPS–left M1 interaction when a CS intensity of 90% rMT was used [but not higher (110% rMT) or lower (70% rMT) intensities], which was maximal at an ISI of 6 and 12 ms. Further, they demonstrated a similar facilitatory left cIPS–right M1 interaction, but a higher CS intensity was needed (110% rMT) as compared to conditioning right cIPS (90% rMT). In contrast, an inhibitory influence on the contralateral M1 was reported, using the same parameters to condition right aIPS. The authors speculated that the early (6 ms) and later (12 ms) peaks of IHF were mediated by a direct transcallosal PPC–M1 pathway and indirect (PPC–PPC_{contra}–M1 or PPC–$M1_{ipsi}$–$M1_{contra}$) pathway, respectively (Koch et al. 2009). A similar result was reported by Lebon et al. (2012), who targeted the IPL (Fan et al. 2016). More specifically, they demonstrated a facilitatory right IPL–left M1 interaction with an ISI of 6 ms, but not at 12 ms.

Task-related interactions

Motor imagery and mental rotation task. Lebon et al. (2012) examined the interaction between right IPL and left M1 in the context of both a motor imagery (MI) and a mental rotation (MR) task. During the MI task, subjects had to imagine a pinching movement with thumb and index finger following the actual performance of this movement. For the MR task, images of a left or right hand were shown in different orientations, while participants were requested to identify which hand was shown. Results indicated that the facilitatory interhemispheric IPL–M1 interactions found at rest were abolished during the execution of a mental rotation task (TMS at 650 ms after presentation of a rotated image of a right or left hand), and even inverted to inhibition during motor imagery (TMS at 50 ms before auditory paced pinch grasp imagery) (Lebon et al. 2012).

Summary and discussion interhemispheric PPC–M1 interactions

The different subregions of the PPC each exert a different influence on the contralateral M1 at rest. That is, while both the left and the right cIPS exert a facilitatory influence on contralateral M1 at short latencies, the right aIPS had an inhibitory influence on the contralateral M1 when using the same parameters (i.e., CS intensity = 90% rMT, ISI 6 and 12 ms) (Koch et al. 2009). A similar result was reported by Lebon et al. (2012) who demonstrated a facilitatory right IPL–left M1 interaction with an ISI of 6 ms. However, they could not demonstrate facilitation at 12 ms. As suggested by the authors, this discrepancy could possibly be explained by differences in the CS stimulation location (Lebon et al. 2012). With regard to motor tasks, interhemispheric interactions between PPC and M1 have only been examined during motor imagery and mental rotation tasks, using ds-TMS (Lebon et al. 2012). In contrast to the IHF demonstrated at rest, these left IPL–right M1 interactions were abolished (i.e., from facilitation to neutral) and even inhibited during mental rotation and motor imagery, respectively. It has been suggested that this pathway is involved in movement inhibition necessary to prevent an actual execution of the imagined motion (Lebon et al. 2012).

Intrahemispheric

At rest

Studies investigating the PPC–M1 interaction at rest suggest that connective pathways from the anteriorly located subregions of the IPL to ipsilateral M1 are mainly facilitatory while pathways from the posteriorly located subregions of the IPL exert an inhibitory influence on ipsilateral M1. In particular, Koch et al. (2007) applied a CS to the P3 and P4 position of the 10–20 EEG system [corresponding to the cIPS of the left and right hemisphere, respectively (Herwig et al. 2003; Rushworth and Taylor 2006)]. A facilitatory influence of PPC (cIPS) on ipsilateral M1 was found at a 4- and 15 ms ISI for the right hemisphere, and at an ISI of 4- and 6 ms for the left hemisphere (Koch et al. 2007). This facilitation could be elicited using CS intensity of 90% rMT, but not with higher or lower intensities, and preferentially inducing a PA-directed current in the brain (Koch et al. 2007). Furthermore, these effects were found to be both region- and subregion-specific as stimuli applied 2 cm medial or lateral to P4 did not

Table 10: Overview of studies investigating interhemispheric PPC–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coil (wing- diameter)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Koch et al. (2009) [*N* = 17]	At rest	– R PPC: cIPS/ aIPS – L PPC: cIPS	– L M1 – R M1	70/90/110% rMT	1 mV	4–12∗/ 15/20 ms	TS: fig8 (50mm∗) CS: fig8 (70 mm∗) ∗ outer diamater	– AP – PA – ML – LM	– PA – AP	R & L FDI	– Facilitation R cIPS–L M1 at ISI = 6 or 12 ms with CS intensity = 90% rMT, but not 70 or 110% rMT; IHF for CS intensity = 90% rMT and ISI = 12 ms only with PA, but not AP current direction for TS – Inhibition R aIPS–L M1 with CS intensity = 90% rMT at ISI = 10 or 12 ms – Facilitation L cIPS–R M1 with CS intensity = 110% at ISI = 6 or 12 ms
Lebon et al. (2012) [*N* = 11]	– At rest – During motor imagery (pinch grip) – During mental rotation (images of R or L hand)	R IPL	L M1	90% rMT	50% of maximal MEP amplitude at rest	6/12 ms	2 x fig8 (85 and 80 mm outer diameter), ns which coil for TS or CS	PA	PA	R FDI	At rest: facilitation at ISI = 6 but not 12 ms During motor imagery: Inhibition at ISI = 12 ms During mental rotation: No interaction R IPL–L M1, irrespective of ISI

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range. A "∗" was used to indicate 2 ms increments within a range. aIPS, anterior intraparietal sulcus; AP, anterior-to-posterior-directed current; cIPS, caudal intraparietal sulcus; CS, conditioning stimulus; FDI, first dorsal interosseus muscle; fig8, figure-of-eight coil; IPL, inferior parietal lobe; ISI, interstimulus interval; L, left; LM, lateral-to-medial-directed current; M1, primary motor cortex; ML, medial-to-lateral-directed current; ns, not specified; PA, posterior-to-anterior-directed current; PPC, posterior parietal cortex; R, right; rMT, resting motor threshold; TS, test stimulus.

influence ipsilateral M1 excitability. It should be noted that subsequent studies (described below) all used the same CS intensity (90% rMT) and TS current direction (PA) to examine intrahemispheric PPC–M1 interactions at rest as well as during motor task preparation and performance, irrespective of the targeted subregion within the PPC. In a sub-experiment (N = 4 participants), Koch et al. (2007) additionally applied a CS to the aIPS, a mid-sulcus region (mIPS), and the cIPS, within the right hemisphere. Interestingly, intrahemispheric PPC–M1 connectivity changed along the IPS as conditioning the cIPS resulted in MEP facilitation (Koch et al. 2007) while conditioning the aIPS inhibited MEPs within ipsilateral M1 (Koch et al. 2007; Vesia et al. 2013). In line with these results, Karabanov et al. (2013) established an inhibition of MEPs elicited in M1 following stimulation of the anterior part of the IPL (aIPL). While, in contrast to the results of Koch et al. (2007), facilitation within the ipsilateral M1 could be evoked after conditioning the middle (mIPL) and caudal part (cIPL) of the IPL in the left but not the right hemisphere (Karabanov et al. 2013).

Results acquired when examining intrahemispheric interactions between different subregions within the inferior PPC and ipsilateral M1, resemble the results of interhemispheric PPC–M1 interactions. In contrast, a CS applied to the superior parietal–occipital cortex (SPOC), which is located at the medial surface of the parietal lobe, medial to the IPS, bordered by the sub-parietal sulcus at the front and the parieto–occipital sulcus at the back (Vesia et al. 2010), did not influence ipsilateral M1 excitability at rest (Vesia et al. 2013). Within the superior parietal lobe not only the SPOC but also BA 5 [a subdivision of the superior parietal lobule (Scheperjans et al. 2008)], situated just posterior to the primary somatosensory cortex, has been examined in the context of PPC–M1 connectivity. Left BA 5 did neither seem to exert a facilitatory nor an inhibitory influence on left M1 (Mackenzie et al. 2016; Ziluk et al. 2010). Taken together, these data show that distinct parts of the PPC have a different influence on ipsilateral M1 excitability. Furthermore, different target locations may be associated with differences regarding the optimal ISI to provoke intrahemispheric PPC–M1 interactions at rest [4 ms (Vesia et al. 2013) and 6 ms in the right hemisphere (Koch et al. 2007, 2008), and 4 (Koch et al. 2007, 2008), 8 ms (Karabanov et al. 2013) and 15 ms in the left hemisphere (Koch et al. 2007, 2008)].

Task-related interactions

Reaching and grasping. In the context of motor tasks, Koch et al. (2008) tested the influence of the cIPS on ipsilateral M1 during a reaching and touching task in which subjects had to reach and touch a visual target on the left or right hemifield using the same hand following an auditory cue. Starting from a midline position, participants received a warning signal, followed by an auditory 'Go' signal 1–3 s later that indicated a left- or right-ward reaching movement. A 90% rMT CS was applied over cIPS 4 ms prior to TS delivered over the ipsilateral M1 at different delays of 25–150 ms after the auditory warning cue. The results demonstrated a facilitatory left cIPS–left M1 interaction at 50 and 125 ms after the auditory warning cue when a rightward reaching movement was required. Interestingly, at the 50 ms delay, this facilitation was present irrespective of whether participants could visually target the movement endpoint or not, i.e., they were either blindfolded or could only see the target for a brief period. However, facilitation at 125 ms only occurred when participants could see the movement target. A similar facilitatory cIPS–M1 interaction was identified in the right hemisphere, associated with the planning of leftward reaching movements at the 50 and 100 ms delay (Koch et al. 2008).

In a subsequent study, Koch et al. (2010a) used the same approach to examine the contribution of different subregions of the left IPS, i.e., the more anterior location corresponding to supramarginal gyrus (aIPS) and the posterior location within angular gyrus (cIPS). They focused on the preparatory period of reaching and grasping movements. Participants had to reach to a cup located centrally or laterally on their right side using their right hand, and lift it with either a pinch grip (handle of the cup) or a whole handgrip (whole cup from the top), depending on the auditory cue. The results revealed that interactions between distinct subregions of the PPC and ipsilateral M1 were differently modulated during reaching and grasping tasks. That is, the left cIPS–M1 interaction was modulated in the early preparation phase (50 ms after stimulus onset) of reaching and grasping towards an object in the lateral hemispace (but not central) with a whole handgrip but not with precision grip. Conversely, the left aIPS–M1 interaction was modulated later during the preparation phase of both central (75 and 100 ms after stimulus onset) and lateral (125 ms after stimulus onset) reaching and grasping movements with a precision grip but not with a whole handgrip (Koch et al. 2010a). Vesia et al. (2013) tried to distinguish between left SPOC–M1 and left aIPS–M1 interactions during the preparation phase of reaching and grasping movements associated with respectively the transport and the grasping component. To do so, a ds-TMS paradigm was combined with two tasks in which participants were required to either touch or grasp an object placed near or far from the start location of their hand. The net inhibitory left SPOC–M1 connectivity found at rest was shown to be specifically modulated during the

preparatory period of movements involving a transport component as stimulation of left SPOC facilitated MEPs evoked by a TS over ipsilateral M1 (ISI = 4 ms) in the preparatory period of both touch and grasp trials, when the object was located away from the starting position. In contrast, left aIPS facilitated M1 (ISI = 4 ms) during the preparatory period of grasp but not touch movements, irrespective of whether transport was required or not (Vesia et al. 2013). In another study, Vesia et al. (2017) demonstrated that the SPOC–M1 interaction is modulated differently during the preparatory period of distinct types of grip. That is, a CS applied over the left SPOC at 6 ms prior to a TS over ipsilateral M1 during the preparatory period of a whole-hand grasp (150 ms after stimulus onset) facilitated subsequent MEPs as measured in the ADM muscle. In contrast, the FDI was facilitated during task preparation as compared to rest, irrespective of the required grip type. Thus, SPOC–M1 interactions within the left hemisphere were found to be involved in the preparation of reaching and grasping movements (Vesia et al. 2017).

Observation of goal-directed reaching and grasping actions. The influence of the observation of goal-directed reaching and grasping actions on intrahemispheric left aIPL–M1 interactions were examined by Koch et al. (2010b). Similar to the execution of goal-directed reach and grasping movements, left aIPL–left M1 interactions were facilitated (4s after the onset of the video, 3s after the onset of the movement) during the observation of these actions. Interestingly, this facilitation occurred selectively when participants observed videos of successful goal-directed precision grasping towards a small target but not during a whole hand grasp towards a big target. In contrast, observing videos of unsuccessful reaching and grasping actions, e.g., reaching and grasping with a pinch grip towards a big target, or static videos, during which a hand and the target were presented but did not move, did not influence left aIPL–M1 interactions (Koch et al. 2010b).

Go/NoGo task. Although there was no BA5–M1 interaction at rest, a task-related modulation for this interaction was observed during the movement preparation of a Go/NoGo task (Mackenzie et al. 2016). During this task, an auditory warning cue was followed by an auditory signal 2 or 3 s later, indicating whether participants were required to either initiate a mouse click response (i.e., 'Go' trial) or to withhold this response (i.e., 'NoGo' trial). MEPs evoked by a TS over M1 following stimulation of BA5 were greater in 'Go', relative to 'NoGo' trials but not as compared to the resting condition (Mackenzie et al. 2016). These results confirm the hypothesis on the role of BA5 in the decision about whether or not to carry out or withhold a planned movement (Watanabe et al. 2002).

Summary and discussion intrahemispheric PPC–M1 interactions

In sum, PPC–M1 interactions can be elicited by means of a PA-directed TS and CS and a CS intensity of 90% rMT. These interactions are highly dependent on which precise subregion of PPC is targeted. More specifically, evidence suggests that regions located in the SPL (SPOC and BA5) do not influence ipsilateral M1 at rest (Mackenzie et al. 2016; Vesia et al. 2013; Ziluk et al. 2010) but are modulated towards facilitation in the context of motor task execution (e.g., Vesia et al. 2017). On the contrary, regions located in the IPL exert either a facilitatory (cIPS/cIPL/mIPL) (Karabanov et al. 2013; Koch et al. 2007) or an inhibitory (aIPS/aIPL) (Karabanov et al. 2013; Koch et al. 2007; Vesia et al. 2013) influence over M1 at rest, whilst these interactions turn to facilitation during specific motor tasks (e.g., Koch et al. 2008). Furthermore, the influence of IPL and IPS on M1 differs as facilitation induced from the mIPL and cIPL could only be demonstrated in the left but not right hemisphere (Karabanov et al. 2013) while facilitation from mIPS and cIPS could be elicited in both hemispheres (Koch et al. 2007). These PPC–M1 interactions are modulated toward facilitation in a highly task- and time-dependent manner during the preparatory period of reaching and grasping tasks, with each sub-region making a specific contribution to different task components. In particular, the more dorsally located SPOC is involved in reaching for distant targets even without grip, while the anteriorly and inferiorly located regions are more involved in the grasping component. Specifically, the cIPS is involved in reaching and whole-hand grasping movements. The aIPS, on the other hand, is engaged in reaching movements followed by precision grip. Finally, the aIPL plays a role in the observation of precision- but not in whole-hand grasping (for a more detailed description, see 'Reach and grasp preparation'). This is consistent with their respective role in the dorsomedial and dorsolateral circuit, underlying, respectively, reaching and grasping movements (Vingerhoets 2014).

Cerebellar–M1 interactions

The cerebellum is a key part of the motor network involved in planning, initiating and organizing voluntary movement (Allen and Tsukahara 1974; Doyon et al. 2003; Gao et al. 2018; Heiney et al. 2014; Herzfeld et al. 2015; Ito 2006; Koziol et al. 2014; Manto et al. 2012; Proville et al. 2014) as

Table 11: Overview of studies investigating intrahemispheric PPC–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Karabanov et al. (2013) [*N* = 12]	At rest	– L IPL (aIPL/mIPL/cIPL) – R IPL (aIPL/mIPL/cIPL)	– L M1 – R M1	90% rMT	1 mV	2–8* ms	TS + CS: fig8 (70 mm outer diameter)	PA	PA	– R FDI – L FDI	– Facilitation mIPL and cIPL–M1 in L hemisphere, but not R hemisphere – Inhibition aIPL–ipsilateral M1 in L and R hemisphere – Excitability following ds–TMS L hemisphere > R hemisphere – Higher MEP amplitudes for ISI = 8 ms as compared to other ISIs – High inter-individual variability for optimal parietal coil positions
Koch et al. (2007) [*N* = 6–10]	At rest	L: – PPC (P3) R: – PPC (P4) – 2 cm med./lat. Of P4 (control) – aIPS/mIPS/cIPS	– L M1 – R M1	Left: 90/110% rMT Right: 70/90/110/130% rMT	1 mV	Left: 2–10*/15 ms Right: 2–10*/15/20 ms	CS: – fig8 (70 mm*) – fig8 (50 mm*) TS: – fig8 (50 mm*) – Circular coil (100 mm*) * outer diameter	– PA – AP	– PA – Clockwise	– R FDI – L FDI	R hemisphere: – Facilitation R PPC (P4)–R M1 at ISI = 4 or 15 ms, only with CS intensity = 90% rMT and PA-directed current induced in the brain; no interaction at 2 cm med./lat. From P4 – Facilitation R cIPS–R M1 at ISI = 4 ms with CS intensity = 90% BUT inhibition R aIPS–R M1 for the same parameters L hemisphere: – Facilitation L PPC (P3)–L M1 at ISI = 4 or 6 ms, only with CS intensity = 90% rMT
Koch et al. (2008) [*N* = 15]	– At rest – During reaching and touching	– L PPC (cIPS) – R PPC (P4) (cIPS)	– L M1 – R M1	90% rMT	1 mV	L: 6 ms R: 4 ms	CS: fig8 (70mm*) TS: fig8 (50 mm*) * outer diameter	PA	PA	– R FDI – L FDI	At rest: facilitation PPC–M1 at CS intensity = 90% rMT and – ISI = 4 ms for R hemisphere – ISI = 6 ms for L hemisphere During reaching and touching: Facilitation PPC–M1 during planning period of reaches with the contra- but not ipsilateral side

Table 11: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
											– At 50 and 125 ms after stimulus onset for R hemisphere (L hand) – At 50 and 100 ms after stimulus onset for L hemisphere (R hand)
Koch et al. (2010a) [*N* = 10]	During reaching and grasping (whole hand or precision grip; laterally or centrally directed)	– L SMG (aIPS) – L AG (cIPS)	L M1	90% rMT	1 mV	4 ms	TS + CS: fig8 (50 mm outer diameter)	ns	PA	R FDI/ ADM	L SMG (aIPS)–L M1 facilitation (only for FDI): – At 75 and 100 ms after stimulus onset for central precision grip – At 125 ms after stimulus onset for lateral (to R) precision (but not whole hand) grip L AG (cIPS)–L M1 interactions: – Not influenced when the target was located centrally – Facilitation (for FDI and ADM) during preparation of lateral (to R) whole hand (but not precision) grip at 50 ms after stimulus onset
Koch et al. (2010b) [*N* = 12]	During observation of goal-directed reaching and grasping	L aIPL	L M1	90% rMT	1 mV	6 ms	TS + CS: fig8 (50 mm outer diameter)	ns	PA	R FDI/ ADM	Facilitation L aIPL–L M1 (only for FDI) during observation of successful, but not unsuccessful, goal-directed reaching and grasping with a precision grip towards a small target, but not with a whole handgrip towards a big target
Mackenzie et al. (2016) [*N* = 12]	– At rest – During Go/NoGo task	L BA 5	L M1	90% rMT	1 mV	8 ms	CS + TS: Fig8 (50 mm, ns)	PA	PA	R FDI	At rest: no L BA 5–L M1 interaction During Go/NoGo task: facilitation L BA 5–L M1 at 125 ms after stimulus onset during 'Go' trials, relative to 'NoGo' trials but not rest

Table 11: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction CS (in brain)	Current direction TS (in brain)	Target muscle	Main results
Vesia et al. (2013) [*N* = 7]	– At rest – During reaching and precision grasping (with/without transport component)	– L SPOC – L aIPS	L M1	90% rMT	120% rMT	4–10* ms	CS + TS: fig8 (50mm inner diameter)	PA	PA	R FDI	At rest: – No L SPOC–L M1 interaction – Inhibition L aIPS–L M1 at ISI = 4 ms During reaching and grasping: – Facilitation L SPOC–L M1 at ISI = 4 ms during preparatory period of movements involving a transport component – Facilitation L aIPS–L M1 at ISI = 4 ms during preparatory period of grasping movements
Vesia et al. (2017) [*N* = 10/11]	During reaching and grasping	L SPOC	L M1	90% rMT	– 0.5 mV (ADM) – 1.25 mV (FDI)	4–8* ms	CS: fig8 (40 mm*) TS: fig8 (50 mm*) * inner diameter	PA	PA	R FDI/ADM	– Facilitation L SPOC–L M1 at 150 ms after stimulus onset in ADM, but not FDI, during preparation of whole hand grasp relative to the 'TS only' trials, only for ISI = 6 ms – Generally increased L SPOC–L M1 excitability for FDI during task preparation (whole hand/pinch grip and touch) as compared to rest, irrespective of ISI

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range. A "*" was used to indicate 2 ms increments within a range. ADM, abductor digiti minimi muscle; AG, angular gyrus; aIPL, anterior inferior parietal lobe; aIPS, anterior region of the sulcus intraparietalis; AP, anterior-to-posterior-directed current; BA, Brodmann area; cIPL, caudal inferior parietal lobe; cIPS, caudal part of the sulcus intraparietalis; CS, conditioning stimulus; FDI, first dorsal interosseus muscle, fig8, figure-of-eight coil; IPL, inferior parietal lobe; IPS, intra parietal sulcus; ISI, interstimulus interval; M1, primary motor cortex; mIPL, middle part of the lobus parietalis inferior; mIPS, mid-sulcus region of the sulcus intraparietalis; ns, not specified; P3, P3 position according to the EEG 10–20 system.

well as in motor learning (Ito 2000; Manto et al. 2012; Medina and Lisberger 2008; Yanagihara and Kondo 1996) and intra- and inter-limb coordination tasks, including bimanual tasks and gait (Richard et al. 2017). Furthermore, studies indicated cerebellar engagement in action observation, understanding the actions of others, and observational learning (Grossman et al. 2000; Kostorz et al. 2020; Sokolov et al. 2010; Vaina et al. 2001). Moreover, earlier work identified the existence of anatomical connections between the cerebellum and respectively motor and non-motor areas of the cerebral cortex through cerebello–thalamo–cortical pathways (Bostan et al. 2013; Kelly and Strick 2003). Cortico–cerebellar connections cross the midline (e.g., the left cerebellar hemisphere projects to regions within the right cortical hemisphere and vice versa) (Palesi et al. 2015). Furthermore, these pathways appear to be rather complex, via disynaptic or polysynaptic connections (Futami et al. 1986; Holdefer et al. 2000), axons of these pathways can terminate on both excitatory and inhibitory neurons (Daskalakis et al. 2004; Na et al. 1997) in the cortical layers I, III, V and VI (Ando et al. 1995; Na et al. 1997). The disynaptic dentate–thalamo–cortical pathway, which has a facilitatory influence on the motor cortex, constitutes the cerebellar–M1 connection (Allen and Tsukahara 1974; Groiss and Ugawa 2013; Holdefer et al. 2000). This pathway, originating from the dorsal part of the dentate nucleus, receives an inhibitory influence from the Purkinje cells (Grimaldi et al. 2014; Groiss and Ugawa 2013; Na et al. 1997; Stoodley and Schmahmann 2010). Therefore, cerebellar TMS, which is postulated to activate these Purkinje cells, has an inhibitory effect on the dentate nucleus and hence, reduces the excitatory influence on M1 (Allen and Tsukahara 1974; Daskalakis et al. 2004; Galea et al. 2009; Grimaldi et al. 2014; Groiss and Ugawa 2013; Na et al. 1997; Shinoda et al. 1993). This reduction in corticospinal excitability is referred to as cerebellar brain inhibition (CBI).

Connectivity between the cerebellum and M1 has successfully been assessed using ds-TMS (Daskalakis et al. 2004; Grimaldi et al. 2014; Groiss and Ugawa 2013; Reis et al. 2008). An overview of the studies examining cerebellar–M1 connectivity included in this review can be found in Table 12.

The (lateral) cerebellum was most often targeted at a point either (1) 3 cm lateral (Daskalakis et al. 2004; Hardwick et al. 2014; Jayaram et al. 2011; Kassavetis et al. 2011; Pinto and Chen 2001; Schlerf et al. 2012, 2015; Spampinato and Celnik 2017; Spampinato et al. 2017, 2020a,b; Tanaka et al. 2021) or (2) 3 cm lateral and 1 cm inferior relative to the inion on the line joining the external auditory meatus (Fernandez et al. 2018b; Hardwick et al. 2014; Panyakaew et al. 2016; Tanaka et al. 2018). The latter target location corresponds to the cerebellar hand representation in lobule V and VIII which has been verified with MRI-based neuronavigation (Hardwick et al. 2014). Along the same line, Fisher et al. (2009), Baarbé et al. (2014), and Zabihhosseinian et al. (2020) targeted a point midway through the inion and the external auditory meatus although they did not specify the exact distance at which it was located. Ugawa et al. (1995) examined twelve points located +4 cranial to −2 cm caudal relative to the inion, the mastoid line, and the intermediate line (i.e., midline between the inion and processus mastoideus). While targeting a point 2–4 cm lateral to the inion on the line joining the external auditory meatus using a double-cone (DC) coil, Werhahn et al. (1996) positioned the coil junction of a figure-of-eight coil over a point 8 cm lateral to the inion. Alternatively, Torriero et al. (2011) determined the cerebellar target based on anatomical landmarks obtained from an individual MRI scan i.e., the superior posterior lobule of the right cerebellar hemisphere. Coil orientations are visualized in Figure 4. A more detailed description can be found in the appendix.

At rest

Due to the deeper location of the cerebellum as compared to cortical targets such as M1 for example, the efficacy of cerebellar stimulation strongly depends on the design of the coil (Hardwick et al. 2014). Although standard figure-of-eight coils, designed for the focal stimulation of relatively superficially located cortical targets, have been used to stimulate the cerebellum (Torriero et al. 2011; Werhahn et al. 1996), no inhibitory cerebellar–M1 interactions could be evoked (Fernandez et al. 2018b; Hardwick et al. 2014; Werhahn et al. 1996). In contrast, CBI could reliably be evoked using the double cone (DC) or Batwing coil as they have an angled design that promotes the stimulation of deeper brain regions. Yet, it has been established that the Batwing coil (70 mm) required higher CS intensities (75–80% MSO) to induce CBI relative to the larger, more sharply angled DC coil, which could elicit inhibition at CS intensities ranging from 60–80% MSO (Fernandez et al. 2018b; Hardwick et al. 2014). In addition, a recent study by Spampinato et al. (2020a) revealed differences between the DC coils of different manufacturers in the ability to provoke CBI. That is, the smaller Magstim DC coil (70 mm wing diameter) could elicit a reliable CBI but only at the maximum tolerated stimulus intensity whereas the larger DC coils from both Magstim and Deymed (110 mm wing diameter) were able to elicit CBI at lower intensities,

i.e., 90% (Magstim; coated and uncoated) and even 80% (Deymed) of the maximum tolerated stimulus intensity (Spampinato et al. 2020a). In contrast, it was not possible to elicit CBI using the MagVenture DC coil (model D-B80). Therefore, at present, the Magstim and Deymed DC coils (110 mm wing diameter) can be considered most optimal to investigate cerebellar–M1 interactions, although Magstim coils require slightly higher CS intensities (Spampinato et al. 2020a).

An important aspect when applying TMS over the cerebellum is the degree of subject tolerance associated with cerebellar stimulation as it might cause a contraction of the dorsal neck muscles and may be perceived as uncomfortable. Here, a trade-off between tolerance and reliability should be taken into account. In this context, a recent feasibility study by Fernandez et al. (2018b) examined both the range of CS intensities for which CBI could reliably be provoked and the subject tolerance for each of these intensities, using a traditional DC coil (Magstim, 110 mm) on the one hand and a highly powered figure-of-eight coil (Magstim D702, +25% power as compared to traditional figure-of-eight coils) on the other hand. While their results showed that stimulation by means of the D702 is experienced as less painful as compared to the DC coil, this figure-of-eight coil was not able to reliably assess CBI at any intensity tested. As expected, perceived discomfort during DC coil stimulation increased with increasing CS intensities. However, since CBI could already reliably be elicited with a DC coil at a lower CS intensity (60% MSO) and CBI strength did not significantly vary among the different studied intensities (>60% MSO), the authors suggested that stimulating each participant at 60% MSO when using a DC coil will provide the researcher with the most reliable results while minimizing participant discomfort (Fernandez et al. 2018b).

Despite a lack of consensus and evidence on which current direction is most appropriate for examining cerebellar–M1 functional connectivity, the coil for applying the CS was typically aimed at producing an upward current flow in the brain (Koch et al. 2006), although the reverse direction is also efficient (Fernandez et al. 2018a). Inhibitory cerebellar–M1 interactions have been systematically observed following cerebellar stimulation within an ISI ranging from 5 to 7 ms (Daskalakis et al. 2004; Fisher et al. 2009; Groiss and Ugawa 2013; Pinto and Chen 2001; Saito et al. 1995; Torriero et al. 2011; Ugawa et al. 1995; Werhahn et al. 1996). In particular, inhibitory right cerebellar–left M1 interactions were the highest at a 5 ms or 7 ms ISI following, respectively, a PA- or AP-directed TS over left M1 (Spampinato et al. 2020b). Additionally, CBI was greater in the dominant as compared to the non-dominant cerebral hemisphere in right-handed individuals (i.e., right cerebellar–left M1 CBI was stronger than left cerebellar–right M1 CBI) (Schlerf et al. 2015). CBI increased (i.e., decreasing MEP amplitudes) with increasing CS intensity (Panyakaew et al. 2016; Schlerf et al. 2015) and decreased (i.e., increasing MEP amplitudes) when TS intensities were larger than 1 mV (Daskalakis et al. 2004; Pinto and Chen 2001; Ugawa et al. 1995).

As the cerebellum is located near the corticospinal tract, a substantial concern refers to the antidromic effects caused by the activation of pyramidal neurons in the corticospinal tract which might be a consequence of a TMS pulse delivered to the back of the head (Fisher et al. 2009; Ugawa et al. 1995). These effects of the CS might coincide with the descending volleys deriving from subsequent M1 stimulation. Consequently, the source of MEP reduction becomes obscured and might not relate entirely to the cerebello–thalamo–cortical pathway. In order to avoid this, the intensity of the cerebellar CS should be set 5–10% (Werhahn et al. 1996) or even 15–20% (Fisher et al. 2009) below the aMT of the descending motor pathways, i.e., below the threshold for eliciting cervico–medullary evoked potentials (CMEPs). This threshold, defined as the minimum stimulator intensity to elicit MEPs greater than 50 μV amplitude in at least five out of ten trials, can be established by a TMS pulse administered over the posterior fossa (i.e., the posterior part of the cranial fossa, which contains the brainstem and cerebellum) during a weak isometric contraction (usually 10% MVC) of the target muscle. Likewise, a DC coil is most often used, as a regular flat figure-of-eight coil over the inion could potentially activate the brachial plexus (Werhahn et al. 1996).

Using the aMT for determining the CS intensity requires high stimulation intensities, which are often perceived as uncomfortable and can cause a contraction of dorsal neck muscles (Baarbé et al. 2014; McNeil et al. 2013). Furthermore, in some participants, it may be challenging or even impossible to establish the aMT. Therefore, to determine the CS intensity in a more comfortable way, Baarbé et al. (2014) combined a range of CS intensities (55–85% MSO) with the TS, in order to optimize CS intensity selection that led to a TS suppression of 50%. This method has been adopted by Zabihhosseinian et al. (2020) and Tanaka et al. (2021). The latter used a TS suppression of 30% inhibition to optimize patient comfort. To make sure this CS intensity did not elicit CMEPs or cortical root activity, the EMG trace was analyzed for each intensity

(Baarbé et al. 2014). When detected in the FDI EMG trace, CMEPs and cortical root activity had a latency of respectively 18 and 15 ms, while cerebellar–M1 interactions or single-pulse TMS elicited MEPs at a latency of 21 ms (Martin et al. 2009). Panyakaew et al. (2016) based their CS intensity on the M1 threshold (i.e., 90–120% rMT), which was adapted to stimulate deeper structures in order to compensate for magnetic field attenuation due to brain–coil distance using the equitation of Stokes et al. (2005).

Note that, similar to IHF between homologous M1, cerebellar–M1 facilitation is weak and can only be exerted under specific conditions, i.e., at short ISIs (3 ms) and a low-intensity CS, evoked by electrical stimulation over the cerebellum (not discussed in detail as this is beyond the scope of this review) (Iwata et al. 2004; Iwata and Ugawa 2005).

Task-related interactions

Numerous studies used CBI as a marker for investigating the cerebellar contribution to motor control. That is, these studies evaluated whether the inhibitory influence of the cerebellum on M1 is modulated, and hence, increased or decreased under the influence of different behavioural requirements (Hallett et al. 2017).

Tonic contraction of the target muscle. Pinto and Chen (2001), Kassavetis et al. (2011) and Panyakaew et al. (2016) examined the effect of muscle activity on CBI and found a substantial decrease of CBI during tonic contraction of the target muscle. That is, the inhibitory effect exerted by the right cerebellum on left M1 as found at rest was reduced during a tonic contraction of the right FDI (Pinto and Chen 2001). Moreover, CBI was found to be reduced in both active (i.e., right FDI) and surrounding (i.e., ADM) muscles during the onset of a tonic contraction of the right FDI as compared to rest (Kassavetis et al. 2011). In contrast, another study, from Panyakaew et al. (2016), suggested that the cerebellum might in particular be responsible for surround inhibition during the maintenance of a tonic contraction. Specifically, a reduced CBI of the target muscle (i.e., FDI) but not the surround muscles (i.e., ADM, FCR and ECR) were found during maintained tonic contraction of the FDI as compared to rest (Panyakaew et al. 2016).

Simple reaction time task. Spampinato et al. (2017) examined cerebellar–M1 interactions in the context of movement preparation. Here, CBI was measured during the preparatory period (at 90% of the RT) of a simple RT task during which participants were required to lift, either their right index finger or foot (dorsiflexion) upon the presentation of a visual 'Go' signal, presented on a screen in front of them. Their results indicated that cerebellar–M1 interactions during the movement preparation of a simple RT task are modified in a muscle-specific manner. More specifically, the magnitude of CBI in the FDI was reduced during the preparatory period of finger but not ankle movements, whereas a reduction of the amount of CBI in the TA was observed only during the movement preparation of foot but not finger movements (Spampinato et al. 2017).

Motor imagery. The influence of imagery voluntary muscle contraction on cerebellar–M1 interactions was investigated by Tanaka et al. (2018). After a brief familiarization session during which participants actually alternately maximally contracted and relaxed the FDI, CBI was subsequently measured during both imagery contraction and relaxation. The authors found a CBI disinhibition during imagery contraction relative to the imagery muscle relaxation condition. As opposed to imagery contraction, the inhibitory cerebellar–M1 interaction found at rest was not modified in the context of imagery muscle relaxation. Hence, similar to actual muscle contraction, there was a reduced inhibitory cerebellar effect on contralateral M1 (Tanaka et al. 2018).

Motor learning

Motor sequence learning. Torriero et al. (2011) assessed cerebellar–M1 interactions during motor sequence learning, and more specifically, during the actual or observation of training on a serial RT task using index finger tapping. Their results indicated a facilitation of cerebellar–M1 pathways during the ongoing learning process. More specifically, a facilitatory cerebellar–M1 interaction (i.e., reduced CBI) was found during the execution or mere observation of the fixed-ordered sequence relative to the random sequence. However, when learning already had occurred during prior observational training, facilitatory cerebellar–M1 interaction was no longer observed. These results suggest an association between cerebellar–M1 facilitation and motor sequence learning (Torriero et al. 2011).

Another study investigated cerebellar–M1 interactions in the context of motor acquisition (Baarbé et al. 2014), where participants were required to type sequences of eight letters with their right index finger for about 15 min. They found that MEP amplitudes, evoked by a TS applied

over left M1 after conditioning the right cerebellar hemisphere (ISI = 5 ms), increased following the motor sequence learning task relative to the pre-motor learning phase. Hence, the inhibitory cerebellar–M1 interactions found at rest seemed to be abolished (i.e., disinhibition; reduction of CBI) in the context of motor sequence learning. As established in a study by Spampinato and Celnik (2017), these changes in cerebellar–M1 interactions seem to be specific to early skill learning (i.e., after the first block of training). Indeed, the amount of CBI decreased following early skill learning of a sequential visual isometric pinch task. In contrast, the amount of CBI returned to baseline again later in the skill learning session, despite further performance improvement (Spampinato and Celnik 2017). In a further study, Spampinato et al. (2020b) examined how the learning of two different motor tasks (i.e., a sequential visual isometric pinch task and a finger tapping sequence training) affected CBI as elicited with either an AP- or a PA-directed TS current in the brain. Consistent with previous studies, the amount of CBI decreased during the early training phase of both motor tasks when the TS induced a PA-directed current in the brain. In contrast, CBI elicited by TS inducing an AP-directed current was only reduced during the late learning phase of the complex sequential visual isometric pinch task but not during the easier sequence learning. The authors suggest that PA- and AP-directed currents may stimulate different pathways which both play a distinct role during the learning of different tasks. In this way, CBI changes evoked by a PA-directed current could be responsible for error-dependent learning in the early learning phase of both tasks. In addition, CBI changes, evoked by AP-directed TS, may be involved in automatizing the task during late learning phase of a complex task (Spampinato et al. 2020b).

Adaptation learning. Studies that probed the role of cerebellar–M1 interactions demonstrated modulation of CBI during adaptation task practice for the upper (Schlerf et al. 2012, 2015) as well as lower (Jayaram et al. 2011) extremities. Indeed, Schlerf et al. (2012) examined the influence of adaptive visuomotor learning on CBI by means of a 'center out reaching task'. During this task, a stylus was attached to the right index finger. This was used to control a cursor that had to be moved from a central starting point to one of the eight radial points, presented in alternating order, by moving the stylus over a tablet. Participants could not look directly at their own hands during the task but received online feedback on a monitor, displaying the current cursor position. A visuomotor perturbation was presented both during the early and late learning blocks. This perturbation consisted of a rotation between the movement of the stylus on the tablet and the movement of the cursor on the monitor and could be either constant (a 30° clockwise rotation), or random (randomly selected rotations of 60° clockwise, 60° counter-clockwise, or 0°). The magnitude of CBI reduced (i.e., less right cerebellar–left M1 inhibition) after the early learning phase, followed by a CBI increase towards baseline levels during the late learning phase. This modulation did only occur during the constant condition. In contrast, cerebellar–M1 interactions were not modulated when perturbations were either random or gradual, or during unperturbed trials (Schlerf et al. 2012), thus when no effective learning could take place. This reduction of CBI, after adaptive learning, was later confirmed by Spampinato et al. (2017) using the same 'center out reaching task'. In another study, Schlerf et al. (2015) established a positive correlation between CBI modulation and performance during early learning, i.e., less endpoint variance across trials with stronger release of CBI.

In addition to its role in spatial adaptation, inhibitory cerebellar–M1 interactions have also been found to be modulated in the context of temporal adaptation. Specifically, Tanaka et al. (2021) examined CBI modulation before (baseline) and during (early and late learning phase) a coincident timing task, in which participants controlled the batting movement of a virtual batter by left-clicking a computer mouse using their right index finger. While for one group, the swing speed of the bat was increased, for the other group, the swing speed decreased. In addition, for both groups, there was a random condition in which the perturbation (i.e., higher or lower swing speed) was randomized. Similar to spatial adaptation tasks, the amount of CBI reduced during early learning as compared to baseline. This was the case for both groups when the bat swing speed was increased or decreased but not during the variable perturbation (in which adaptive learning was not possible). Furthermore, the authors demonstrated an association between CBI modulation and the degree of temporal adaptation, as participants displaying a larger reduction in CBI demonstrated greater progress in their mouse click timing (Tanaka et al. 2021).

Along the same line, Jayaram et al. (2011) have shown cerebellar–M1 modulation during locomotor adaptation on a split-belt treadmill. This movement adaptation experiment consisted of three sessions in which subjects were exposed to one of three possible locomotor conditions. Namely, a 'split-belt adaptation' condition, during which one belt

moved three times faster than the other, a 'tied random' condition, during which both belts were tied but moved at changing, unpredictable speeds and finally a 'tied constant' condition, during which both belts constantly moved at the same speed. Consistent with the findings by Schlerf et al. (2012) and Tanaka et al. (2021), a reduction of the CBI was only demonstrated during motor adaptation ('split adaptation' condition), but not in the 'tied random' and 'tied constant' condition in which adaptive learning was not required. In addition, the more CBI decreased within a session, the better participants could adapt to the 'split belt' condition (Jayaram et al. 2011).

Tracking task learning. Zabihhosseinian et al. (2020) demonstrated that the CBI modulation typically associated with motor learning decreased in participants with neck muscle fatigue. During this motor learning protocol, participants had to trace various sinusoidal waves on a touchpad using their right index finger. The amount of CBI (right cerebellum–left M1) reduction following motor learning was less in participants with neck extensor fatigue, as compared to controls. Furthermore, although both groups presented a motor learning effect (i.e., an increased accuracy), this effect was smaller in the neck muscle fatigued group relative to the control group, both immediately after the learning task and during retention. In addition, a sub-experiment revealed that neck muscle fatigue in the absence of a motor learning task increased the amount of CBI (Zabihhosseinian et al. 2020).

Summary and discussion cerebellar–M1 interactions

In sum, predominantly inhibitory cerebellar–M1 interactions were demonstrated at rest. In particular, CBI has been persistently observed at an ISI range of 5–7 ms and was found to be greater in the dominant relative to the non-dominant hand in right-handed individuals. The amount of CBI increased with increasing CS intensities, while the amount of CBI decreased with TS intensities larger than 1 mV. In contrast, facilitatory cerebellar–M1 interactions have not yet been demonstrated using ds-TMS. While the dentate–thalamo–cortical pathway has a facilitatory influence on the contralateral M1 (Allen and Tsukahara 1974), it's inhibited by the activation of Purkinje cells. With TMS over the cerebellum, it seems only possible to reach the dentate nucleus indirectly via the more superficial Purkinje cells but not via direct activation of the dentate nucleus or its fibers (i.e., superior cerebellar peduncle) (Groiss and Ugawa 2013).

Taking into account the deeper location of the cerebellum and the degree of discomfort associated with cerebellar stimulation, the use of DC coils is recommended as they reliably provoke CBI using a relatively low CS intensity (60% MSO). Additionally, in order to avoid stimulating the corticospinal tract, located in the vicinity of the cerebellum, the CS intensity should be set below the threshold for eliciting CMEPs. Alternatively, the CS intensity can be based either on a combined CS and TS, which leads to a CBI of 50%, or on the M1 threshold, correcting for the larger brain-coil distance.

Compared to other motor-related areas, cerebellar–M1 interactions were more extensively studied in the context of different motor tasks. Specifically, several studies examined this interaction during adaptation learning (Jayaram et al. 2011; Schlerf et al. 2012, 2015; Spampinato et al. 2017; Tanaka et al. 2021), motor sequence learning (Baarbé et al. 2014; Spampinato and Celnik 2017; Spampinato et al. 2020b; Torriero et al. 2011), observation of sequence learning (Torriero et al. 2011), motor imagery (Tanaka et al. 2018), and during tonic contraction of the target muscle (Kassavetis et al. 2011; Panyakaew et al. 2016; Pinto and Chen 2001) or a muscle in another limb (Pinto and Chen 2001). Specifically, the amount of CBI demonstrated at rest was found to decrease in the context of most motor tasks. Especially, CBI reduction was observed during a tonic contraction of the target muscle as well as during imagery tonic contraction. Whether the amount of inhibition is reduced both in the target and in surrounding muscles or only in the target muscle is still unclear. Additionally, CBI decreases during the preparatory period of simple RT tasks and early learning (which would correspond to peak cerebellar activity) (e.g., Spampinato and Celnik 2017). However, this reduction was also present for an extended period in the context of a temporal adaptation task (Tanaka et al. 2021), and accordingly might depend on task complexity. This task-related reduction in CBI might facilitate the acquisition of new motor skills. The cerebellar–M1 interaction appears to exhibit the greatest modulation in tasks that initially require a large degree of corrective behaviour, e.g., when one must adapt to an abrupt rather than a gradual disruption, whereas no modulation occurs when random stimuli are used. Finally, it has become apparent that the degree of CBI modulation is not only influenced by task-related factors but also other factors come into play, such as neck muscle fatigue that is related to less CBI modulation (reduction) and a lower degree of motor learning (Zabihhosseinian et al. 2020).

Table 12: Overview of studies investigating cerebellar–M1 interactions.

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction TS (in brain)	Current direction CS (in brain)	Target muscle	Main results
Baarbé et al. (2014) [*N* = 20; *16 R-handed, 4 ambidextrous*]	During motor sequence learning	R CB	L M1	CS intensity with ±50% CBI ('CBI_{50}')/ CBI_{50} + 5% MSO/ CBI_{50} + 10% MSO	0.5 mV	5 ms	TS: fig8 (90 mm, ns) CS: DC (110 mm, ns)	ns	ns	R FDI	– Disinhibition R CB–L M1/CS excitability following the motor learning task ≥ corticospinal excitability during the premotor learning condition – Inhibition ↑when the CS intensity ↑
Daskalakis et al. (2004) [*N* = 11]	At rest (influence of TS intensity)	R CB	L M1	95% aMT for CMEPs	0.2/1/4 mV	5 ms	TS: fig8 (70 mm, ns) CS: DC (110 mm)	PA	Upwards	R FDI	Inhibition R CB–L M1 at an ISI of 5 ms ↓ when TS intensity ↑ (a TS of 0.2 and 1 mV but not 4 mV resulted in inhibition)
Fernandez et al. (2018b) [*N* = 14]	At rest (influence of coil type and CS intensity)	R CB	L M1	40/50/60/70/ 80% MSO	0.8 mV	5 ms	TS: fig8 (70 mm, ns) CS: – DC (110 mm, ns) – fig8 (70 mm inner coil diameter, highly powered '$D70^{2}$')	ns	ns	R FDI	– DC coil: inhibition R CB–L M1 at intensities 60, 70, and 80% MSO, with no difference between stimulus intensities – D70 coil: did not influence corticospinal excitability at any intensity
Fisher et al. (2009) [*N* = 11]	At rest	– R CB (in between inion and R mastoid incisura) – Inion (posterior fossa)	L M1	0–20% below aMT for CMEPs	0.5 mV	3/5/ 7 ms	TS: Circular coil (ns) CS: DC (ns)	ns	– Upwards – Downwards	R FDI/ABP/ EDC/FDS	– Inhibition R CB–L M1 at ISI 5 and 7 ms but not at 3 ms – CMEPs are more easily evoked with a downwards directed current
Hardwick et al. (2014) [*N* = 15]	At rest (influence of coil type)	R CB	L M1	65/70/75/80% MSO	1 mV	5 ms	TS: fig8 (70 mm, ns) CS: – fig8 (70 mm, ns) – DC (90 mm inner diameter)	ns	ns	R FDI	– DC coil: inhibition R CB–L M1 at all intensities – Batwing coil: Inhibition at 75–80% MSO – fig8 coil: unable to provoke reliable CBI

Table 12: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction TS (in brain)	Current direction CS (in brain)	Target muscle	Main results
							– Batwing coil (70 mm, ns)				– Discomfort: DC coil + batwing coil stimulation > fig8 coil
Jayaram et al. (2011) [*N* = 9]	During adaptive learning (split-belt walking)	R CB	L M1	5% below aMT for CMEPs	ns	5 ms	TS: fig8 (70 mm, ns) CS: DC (110 mm diameter)	ns	Upwards	L TA	– CS excitability ↑ (CBI↓) after a locomotor adaptive learning task – Greater adaptation during the task correlated with larger reduction in CBI
Kassavetis et al. (2011) [*N* = 16]	During onset of tonic contraction (R FDI, 10% MVC)	R CB	L M1	5% below aMT for CMEPs	0.5–1 mV at rest (in ADM)	5 ms	TS: fig8 (90 mm outer diameter) CS: DC (110 mm)	PA	Upwards	R FDI; R ADM (surround muscle)	CS excitability ↑ (CBI ↓) in both active (i.e., R FDI) and surrounding muscles (i.e., ADM) during tonic contraction as compared to rest
Panyakaew et al. (2016) [*N* = 21]	– At rest – During tonic contraction (R FDI, 10% MVC)	R CB	L M1	90–120% adjusted* rMT (*: Equitation of Stokes et al. (2005) to accommodate brain–coil distance)	TS intensity eliciting 50% of maximum MEP	5 ms	TS: fig8 (60 mm outer diameter) CS: DC (110 mm)	ns	Upwards	R FDI; R ADM/ FCR/ECR (surround muscles)	At rest: inhibition R CB–L M1 ↑ with increasing CS intensity During tonic contraction: CS excitability ↑ (CBI ↓) in the FDI but not in the surround muscles (ADM, FCR and ECR) during tonic contraction as compared to rest
Pinto and Chen (2001) [*N* = 10]	– At rest – During tonic contraction (R FDI, 10% MVC) – During tonic contraction of another limb (L arm extension)	R CB	L M1	5% below aMT for CMEPs	0.5/2 mV	3–9/ 15 ms	TS: fig8 (70 mm) CS: DC (110 mm)	PA	Upwards	R FDI	At rest: – Inhibition R CB–L M1 at an ISI of 5–15 ms with a TS intensity of 0.5 mV – Inhibition R CB–L M1 at an ISI of 5 ms with a TS intensity of 2 mV – CBI ↓ with increasing intensity of TS (0.5 mV → 2 mV) During tonic contraction: – No inhibition during tonic contraction of the FDI, irrespective of ISI

Table 12: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction TS (in brain)	Current direction CS (in brain)	Target muscle	Main results
											During right arm extension: – No inhibition, irrespective of ISI – Facilitation R CB–L M1 at an ISI of 3 ms with right arm extension
Schlerf et al. (2012) [*N* = 26]	During adaptive learning (center out reaching task)	R CB	L M1	5% MSO below aMT for CMEPs	1 mV	5 ms	TS: fig8 (70 mm, ns) CS: DC (110 mm)	ns	Upwards	R FDI	– M1 excitability ↑ (CBI↓) early during adaptation to a visuomotor rotation task when adjusting to an abrupt but not gradual perturbation – Excitability returns to baseline later in adaptation – No correlation between CBI and the amount of learning
Schlerf et al. (2015) [*N* = 14]	– At rest – During adaptive learning (center out reaching task)	– R CB – L CB	– L M1 – R M1	5/10/15% MSO below aMT for CMEPs	1 mV	5 ms	TS: fig8 (70 mm, ns) CS: DC (110 mm, ns)	ns	Upwards	– R FDI – L FDI	At rest: – Inhibition R CB–L M1 (dominant hemisphere) > inhibition L CB–R M1 (non-dominant hemisphere) – CBI ↓ with decreasing CS intensity During adaptive learning – No correlation between the amount of CBI and the amount learned – Stronger CBI modulation (CBI ↓) is associated with fewer variance in reach amplitude in both task variants
Spampinato and Celnik (2017) [*N* = 29]	During motor sequence learning (visual isometric pinch task)	R CB	L M1	70% MSO	1 mV	5 ms	TS: fig8 (70 mm, ns) CS: DC (110 mm)	ns	Downwards	R FDI	– Inhibition R CB–L M1↓ (CBI ↓) reduced from pre-training to early skill learning, but not from pre-training to late skill learning, within the same training session

Table 12: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction TS (in brain)	Current direction CS (in brain)	Target muscle	Main results
Spampinato et al. (2017) [*N* = 22]	– During adaptive learning (center out reaching task) – During simple RT task	R CB	L M1	5/10/15/20% below rMT for CMEPs	1 mV	5 ms	TS: fig8 (70 mm, ns) CS: DC (ns)	ns	ns	R TA/R FDI	Center out reaching task: – Disinhibition R CB–L M1 (CBI ↓) after adaptive learning with the right hand, both for the FDI and TA muscles Simple RT task: – ↓ CBI in the FDI during the preparatory period (90% RT) of hand movements but not foot movements – ↓ CBI in the TA during the preparatory period (at 90% RT) of foot movements but not hand movements
Spampinato et al. (2020a) [*N* = 13]	At rest (influence of coil manufacturer)	R CB	L M1	0/−10/−20% maximum tolerated stimulus intensity	1 mV	5 ms	TS: fig8 (70 mm, ns) CS: – DC MagStim (70 mm/ 110mm coated/110 uncoated, ns) – DC MagVenture (model: D-B80; 95 mm outer diameter) – DC Deymed (model: 120BFV; 120 mm, ns)	ns	Downwards	R FDI	Deymed DC coil: – CBI could already be elicited at low intensities (from 80 to 100% of maximum tolerated stimulus intensity) MagStim DC: – The 110 mm coated/uncoated coil could elicit a reliable CBI at the maximum tolerated-stimulus intensity at high intensities (90–100% maximum tolerated stimulus intensity) – The 70 mm DC coil could only elicit CBI at the highest intensity MagVenture coil: – CBI could not be evoked

Table 12: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction TS (in brain)	Current direction CS (in brain)	Target muscle	Main results
Spampinato et al. (2020b) [*N* = 24]	– At rest – During motor sequence learning (visuomotor isometric pinch force task/finger tapping sequence)	R CB	L M1	5% below aMT for CMEPs	1 mV	3/5/7 ms	TS: fig8 (70 mm, ns) CS: DC (110 mm)	– PA – AP	Downwards	R FDI	At rest: inhibition R CB–L M1 was the highest at 5 ms following a PA-directed TS over M1 <–> inhibition R CB–L M1 was the highest at 7 ms following an AP-directed TS over M1 During a sequential visuomotor isometric pinch-force task: inhibition R CB–L M1 after a PA-directed TS reduced (CBI ↓) after early skill learning (one block of training) <–> inhibition R CB–L M1 after an AP-directed TS reduced (CBI ↓) during late skill training (following five blocks of training) During motor sequence learning: Inhibition R CB–L M1 was reduced following early sequence learning only after a PA-directed TS current
Tanaka et al. (2018) [*N* = 9]	During motor imagery (imaginary muscle contraction/relaxation)	R CB	L M1	10% below rMT for CMEPs	0.75 mV	5–7 ms	TS: fig8 (ns) CS: DC (ns)	AP	Upwards	R FDI	– CS excitability was higher during imagery muscle contraction as compared to the no imagery condition. – CBI ↑ during imagery muscle contraction as compared to the no imagery condition. – No difference between the relax and no imagery conditions voluntary relaxation of a muscle inhibits M1 excitability

Table 12: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction TS (in brain)	Current direction CS (in brain)	Target muscle	Main results
Tanaka et al. (2021) [*N* = 20]	Temporal adaptation task	R CB	L M1	CS intensity with ±70% CBI ('CBI_{70}')	1–2 mV	5 ms	TS: fig8 (90 mm outer diameter) CS: DC (110 mm, ns)	ns	ns	R FDI	– CBI ↓ during and after a temporal adaptation task – CBI modification positively correlated with task performance
Torriero et al. (2011) [*N* = 22]	– At rest – During motor sequence learning (serial RT task execution/ observation)	R CB	L M1	90% rMT	1 mV	3/ 5 ms	TS + CS: fig8 (70 mm, ns)	ns	ns	R FDI	At rest: inhibition R CB–L M1 at an ISI of 5 ms During procedural learning: *Execution:* – Facilitation R CB–L M1 at a 5 ms ISI during execution of the of the ordered sequence relative to the random sequence – No facilitation during execution of a previously observed ordered sequence *Observation:* – Facilitation R CB–R M1 during observation of the ordered but not the random sequence relative to baseline
Ugawa et al. (1995) [*N* = 8]	At rest	L CB (12 different positions)	Motor cortex (vertex)	5–10% below aMT for CMEPs	0.5–1 mV	4–8/ 10 ms	CS: DC (ns) TS: Circular coil (ns)	Anti-clockwise	Upwards	R FDI	– Corticospinal excitability ↓ after a +5, 0 or −5% aMT CS was applied over the L CB at ISIs of 5, 6 and 7 ms. – ↑ inhibition with stronger CS; – ↓ inhibition with stronger TS
Werhahn et al. (1996) [*N* = 11]	At rest	R CB (2–4 cm (DC)/8 cm (fig8) lateral to inion)	L sensory-motor cortex (vertex)	fig8: ± 80% MSO DC coil: 5–10% below the threshold for stimulating descending motor pathways	1–2 mV	3–15/ 17/ 20 ms	TS: Circular coil (90 mm) CS: – fig8 (90 mm*) – DC (120 mm*) *outer diameter	Anti-clockwise	– fig8 coil: ML – DC coil: downwards	R FDI	DC coil: inhibition R CB–L M1 at ISI = 5–8 ms fig8 coil: Inhibition R CB–L M1 (fluctuating onset) at ISI = 9–12 ms

Table 12: (continued)

Author (Year) [# subjects]	Application	Location CS	Location TS	CS intensity (% or MEP amplitude in mV)	TS intensity (% or MEP amplitude in mV)	ISI (ms)	Coils (wing diameter, average or specified)	Current direction TS (in brain)	Current direction CS (in brain)	Target muscle	Main results
Zabihhosseinian et al. (2020) [*N* = 16]	Motor skill acquisition (Tracing task); influence of induced neck muscle fatigue	R CB	L M1	– CS intensity with ±50% CBI ('CBI_{50}') – CBI_{50} + 5% MSO – CBI_{50} + 10% MSO	0.5 mV	5 ms	CS: DC (110 mm; ns) TS: fig8 coil (90 mm; ns)	ns	Upwards	R FDI	– No effect of CS intensity Control group: – CBI ↓ following motor skill learning Neck muscle fatigue group: – Less CBI reduction following motor skill learning than control group – Neck muscle fatigue in absence of motor task = ↑ CBI – Performance accuracy improvement: Fatigue < control group both directly after motor task learning and during retention

The interstimulus interval category was organized using a "/" when several ISIs were examined without a fixed interval and a "–" was used to indicate a range with 1 ms increments. ADM, abductor digiti minimi muscle; aMT, active motor threshold; AP, anterior-to-posterior-directed current; APB, abductor pollicis brevis muscle; CB, cerebellum; CBI, cerebellar brain inhibition; CMEP, cervico-medullary evoked potential, i.e., by stimulating descending motor pathways; CS, conditioning stimulus; DC, double cone coil; ECR, extensor carpi radialis muscle; EDC, extensor digitorum communis muscle; FCR, flexor carpi radialis muscle; FDI, first dorsal interosseus muscle; FDS, flexor digitorum superficialis; fig8, figure-of-eight coil; ISI, interstimulus interval; L, left; L CB, left cerebellar hemisphere; M1, primary motor cortex; ML, medial-to-lateral-directed current; MSO, maximal stimulator output; MVC, maximal voluntary contraction; ns, not specified; PA, posterior-to-anterior-directed current; R, right; R CB, right cerebellar hemisphere; rMT, resting motor threshold; RT, reaction time; TA, tibialis anterior muscle; TS, test stimulus.

Discussion

For each interaction, a summary of the overall findings and a brief discussion are provided at the end of each section in Results. Yet, the inter- and intra-hemispheric interactions described above share some particular similarities which will be discussed below. Nevertheless, some findings show inconsistencies that can be explained by methodological differences to a considerable extent. In general, it should be noted that differences in coil placement (target location) and orientation (direction of current flow), along with other parameters, may cause the recruitment of a different neural population and subsequently affect the net M1 output.

The role of the conditioned region and CS intensity at rest

Aside from some inconsistencies, it can be generally stated that, when applying a suprathreshold CS, the different motor network areas mainly inhibit M1 at rest. In contrast, rather facilitation (i.e., an increase in M1 excitability) than inhibition occurs when using a low-intensity (typically subthreshold) CS (Reis et al. 2008). As facilitatory neurons are scarce, a facilitatory effect might easily be canceled out by the much stronger inhibition since inhibitory neurons are much larger in number (Asanuma and Okuda 1962). This general tendency applies to most conditioned regions and both inter- and intrahemispheric interactions at rest, with the exception of intrahemispheric PMd–M1 interactions and interhemispheric PPC–M1 interactions. For these interactions, either the reverse phenomenon was observed, (i.e., facilitation or inhibition when conditioning PMd with a respectively lower or higher CS intensity, as suggested by Civardi et al. 2001), or the net modulation of the M1 output seemed to depend on the conditioned subregion of the PPC rather than the CS intensity [e.g., facilitation or inhibition for conditioning cIPS or aIPS, respectively, e.g., Koch et al. (2007)]. An overview of the intra- and inter-hemispheric interactions at rest is illustrated in Figure 3. To illustrate the "degree" to which results from different studies were consistent, a scale was used in which the thick, intermediate, and thin lines represent a concordance of respectively >75%, 25–75% and <25% between the results of all studies looking into this specific interaction. Yet, it should be kept in mind that not every interaction was investigated to the same extend, which means that this resulting degree should be interpreted with caution.

Interhemispheric interactions: resting-state versus task-related conditions

It is in the context of task-related ds-TMS that this technique reaches its maximal potential as it enables researchers to look into the direct influence of a certain brain region on M1 in a specific context allowing us to define the function and timing of this region's influence during certain motor actions. In general, the predominantly inhibitory interhemispheric interactions at rest often become disinhibited or modulated towards facilitation during motor tasks. More specifically, the (pre)activation of a target muscle before or during movement onset is characterized by a release of the inhibitory influence from motor areas in the resting hemisphere on M1 (i.e., disinhibition of interhemispheric interactions) or even a modulation towards facilitation, which is also apparent in movement observation tasks. This facilitatory modulation applies to M1, PMv, SMA, DLPFC and CB and happens to be task-specific as it mainly affects the MEPs of task-relevant muscles (Davare et al. 2009; de Beukelaar et al. 2016; Koch et al. 2010b; Vesia et al. 2017). Such specificity lends credibility to the genuine nature of the interaction. This modulation might be interpreted as an information exchange supporting successful task performance (Serrien et al. 2006) since a positive relationship between a facilitatory modulation and performance on the task has been demonstrated (Fujiyama et al. 2016a; Jayaram et al. 2011; Liuzzi et al. 2011; Tanaka et al. 2021).

Yet, these general statements do not apply to all regions. Specifically, for interhemispheric interactions, the right IPL had a facilitatory influence on M1 at rest, which was reduced to zero or even shifted to inhibition in a task-related context (Lebon et al. 2012). According to recent literature, this initial inhibition of both effectors and surround muscles, might down-regulate the motor system (i.e., 'preparatory suppression') to assist the gain excitatory processes delivered by facilitatory interactions to activate the effectors of the upcoming task (Derosiere et al. 2020; Duque et al. 2017). In addition, there is ambiguity with regard to interhemispheric PMd–M1 interactions. Although most studies demonstrated that PMd, like other premotor regions, exerts a predominantly inhibitory influence on the contralateral M1 at rest (e.g., Fujiyama et al. 2016a; Mochizuki et al. 2004a), a facilitatory influence could be elicited when applying subthreshold CS intensities on the dominant (left) PMd (Bäumer et al. 2006; Koch et al. 2006) or after stimulating the non-dominant (right) PMd with an ISI of 80 ms (Fiori et al. 2017). However, it should be kept

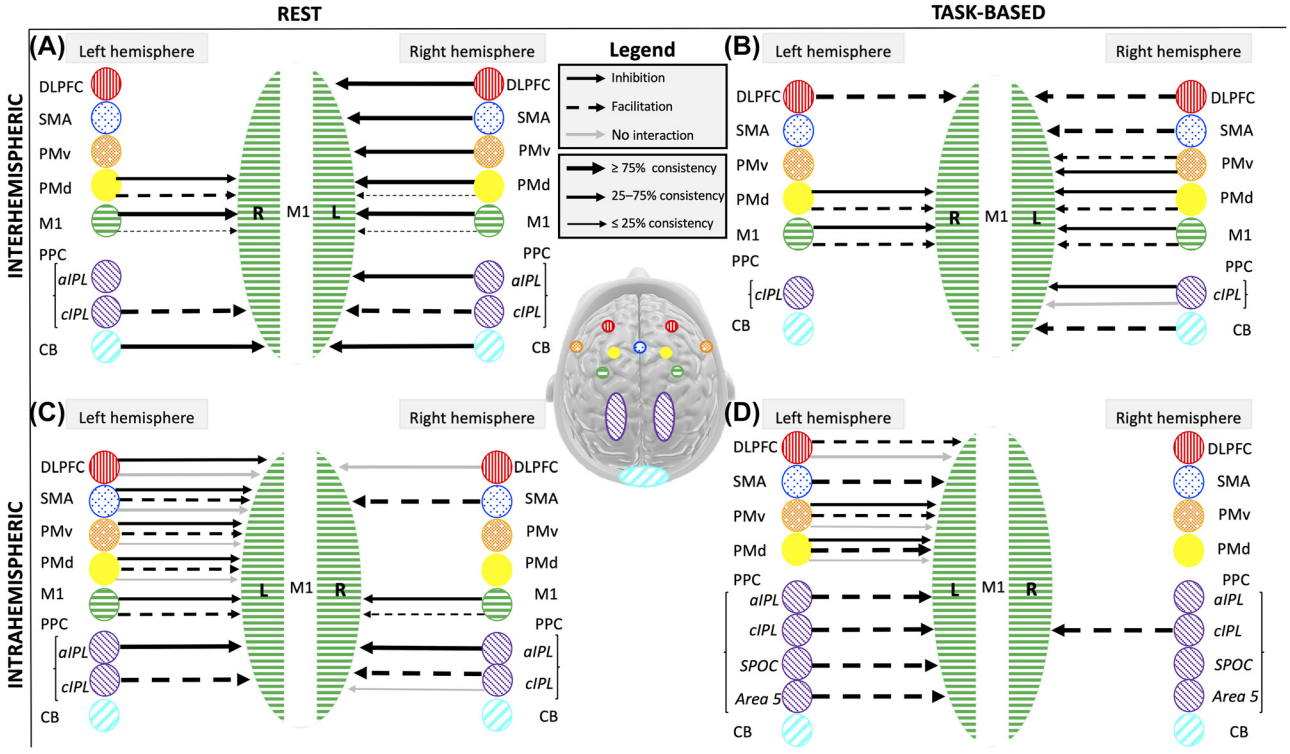

Figure 3: Overview of inter- and intrahemispheric interactions at rest and in the context of a motor task. Full arrows represent a facilitatory influence while dashed lines indicate an inhibitory influence. In contrast, gray lines indicate that no interaction was found, while thinner/thicker lines indicate the degree to which this particular influence (i.e., facilitation or inhibition) was demonstrated. Specifically, the thickest line indicates that ≥75% of the studies demonstrated a specific result while the intermediate and thin line indicate that 25–75% and ≤25% of the studies demonstrated similar results, respectively. aIPL, anterior part of the lobus parietalis inferior; BA5, Brodmann area 5; CB, cerebellum; DLPFC, dorsolateral prefrontal cortex; IPL, lobus parietalis inferior; M1, primary motor cortex; pIPL, posterior part of the lobus parietalis inferior; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PPC, posterior parietal cortex; SMA, supplementary motor cortex; SPOC, superior parietal-occipital cortex.

in mind that not all studies showed consistent results. Moreover, it has been suggested that left PMd–right M1 and right PMd–left M1 interactions are differently modulated in the context of motor tasks (Fujiyama et al. 2016a; Koch et al. 2006). Here, left PMd–right M1 interactions were facilitated during the preparation of uni- (when left-hand movement was required) and bi-manual tasks, whereas right PMd–left M1 interactions were not modulated (Fujiyama et al. 2016a; Koch et al. 2006). These findings suggest a dominant role for the left PMd, controlling both the left and right hand (Verstraelen et al. 2021), and are consistent with the dominant role of the left hemisphere in motor control, in right-handed individuals (Schluter et al. 1998; Serrien et al. 2006). Yet, O'Shea et al. (2007) contradict this, as they did not find a difference between the modulation of left PMd–right M1 and right PMd–left M1 interactions during a simple RT task.

Furthermore, while M1–M1 inhibition at rest was (partially) released during the preparatory period of various tasks requiring movement of the target muscle, a tonic contraction of either the target muscle or its contralateral homologue led to contradictory results, showing either an increase (Chen 2004; Sattler et al. 2012) or decrease (Ferbert et al. 1992; Mochizuki et al. 2004a) in SIHI, or an increase in both SIHI and LIHI (Nelson et al. 2009). Moreover, the decrease in inhibition or modulation towards facilitation observed for SIHI seemed rather specific [e.g., only for the responding hand during simple and choice RT tasks (Duque et al. 2007; Hinder et al. 2018) and not during bimanual movements (Fujiyama et al. 2016a)], whereas task-related LIHI modulation during similar tasks seemed to be more generalized (e.g., affecting both hands) (Duque et al. 2007; Fujiyama et al. 2016a; Hinder et al. 2018).

Finally, for the non-selected limb, M1 and PMd exert an inhibitory influence on the contralateral (resting) M1 which is assumed to be responsible for suppressing involuntary mirror movements during unimanual motor tasks (Duque et al. 2007; Giovannelli et al. 2009; Koch et al. 2006). This phenomenon is suggested to promote the independent

functioning of each hemisphere, as suggested by neuroimaging (Newton et al. 2005) and neurophysiological evidence (Giovannelli et al. 2009; Perez and Cohen 2008). Yet, recent research indicated the involvement of subcortical regions in the occurrence of mirror movements subcortical regions may underly mirror movements (Ejaz et al. 2017, 2018). Moreover, it was proposed that these inhibitory interactions are responsible for a form of surround inhibition that subsequently affects the net output of M1, rather than for an imprecise and undifferentiated inhibition of the contralateral hemisphere (Carson 2020; Derosiere and Duque 2020).

Intrahemispheric interactions: resting-state versus task-related conditions

Although less apparent as interhemispheric interactions, intrahemispheric interactions at rest are predominantly inhibitory and often become disinhibited or modulated towards facilitation in the context of motor tasks executed with the contralateral hand. Exceptions are the intrahemispheric PMd–M1 and SMA–M1 interaction, which demonstrated variable results. Additionally, the aIPL exerts a facilitatory rather than an inhibitory influence on ipsilateral M1 at rest, which remains unchanged in the context of a motor task. It should be noted that there still exists a lack of consensus on the optimal placement of coils and the optimal protocol concerning intrahemispheric (in particular PMd–M1 & SMA–M1) interactions. Hence to draw valid conclusions, the implementation of standardized protocols is required in future research.

Summary

Most interactions were investigated from the non-dominant to the dominant hemisphere or within the dominant hemisphere (in right-handed subjects). Furthermore, M1–M1 interactions were studied much more intensively as compared to other interactions. It could be argued that connectivity between the two motor cortices is central to motor control and, more generally, to the critical interaction between the two hemispheres (Takeuchi et al. 2012). In addition, the established knowledge regarding its underlying mechanisms and pathways, and the ease to localize M1 using TMS could potentially also explain the frequency with which connectivity between both M1s was examined. Finally, it should be noted that intrahemispheric interactions are typically investigated at shorter latencies [i.e., PMd–M1 (ISI = −0.5 to 15 ms (for CS after or before TS, respectively)); PMv–M1 (ISI = 1–15 ms), DLPFC–M1 (ISI = 4–30 ms), SMA–M1 (ISI = 2–8 ms) and PPC–M1 (ISI = 2–20 ms)], while interhemispheric interactions were investigated at both short and longer latencies, with ISIs up to 400 ms [i.e., M1–M1 (ISI = 2–150 ms), PMd–M1 (ISI = 3–150 ms), PMv–M1 (ISI = 8–400 ms), DLPFC–M1 (ISI = 4–100 ms) and SMA–M1 (ISI = 6–150 ms)], except for the PPC–M1 and cerebellar–M1 interaction (ISI = 4–20 ms and 3–17 ms, respectively).

From the results section, it can be concluded that not only the extent to which a particular region was studied but also the extent to which different authors obtained similar results, varied widely.

In conclusion, while interhemispheric interactions from the resting acting on the active hemisphere are dominantly inhibitory at rest, they often become modulated towards facilitation (disinhibited) in the context of performance of motor tasks, based on the specific task demands. Regions exerting an inhibitory rather than a facilitatory influence on M1 during the preparatory period of motor actions, on the other hand, might contribute to the establishment of 'preparatory suppression', allowing facilitatory interactions to activate the effectors by down-regulating the system (Derosiere et al. 2020; Duque et al. 2017). The inhibitory influence exerted on non-selected muscles (e.g., in the context of a choice reaction task) and muscles irrelevant to the emerging task appears to increase progressively and may account for the suppression of mirror movements of the contralateral homologous muscles and undesired motor actions or muscle activity (Derosiere and Duque 2020; Morishita et al. 2012; Uehara et al. 2013; Vercauteren et al. 2008). Yet, it is the net output of M1 that defines motor behaviour. It might be that intra- and inter-hemispheric inhibition not only counteract an excess of excitation of the ipsi- or contra-lateral hemisphere, respectively (resulting in mirror movements) but also shapes the overall output of M1 (Carson 2020; Derosiere and Duque 2020; Georgopoulos and Stefanis 2007). Based on the principle of functional integration, this balance between inhibition and facilitation might mold the output of M1 into more meaningful and economic action, supporting accurate movement control, with each region of the motor network having its specific task (Friston 2005). Moreover, these dynamic interactions between distinct brain regions between and within hemispheres are dependent on the specific task, task complexity, and the skill-level of the performer (Serrien et al. 2006).

It should be kept in mind that ds-TMS does not necessarily reflect a pure quantification of a specific interaction between a particular area and M1, but is rather an expression of the total effect of the various influences acting

simultaneously on M1 (Reis et al. 2008). Changes in ds-TMS induced connectivity between a specific motor-related brain region and M1 in the context of a motor task might therefore depend on the altered influence of another region – which is part of the same functional motor network – also acting on M1. Since the present review illustrates the discrepancy between regions engaged in various tasks and the specific modulation of intra- and inter-hemispheric interactions in the context of different motor tasks and/or states, generalization from a specific task context to a different one should be done with great care.

Limitations of ds-TMS protocols

Using ds-TMS it is possible to investigate the effective connectivity between motor-related regions and M1 (Koch and Rothwell 2009) or between the homologous M1s. This has allowed researchers to identify the origin of modulatory changes in M1 output, and particularly during motor task performance and learning (Di Lazzaro and Rothwell 2014). Nevertheless, studies using this methodology face some practical limitations, which are briefly discussed below.

First, even though ds-TMS allows identifying the motor regions that influence M1 in a given context, it does not allow pinpointing the anatomical pathways that mediate this interaction. In particular, it is unclear whether influence on M1 is exerted directly by the conditioned region or whether this region exerts an indirect influence via other relay regions. For example, in line with the disynaptic anatomical pathway connecting the PPC to both M1s and the PMv (Matelli et al. 1998), it has been suggested that the PPC, at least partly, influences M1 via PMv, during grasping and reaching related motor tasks (Koch et al. 2010a; Shields et al. 2016). The PMv would obtain visual information about the properties of the object "to-be-grasped", necessary for selecting the correct grasping configuration, through the PPC (Luppino and Rizzolatti 2000; Murata et al. 1997). Hence, while for some of the pathways depicted in Figure 3 there is sufficient evidence to make an educated guess about the brain regions involved, others are speculative and need further testing. DWI studies using tractography might provide more insight into the putative interconnectivity between different brain regions. A combination between DWI and TMS may allow researchers to identify potential direct and/or indirect connections, and based on the duration of ISIs, provide insight into which connection may be mediating the interaction (Fujiyama et al. 2016b). Consequently, we would like to point out that the enclosed figure should be regarded as a summary of currently available evidence, without being an exhaustive depiction of the motor network and all its pathways.

Second, as highlighted by Chipchase et al. (2012), there is considerable inter- and intra-individual variability in TMS findings, and TMS responses can be impacted by methodological, physiological and environmental differences among studies.

A third common concern is the limited number of participants included. Specifically, a minimum of 3 and a maximum of 33 participants, and on average 15 participants per study, with subgroups ranging from 3 to 11 participants, were included. This affects statistical power and compromises the reproducibility of results (Button et al. 2013).

A fourth limitation concerns the variability of MEPs (Kiers et al. 1993; Roy Choudhury et al. 2011) and consequently the number of pulses required per TMS condition. As compared to sp-TMS, ds-TMS might be even more prone to variability as two, instead of one coil, need to be positioned correctly (Kiers et al. 1993; Magistris et al. 1998; Rosler et al. 2002; Roy Choudhury et al. 2011). Chang et al. (2016) and Biabani et al. (2018) showed that the most accurate estimate of corticospinal excitability can only be achieved employing at least 20–23 consecutive stimuli using sp-TMS, while 20–26 pulses were required to obtain reliable results using double-pulse TMS. For ds-TMS, there are currently no guidelines referring to the most optimal number of TMS pulses per condition, but based on the current literature, we recommend at least 20–30 pulses per condition. However, participant comfort should also be taken into account, and thus both the duration of the experiment, the discomfort due to postural requirements, and the number of stimuli should be kept to a justifiable minimum. Secondly, the recording of MEPs at rest as well as prior to or during motor tasks necessitates the monitoring of background EMG activity, which might alter MEP amplitude, thereby influencing inter-regional interactions. It is therefore proposed to register the MEPs in both muscles selected for the upcoming action (e.g., in the right FDI muscle before or during movement of the right index finger), and non-selected muscles that are part of the effector repertory (e.g., in the left FDI muscle before the movements of the right index finger). Individual MEPs are often excluded from analysis if the root mean square EMG exceeds 20 μV (Cuypers et al. 2020, 2021). Alternatively, it can be argued that only those MEPs that deviate more than

2 standard deviations (i.e., variation limits of background EMG activity) from the mean EMG activity are removed rather than those MEPs that exceed a fixed value since some people have a higher standard background EMG [e.g., elderly (Skarabot et al. 2019)].

A fifth limitation is the determination of the target location and coil orientation for applying the CS. Although various techniques have been used to determine the optimal target location, they are not equally reliable due to factors such as inter-individual differences in head shape and brain surface (Good et al. 2001; Laakso et al. 2014; Menzler et al. 2011). This lack of standardized procedures for determining the target position might be a possible explanation for the diversity in results between studies, as small differences in coil position may result in recruitment of different neural populations and, hence, give rise to different findings. According to the study of Sack et al. (2008), navigating the TMS coil relative to positions in the 10–20 EEG system only has limited spatial accuracy (about 1 cm). On the other hand, (f)MRI-based anatomical landmarks of an individual, guided by neuronavigation, was found to be a more effective approach, yielding the most reliable results. This navigated brain stimulation is based on the co-registration of the coil and subject's head in a virtual space permitting an exact determination of a cortical target on a three-dimensional reconstruction of the brain from individual MRI data (Ahdab et al. 2010; Ruohonen and Karhu 2010). Even though neuronavigation based on structural MRI takes interindividual differences in cranial shape and underlying brain structure into account, few motor-related regions have reliable anatomical landmarks (Sandrini et al. 2011). In addition, individual differences in gyral folding and cortical layering must be taken into account. Finally, it does not account for inter-individual variation in the functional organization (i.e., structure–function differences) of the brain. Neuronavigation based on fMRI on the other hand enables the identification of target locations based on individually determined functional activation maps and is therefore considered to yield the highest stimulation accuracy (Sack et al. 2008; Sandrini et al. 2011; Sparing et al. 2008). Nevertheless, it is not always possible to place both coils at their optimal target location or orientation (i.e., constraints on the direction of stimulation due to coil geometry), especially in intrahemispheric interactions when the targets are in close proximity [e.g., intrahemispheric PMd–M1 interactions (Van Hoornweder et al. 2021) or SMA–M1 interactions (Shirota et al. 2012)]. The wide range of coil orientations, visualized in Figures 4 and 5, has been applied to overcome this problem. In addition, major innovation in coil manufacturing may also partly explain

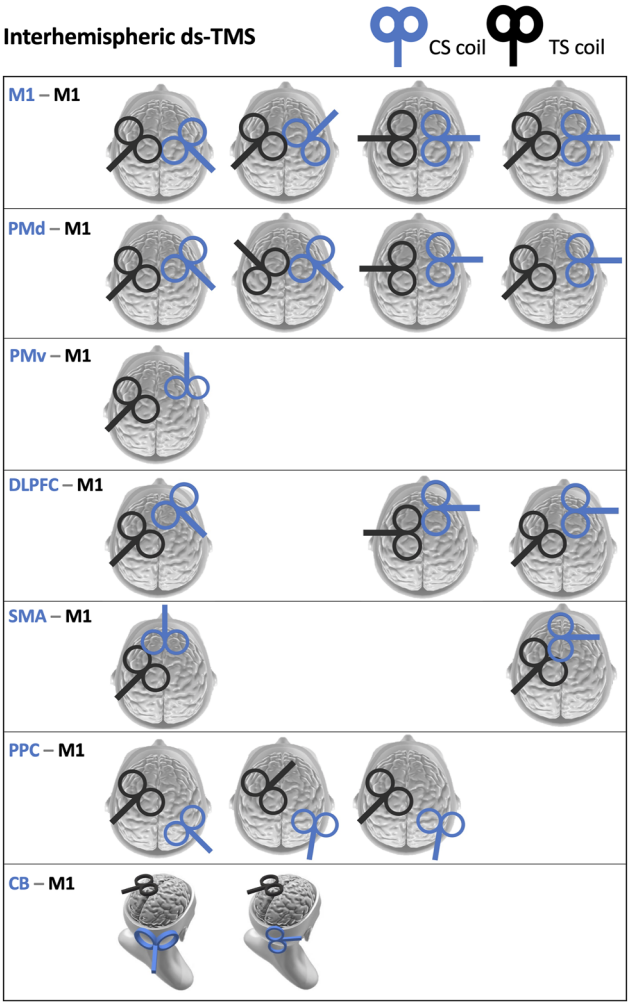

Figure 4: Overview of the coil orientations used to examine interhemispheric interactions. This figure provides an overview of the different coil orientations used to stimulate a certain brain region. The reader should note that interhemispheric interactions were illustrated only from the left (M1) to the right hemisphere. In addition, no distinction was made between the actual coil size and the orientation of the coil handle (i.e., in plane or orthogonal to the coils). This simplification provides a better overview with respect to the number of different orientation choices made. CS, conditioning stimulus; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PPC, posterior parietal cortex; SMA, supplementary motor area; TS, test stimulus.

this variety as coils with various shapes, sizes, cooling options, etc. might allow for more optimal coil orientations. An additional element that may contribute to the suboptimal localization of the target area is the design of the TMS coils (e.g., circular coil, figure-of-eight coil, or DC coil); besides the desired stimulation, these also generate distinct/undesired current flow in the brain. Whereas a circular coil produces a non-focal ring-shaped electric field that may also stimulate a large part of the brain areas

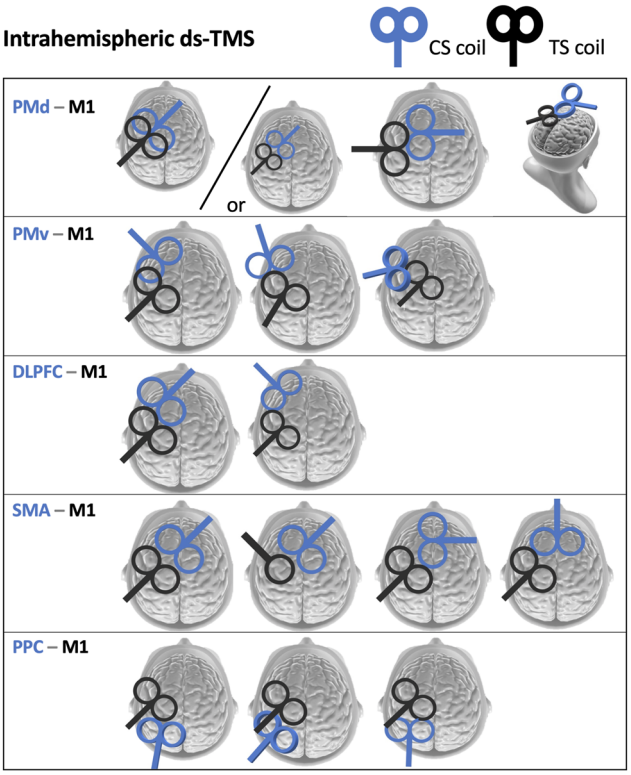

Figure 5: Overview of the coil orientations used to examine intrahemispheric interactions. This figure provides an overview of the different coil orientations used to stimulate a certain brain region. The reader should note that intrahemispheric interactions were illustrated only in the left hemisphere. In addition, no distinction was made between the actual coil size and the orientation of the coil handle (i.e., in plane or orthogonal to the coils). This simplification provides a better overview with respect to the number of different orientation choices made. CB, cerebellum; CS, conditioning stimulus; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PPC, posterior parietal cortex; SMA, supplementary motor area; TS, test stimulus.

located below the coil circumference, figure-of-eight coils are more focal (Deng et al. 2013; Ravazzani et al. 1996). Along the same lines, DC coils are used for targeting deeper structures (e.g., leg muscles or the cerebellum) since they generate a more deeply penetrating magnetic field (Deng et al. 2013; Lontis et al. 2006). Nevertheless, the magnetic field depth of this coil appears to come at the expense of focality (Deng et al. 2013; Schecklmann et al. 2020). It should be noted that subcortical structures cannot be examined with TMS since they are located too far from the surface to be reached by TMS. As a consequence, their influence on M1 excitability received only limited attention in the context of ds-TMS studies.

A final methodological limitation concerns the lack of reporting stimulation parameters in sufficient detail, and especially the current flow direction and waveform of the magnetic pulse. It is important to note, that the exact neural population/pathway that is stimulated depends on both parameters [(e.g., Casula et al. 2018; Davila-Perez et al. 2018; Di Lazzaro et al. 2001; Sommer et al. 2018; Spampinato 2020); reviewed in (Derosiere et al. 2020)]. The absence of this information limits the comparability of study results, as well as their reproducibility (Chipchase et al. 2012). In addition, it is not always possible to induce a certain current direction due to spatial limitations when both coils are positioned in close proximity to each other, or when the coil and head geometry do not allow it. For example, when a DC coil is placed at the back of the head to target the cerebellum, it can only be done horizontally (inducing an up- or downward current in the brain), since the angle of this coil corresponds to the curvature of the head only in this position.

Future perspectives and suggestions for optimizing the reliability and reproducibility of ds-TMS experiments

As indicated, future ds-TMS studies should focus on increasing their reliability, reproducibility and comparability. This might be reached by optimizing two main factors, namely the clear record of all methodological characteristics of a study, and the use of tools in order to reduce the variability of ds-TMS output. Furthermore, it is also important that a sufficient number of subjects are included per group and enough pulses are given per TMS condition.

As for reporting the methods, an expert panel noted in the study of Chipchase et al. (2012), that gender, age (Pitcher et al. 2003) and methodological factors including the current direction (Hill et al. 2000) and waveform of the TMS pulse (Sommer et al. 2006, 2018), coil positioning (Conforto et al. 2004), stability of coil location (Ahdab et al. 2010) and EMG electrode placement (Rossini et al. 1999) must be reported as they contribute significantly to TMS variability. Furthermore, basic parameters such as coil type and size should always be clearly stated (e.g., Fernandez et al. 2018b). In addition to reporting the coil type, their respective coil position, pulse shape and the current directions used, as stated in the review of Chipchase et al. (2012), mentioning the specific stimulation coordinates (when using MRI images) is recommended. Reporting these parameters promotes the reproducibility of studies.

Furthermore, it is preferable to use an individual anatomical, neuronavigation-based, approach to reliably

define cortical targets because craniometric methods do not take into account inter-individual variability, with the risk of stimulating adjacent brain regions (Sack et al. 2008). Moreover, the use of neuronavigation during data acquisition is recommended for stereotactic reasons, i.e., to keep coil position, rotation and angle stable and consequently reduce variability in coil placement. This is especially relevant for ds-TMS as using two different coils increases the risk of coil movement, further increasing variability. Moreover, electric field simulations (Thielscher et al. 2015) can be valuable to verify the stimulated brain regions post-hoc.

In addition or alternatively, given the large inter-individual variability concerning the optimal stimulation location to induce either facilitation or inhibition, Karabanov et al. (2013) suggested determining the optimal stimulation point (for the PPC) using a mapping method similar to the procedure for determining the M1 hotspot as localization of these areas was found to be difficult when using anatomical information alone. Thus, researchers might systematically move the CS coil in small steps over a specific cortical region, while recording conditioned MEPs at each location and finally choose the CS location with the highest modulation of the M1 output, based on anatomical prerequisites.

Furthermore, it is recommended to always include a rest measurement as a baseline when investigating connectivity changes in the context of a specific motor task since the initial state of the targeted brain region influences the neural impact of a task-related stimulus (i.e., state-dependency of TMS) (Silvanto et al. 2007; Silvanto and Pascual-Leone 2008).

When targeting multiple brain regions in close vicinity, sufficiently small coils should be chosen to avoid coil overlap. However, a trade-off between coil size, stimulation depth, and focality, where smaller figure-of-eight coils are more focused but unable to stimulate deeper structures, should be kept in mind (Deng et al. 2013). Additionally, smaller coils require higher stimulus intensities to elicit an MEP, leading to participant exclusion when the (individually determined) required stimulation intensity cannot be reached. Another issue of small coils used at high stimulation intensities is coil heating, necessitating a cooling solution or reducing the number of consecutive pulses applied, in turn increasing the variability of study results.

Finally, researchers should calculate the number of participants required *a priori* in order to include a sufficient number of subjects per group. Since effect sizes and/or individual data of studies are rarely reported and the estimates of effect sizes are often exaggerated in smaller studies with too little power, i.e., the 'winner's curse' (Button et al. 2013), *a priori* power calculations are preferably based on pilot data. In addition, it is important to report the effect size (or alternatively individual data).

Alternatives to ds-TMS

An alternative to ds-TMS is multi-locus TMS. This is a promising technique in which a set of overlapping coils is used, rendering the choice of any target location in the cortex while stimulating this target location in the desired direction (Koponen et al. 2018). The advantage of this technique is the ability to stimulate distant brain regions in close succession and, hence, to measure causal connectivity between different nodes of a pathway. However, the use of this technique is to date limited due to its novelty, and currently, only a number of methodological papers have been published (Koponen et al. 2018; Nieminen et al. 2019; Salo et al. 2019; Tervo et al. 2020).

Furthermore, ds-TMS protocols can be enhanced by the use of alternative TMS techniques. Anatomical studies, both in monkeys and humans, show that the influence of one brain region on another can be exerted through one or more relay regions [e.g., PPC–M1 interactions might be relayed via ipsilateral PMv (Koch et al. 2010a; Matelli et al. 1998)]. While ds-TMS cannot distinguish whether interactions occur via a direct or indirect pathway, there are TMS paradigms in addition to (a combination of) medical imaging techniques that can be used to determine the influence of a third region. Firstly, ds-TMS can be combined with rTMS. Here, an area that presumably acts as an intermediate link can be transiently "disrupted" by rTMS, after which the interaction between the two remaining areas is re-examined by ds-TMS. When this interaction is disrupted by rTMS, it may be assumed that the interaction is mediated by that region. For example, Koch et al. (2010a) revealed that the initially facilitating left PPC–left M1 interaction was disrupted after applying continuous theta-burst stimulation (cTBS) on the left PMv to create a transient lesion. Secondly, a "three-pulse technique" can also be used in which a preconditioning, a conditioning, and a testing stimulus are applied sequentially. For example, Shields et al. (2016) demonstrated that the initial inhibitory intrahemispheric left PMv–M1 interaction was reversed when a preconditioning stimulus was applied over the ipsilateral PPC, suggesting a PPC–PMv–M1 pathway in the left hemisphere.

Conclusions

Ds-TMS is an emerging valuable technique to assess the causal influence of remote (motor-related) brain regions interconnected to the ipsi- and/or contra-lateral M1. This extensive literature review highlights that intra- and inter-hemispheric interactions are engaged in a wide range of motor performance and learning tasks, and are often modulated in a muscle-, task- and timing-specific manner.

However, this review has also revealed remarkable variability in the experimental context for assessment of inter- and intra-hemispheric interactions as well as in the use and reporting of stimulation parameters. Since these parameters crucially determine the outcome, their inconsistency hampers an objective comparison of results among studies. While some paradigms have led to predictable and consistent results, others stand out in inconsistency. Therefore, we strongly suggest that future studies should include a sufficient number of participants, an optimal amount of TMS pulses per condition, and carefully report all critical parameters. Finally, we hope that the results of this review can help to clarify inconsistencies between previous studies, identify novel research questions and experimental contexts, and serve as a guide for both the experimental design and reporting of future studies.

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