Neuroscience and Biobehavioral Reviews 113 (2020) 39–50

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Are unimanual movements bilateral?

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ARTICLE INFO

Keywords:
Unimanual
Interhemispheric
Motor cortex
Motor coordination
Corpus callosum
Bilateral activation
Electroencephalography (EEG)
Magnetoencephalography (MEG)
Transcranial magnetic stimulation (TMS)
Functional magnetic resonance imaging (fMRI)
Structural MRI

ABSTRACT

Motor control is a fundamental challenge for the central nervous system. In this review, we show that unimanual movements involve bi-hemispheric activation patterns that resemble the bilateral neural activation typically observed for bimanual movements. For unimanual movements, the activation patterns in the ipsilateral hemisphere arguably entail processes that serve to suppress interhemispheric cross-talk through transcallosal tracts. Improper suppression may cause involuntary muscle co-activation and as such it comes as no surprise that these processes depend on the motor task. Identifying the detailed contributions of local and global excitatory and inhibitory cortical processes to this suppression calls for integrating findings from various behavioral paradigms and imaging modalities. Doing so systematically highlights that lateralized activity in left (pre)motor cortex modulates with task complexity, independently of the type of task and the end-effector involved. Despite this lateralization, however, our review supports the idea of bi-hemispheric cortical activation being a fundamental mode of upper extremity motor control.

1. Introduction

Coordination between the hands is an important and seemingly easy everyday skill. Arguably, it relies on communication between homologous cortical areas, first and foremost between left and right parts of the motor network (Carson, 2005; Donchin et al., 1999, 1998). This interaction is likely also present when moving hands individually, since a mere, passive crosstalk through commissural white matter tracts may contribute to a ‘communication’ between left and right hemispheres. However, there must be a way to control this interaction to switch from coordinated (bilateral) hand movements to individual ones, with unimanual movements being the most extreme case of the latter.

The largest commissural fiber structure is the corpus callosum (CC) (Gazzaniga, 2000; Innocenti, 1986), which consists of four individual nerve tracts: the genu, the rostrum, the trunk and the splenium (Georgy et al., 1993). Early primate studies underlined the importance of the CC in coordinating the upper extremities (Tanji et al., 1988). Seminal studies on callosotomy revealed deviations from ‘normal’ coordination patterns (Brinkman, 1984; Brinkman and Kuypers, 1972; Gazzaniga, 1966; Mark and Sperry, 1968) and showed that the coupling between two hemispheres results from interhemispheric communication through the CC (Diedrichsen et al., 2003). Transcallosal pathways can be both excitatory and inhibitory (Swinnen, 2002; Ziemann et al., 1999). Arguably, fast excitatory pathways are responsible for synchronized, i.e. in-phase, motor activity targeting homologous brain areas, whereas inhibitory pathways serve to suppress such a ‘spill-over’ and enable individual movements. Such a suppression of excitation could be direct or indirect. In the latter case, activation of the left primary motor area (M1) may excite premotor cortex and/or supplementary motor area (PM and SMA, respectively) in the right hemisphere, which in turn might inhibit the right M1 through inhibitory cortico-cortical connections (Daffertshofer et al., 2005; Stinear and Byblow, 2002). Either way, if excitatory crosstalk is present by default, inhibition has to be ‘optimal’ to produce proper unimanual movements. Unsuccessful

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https://doi.org/10.1016/j.neubiorev.2020.03.002
Received 22 October 2019; Received in revised form 7 February 2020; Accepted 2 March 2020

inhibition potentially yields mirror activity causing, e.g., unwanted mirror movements (Daffertshofer et al., 1999).

Several recent papers provided overviews of behavioral and neural determinants of bimanual coordination (Gooijers and Swinnen, 2014; Maes et al., 2017; Rueda-Delgado et al., 2014; Swinnen, 2002; Van Wijk et al., 2012b). Neural crosstalk can influence movement characteristics, as illustrated by spontaneous switches in coordination patterns (Aramaki et al., 2005; Houweling et al., 2010). This neural crosstalk can also be identified in unimanual movements (Daffertshofer et al., 2000; Fuchs et al., 2000a, b) and therefore it is conceivable that behavioral and neural determinants of bimanual coordination may also apply to unimanual movements (Daffertshofer et al., 2005; Gross et al., 2005; Vercauteren et al., 2008). With the present review, we seek to substantiate this idea by specifying these determinants and the functional role of the often-reported, bilateral activation patterns in the cortex during unilateral hand movements in healthy humans. To do so, we highlight structural and functional transcallosal connectivity during the performance of unimanual movements as assessed via different non-invasive imaging modalities.

1.1. Unimanual movements

We consider unimanual movements a special case of bimanual ones. Both entail activity in bilateral M1s (Babiloni et al., 1999; Baraldi et al., 1999; Ghacibeh et al., 2007; Kim et al., 1993; Rao et al., 1993). In the unimanual case, the contralateral M1 is far more active than its ipsilateral counterpart. The presence of neural activity in both M1s, however, suggests that performing unimanual movements involves the inhibition of ipsilateral motor areas – see also Grillner (2015) for an interesting discussion. As outlined above, this kind of inhibition can suppress the (co-)activation of the homologous limb, eventually allowing for moving one hand only. Suppose that interhemispheric pathways are (primarily) excitatory. Then, the resulting activation has to be inhibited within one hemisphere, i.e. intrahemispherically (Stinear and Byblow, 2002). Daffertshofer et al. (2005) proposed that such an intrahemispheric inhibition may be mediated through premotor areas: Contralateral M1 projects through the CC to ipsilateral M1 yielding – in the case of unimanual movements apparently unwanted – left/right interference. If the same contralateral M1 also projects to the ipsilateral PM that is simultaneously excited, and when assuming that intrahemispheric connections from PM to M1 are primarily inhibitory, then the latter is inhibited whenever PM is activated in time.

The model of interhemispheric excitation and intrahemispheric inhibition is depicted in Fig. 1 (panel B). It will serve as our primary vehicle to elucidate bilateral cortical activity during unilateral movements of the upper extremities. Yet, there are several alternatives, also sketched in the same figure (panels A & C). We will return to these alternatives in the *Discussion* section below.

1.1.1. Task dependence

Dependent on the motor task being performed, more and larger neural populations are recruited in (bilateral) SMA (Freund, 1996; Halsband et al., 1993; Kaiser et al., 2000; Ohara et al., 2000) and (ipsilateral) PM (Stippich et al., 2000), especially during more challenging tasks (Mayville et al., 2002). That is, the bilaterality of neural activation patterns appears strongly affected by timing requirements of movements, e.g., discrete, isolated movements yield predominantly unilateral activation, whereas sequential unimanual motor behaviors are accompanied by (symmetrical) bilateral activation (Andrew and Pfurtscheller, 1999; Babiloni et al., 1999; Cheyne and Weinberg, 1989; Manganotti et al., 1998; Pfurtscheller et al., 2000; Pulvermuller et al., 1995). Transcallosal excitation and intrahemispheric inhibition are hence not constant across all possible unimanual movements. Gerloff et al. (1998b) suggested that even 'simple' voluntary movements cause exigencies prompting the motor system to respond by increasing not only the regional activation but also the information flow between hemispheres.

1.2. Modalities

Since we seek to contribute to a more general understanding of fundamental motor control, we particularly focus on studies including normal, healthy subjects. There are various non-invasive recording methods that can serve to (in-)directly assess brain activation patterns as well as functional and structural connectivity (FC, SC) of the brain. The methods included in this review are transcranial magnetic stimulation (TMS), electro- and magneto-encephalography (EEG and MEG, respectively), functional magnetic resonance imaging (fMRI) as well as structural MRI, including diffusion weighted or tensor imaging (DWI and DTI, respectively). Currently, these are the most prevalent techniques in the study of motor-related neural activity in healthy humans. In the following, we briefly sketch their functioning including advantages and disadvantages when studying structural and functional transcallosal connectivity.

1.2.1. TMS

In TMS, a rapidly changing, focal magnetic field induces an electric current flow in selected cortical areas (Kobayashi and Pascual-Leone, 2003). When applied over the motor cortex, a single magnetic stimulus can elicit muscle activation (a so-called twitch) which can be measured using conventional electromyography (EMG) (Edwards et al., 2008). The resulting motor-evoked potential (MEP) reflects the excitability of

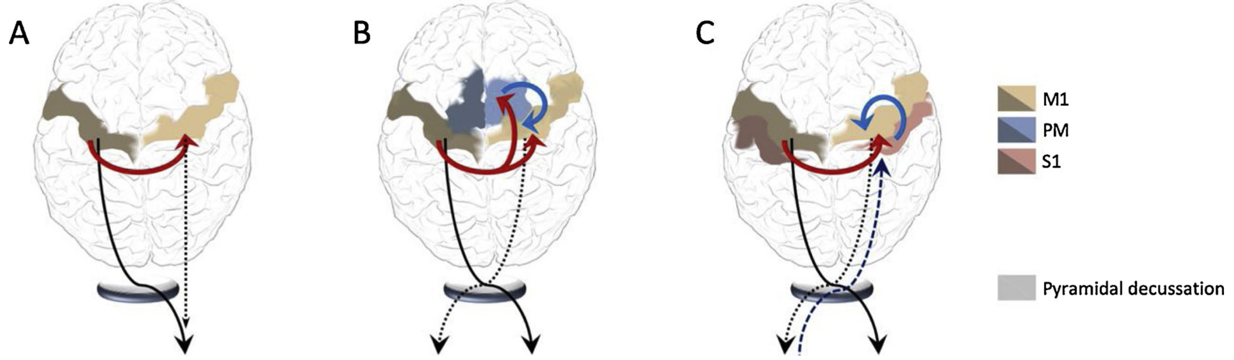

Fig. 1. Three alternative models that may account for bilateral cortical activation during unimanual performance. **A**: Left M1 is activated to generate motor output in a right end-effector, excitatory transcallossal connections activate right M1, which may contribute as ipsilateral controller. **B**: The model outlined in the introductory Section 1.1. Left M1 activation causes a cross-talk through the corpus callosum in both, right M1 and right PM/SMA, with the latter inhibiting the first to prevent motor outflow to the left (homologous) end-effector. **C**: Again, left M1 activates right M1 but peripheral feedback causes activation in right S1 that inhibits right M1 through cortico-cortical connections; see also *Discussion* section.

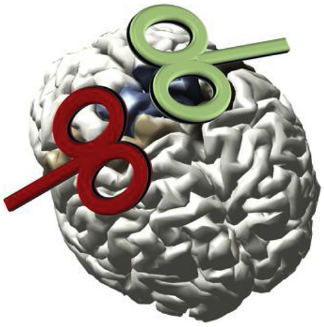

Fig. 2. Illustration of the paired-pulse TMS paradigm. A subthreshold conditioning stimulus is delivered above PM (green coil), followed by a suprathreshold test stimulus above M1 (red coil). The latter elicits a motor-evoked potential that typically depends on the location and timing of the (former) conditioning stimulus. The setting allows for assessing inter-hemispheric inhibition; see body text for more details.

the cortical interneurons, fast corticospinal pathways, and spinal motoneurons (Badawy et al., 2012). A common approach for the study of interhemispheric interactions is a technique involving paired pulses. In brief, a sub-threshold conditioning stimulus is applied to one hemisphere, that is followed by a supra-threshold test stimulus to the other hemisphere (Ferbert et al., 1992); cf. Fig. 2. When measuring the MEP in the muscle that corresponds to the test stimulus location, possible inhibitory effect induced by the conditioning stimulus may be inferred, as evidenced by reduced MEP amplitude. By this, one can assess the presence of *interhemispheric inhibition* (IHI). The strength of IHI is typically expressed via the ratio of the mean peak-to-peak MEP amplitude in conditioned versus unconditioned trials, i.e. paired- vs. single-pulse stimulation. High ratio values represent strong interhemispheric interaction. Interhemispheric inhibition can be further divided into two phases: long-latency and short-latency IHI (Chen et al., 2003).

Studying long-latency IHI involves inter-stimulus-intervals between conditioning and test stimuli of about 40 ms. It is believed to be mediated by postsynaptic gamma-aminobutyric acid type B (GABA_B) receptors. In short-latency IHI, conditioning and test stimuli are only about 10 ms apart. Thus far, the neurotransmitter receptor involved in short-latency IHI is largely unknown (Irlbacher et al., 2007) but is likely to differ from GABA_B, since Ghosh et al. (2013) showed that short- and long-latency IHI merely superimpose, i.e. they remain the same in the presence of each other and are additive. Stimulation in the long- or short-latency phases can therefore provide distinct information about interhemispheric connectivity, though not necessarily reveal details about whether inhibition is realized through direct transcallosal pathways vis-à-vis the aforementioned intrahemispheric connections. For this, an alternative protocol, namely repetitive TMS (rTMS), may be used. Dependent on the stimulation sequence (or frequency), rTMS can increase or decrease cortical excitability, both at the stimulation side and at its interconnected cortical areas (Fitzgerald et al., 2006; Kobayashi et al., 2004; Wassermann et al., 1998). Low stimulation frequencies (~ 1 Hz) typically decrease the corticocortical excitability, i.e. inhibit neural activity around the simulated area (Chen et al., 1997), whereas high stimulation frequencies (> 5 Hz) increase the corticocortical excitability, i.e. rTMS has an excitatory effect (Maeda et al., 2000).

1.2.2. EEG and MEG

Motor-related cortical activity can be measured as changes in electric potentials using surface EEG, or as changes in the strength of magnetic fields using MEG. While the first resembles the sum of postsynaptic potentials of radially aligned superficial neurons, the latter indicates changes in dendritic currents of tangentially aligned cells, typically pyramidal cells in the gyri or sulci, respectively (da Silva, 2013). Typically, one investigates motor-/event-related potentials and event-related fields (ERPs and ERFs, respectively), where cortical activities are averaged after temporal alignment of recurrent motor events. Current analyses often filter the cortical activity to certain frequency bands that are known for their involvement in motor control. Examples are the Rolandic-mu rhythm ($8-14$ Hz) and the beta rhythm ($15-30$ Hz) that both are predominantly present pre- and post-central sulcus, close to primary sensory and primary motor cortex (S1 and M1, respectively). Functional connectivity from EEG/MEG recordings may be quantified using coherence between activity in selected frequency bands (Ford et al., 1986). The higher the coherence, the more similar the (timing/phase relationship) of activity, which suggests strong functional connectivity (Andrew and Pfurtscheller, 1999). Coherence measures come in different forms. They are either based on cross-spectral analysis, i.e. the magnitude or imaginary part of Wiener's coherency (Nolte et al., 2004; Nunez et al., 1997), or they employ more general phase definitions, see, e.g., Bruns (2004); Mormann et al. (2000) for comparison, or template-based likelihood estimated of signal recurrence (Stam and Van Dijk, 2002). Coherence estimates often include baseline correction (Andrew and Pfurtscheller, 1996; Manganotti et al., 1998) and confidence estimates (Amjad et al., 1997) to improve statistical assessments. However, the discriminating activity between different cortical regions, be that between or within hemispheres, strongly relies on proper source localization, which remains a challenge due to the limited spatial resolution of both EEG and MEG (Grefkes et al., 2008).

An example of source-localized EEG during rhythmic unimanual motor performance is shown in Fig. 3 comparing younger and older participants; the latter experienced this task as a challenge already suggesting the influence of (experienced) task complexity (Chettouf et al., 2020).

1.2.3. fMRI

Functional MRI provides high spatial resolution of neural activity. It is the most used neuroimaging recording method to identify the anatomically localized source of (motor-related) activity. However, fMRI comes at the cost of low temporal resolution due to slow hemodynamic response characteristics. It reflects neural (de-)activation in (sub-)cortical regions in terms of blood oxygen level-dependent (BOLD) changes. With this, motor-related activity can be identified via statistical contrast against resting state (no motor activity). Assessment of functional connectivity typically relies on correlation analyses between bilateral BOLD responses, though more recent studies also include dynamic causal modeling (Friston et al., 2003), Bayesian model comparison (Allison et al., 2000; Grefkes et al., 2008; Penny et al., 2004; Volz et al., 2015; Wasserman, 2000), full brain forward modeling (Ritter et al.,

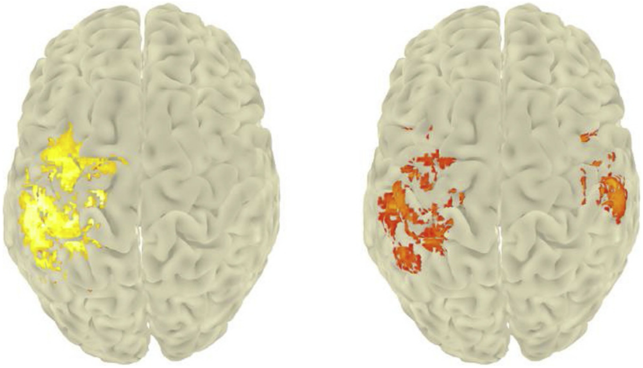

Fig. 3. Illustration of activity in bilateral motor areas during unimanual performance as observed with EEG. The panels show source-reconstructed beta activity during rhythmically squeezing a rubber ball with the right hand. Left panel: group-averaged t-values of twenty younger participants; right panel: idem ditto for twenty older participants. In the latter motor activity was clearly accompanied by activity in bilateral motor areas (Chettouf et al., 2020).

2013; Schirner et al., 2018) or statistical relation to simultaneously acquired EEG (Ritter et al., 2009; Ritter and Villringer, 2006).

Functional MRI reflects neural activity in an indirect way, which may explain some of the differences in the to-be-reported results, at least in parts. Neurons interact through synapses, including the transfer of neurotransmitters from pre- to postsynaptic neurons. Amino acid glutamate is the main (excitatory) neurotransmitter in the brain. After its release, glutamate needs to be removed from the synapse by the uptake into adjacent astrocytes. There, glutamate is converted to glutamine before being returned and recycled. The energy needed to process glutamate is provided by glycolysis, using glucose obtained from blood and, during activity increases, from glycogen storage in the astrocytes. Glucose is broken down anaerobically but fMRI' only' reflects changes in oxygen availability, i.e. aerobic metabolism. In fact, increases in blood flow and glucose consumption might be much greater than those in oxygen consumption (Raichle, 2001). These dominant synaptic activities, both excitatory and inhibitory, are associated with increased metabolic demands. Blood-flow related signals, such as BOLD, depend on the number of active inhibiting synapses, the duration of inhibition and might lead to decreases in both excitatory and inhibitory synaptic activity. Therefore, inhibition might lead to positive, negative or no BOLD signal at all (Ritter and Villringer, 2002).

Again, we illustrate how fMRI may serve to identify activity in bilateral M1s using the rhythmic unimanual motor performance; see Fig. 4 and see Chettouf et al. (2020) for more details.

1.2.4. Adding structural imaging

Diffusion imaging techniques (DWI and DTI) serve to assess structural connectivity. In particular DTI has been used to map the white matter tractography in the brain. Both methods rely on the diffusive properties of water in tissue (Chanraud et al., 2010). Diffusion in white matter tracts is anisotropic, i.e. direction dependent. Using this knowledge, structural integrity of, e.g., motor cortical network tracts (Fling et al., 2013) can be quantified via fractional anisotropy (FA). This is a lump measure of the deviation of the diffusion tensor from the identity matrix, with the latter representing isotropic (i.e., in all directions) diffusion. Normalized FA values range between 0 (~ isotropic diffusion) and 1 (~ anisotropic) indicating weak or strong structural integrity, respectively.

See Fig. 5 for an example of transcallosal fibers identified based on DTI.

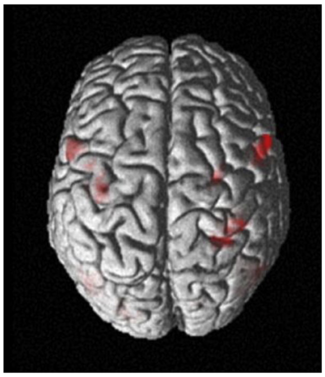

Fig. 4. FMRI BOLD signals in the same (younger) group as shown in Fig. 3. Motor activity was accompanied by activity in M1s although the corresponding EEG patterns appeared lateralized (Fig. 3, left panel). Apparently, fMRI and EEG can provide complimentary information about neural sources (Chettouf et al., 2020).

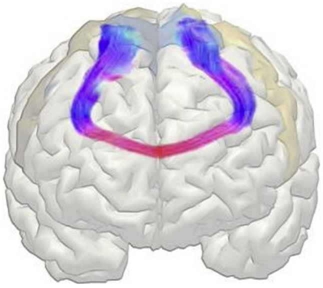

Fig. 5. Sketch of transcallosal pathways connecting bilateral M1s. The figure shows the result of DTI-based tractography in a single subject; see Babaeeghazvini et al. (2019) for more details.

2. Methods

2.1. Research design

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-statement (Moher et al., 2009).

2.2. Literature search

A comprehensive search was performed in the bibliographic databases PubMed, Embase.com, Wiley/Cochrane Library, EBSCO/PsycINFO and Web of Science (Core Collection) from inception up to 21 January 2019, under guidance of the co-authoring medical librarian (RdV). The following terms were used as index terms or free-text words (including synonyms and closely related words): “Corpus Callosum”, “Neural Pathways”, “Brain Mapping”, “Functional Laterality”, “Motor Cortex”, “Somatosensory Cortex”, “Psychomotor Performance”, “Interhemispheric”. The search was performed without date or language restriction. After deduplication all titles were screened and appropriate abstracts reviewed. The full search strategies for all the databases can be found as *Supplementary Material S1*.

2.3. Study selection

An initial selection based on title and abstract was conducted by two researchers (SC and LRD) to minimize a subjective bias. In the case of discrepancies in selection a third researcher (AD) assisted to reach agreement. As said focus of our review was on fundamental aspects of (unimanual) motor control in healthy, normally functioning humans. Hence, only studies were included that met the following criteria: (1) brain recordings or brain stimulation, (2) unimanual motor execution was included or induced by TMS, (3) participants were healthy humans, (4) evaluated interhemispheric connectivity and (5) reported in English. We retrieved the full texts of all potentially relevant studies for further assessments.

2.4. Data extraction

Information about participants, methods, movement type and outcomes were extracted using a standardized format per modality. This led to extraction of the following characteristics: (1) number of participants, (2) mean age of participants, (3) movement type, (4) determinants, (5) outcomes, and (6) main findings. For the TMS studies we additionally extracted (1) TMS paradigm, (2) stimulus location or direction, and (3) EMG location. For the EEG/MEG studies we additionally extracted the number of sensors.

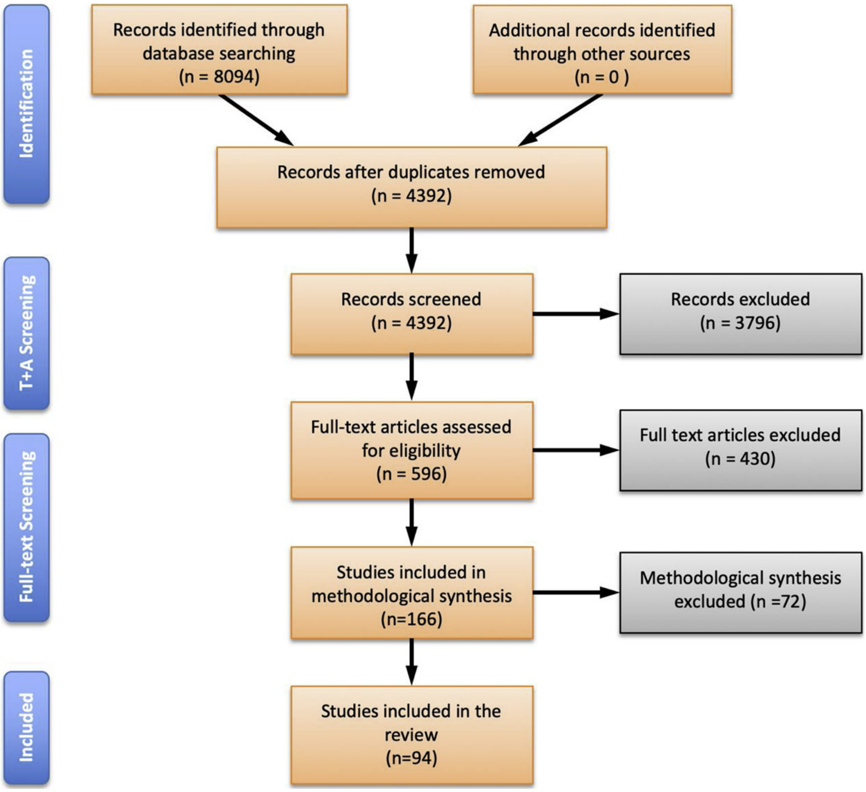

Fig. 6. Flowchart of the selection of studies for the systematic review (Prisma-statement).

3. Results

3.1. Search results

We identified 4392 potentially relevant publications. All of the abstracts were screened and 3796 articles were excluded after this first screening because they did not match the inclusion criteria described in Section 2.4. A further 430 studies were excluded following a full-text assessment for eligibility. This left a total of 166 original articles, from which 94 papers met our inclusion criteria and methodological synthesis, and therefore entered subsequent full data extraction. The procedure is summarized in Fig. 6. All tables containing the full data extraction can be found as *Supplementary Material S2*.

3.2. TMS

3.2.1. Bilateral interaction

The majority of studies reports an overall increase in *interhemispheric inhibition* before or during unimanual task performance, in particular when targeting left/right M1s (Duque et al., 2007; Hinder et al., 2010a, b; Liang et al., 2014; Uehara et al., 2014; Vercauteren et al., 2008). There are, however, exceptions that detail a reduction of IHI (Nelson et al., 2009; Sattler et al., 2012), also during movement preparation (Duque et al., 2007; Sharples and Kalmar, 2012; Tazoe and Perez, 2013). It seems that the reduction in IHI is accompanied by more accurate motor performance or vice versa. Yet, the diversity in IHI persists when zooming into long-latency and short-latency components. Uehara et al. (2014) found an increase in short-latency IHI targeting ipsilateral M1 with increasing conditioning stimulus intensity during isometric contractions of the index finger. This increase appeared to be absent for long-latency IHI. By contrast, Sattler et al. (2012) reported a global, bidirectional reduction in short-latency IHI during unimanual isometric contraction of the wrist contralateral to conditioning stimuli, while long-latency IHI was unaffected. The authors noted, however, that despite the short-latency IHI reduction, a net inhibition between hemispheres remained.

Several studies targeted dorsal premotor cortex (PMd) next to (bilateral) M1, as their interaction arguably discriminates for different types of movements (Crammond and Kalaska, 1996; van den Berg et al., 2010); see also Section 1.1.1 above and Sections 3.1.2 and 3.3.1 below. Mochizuki et al. (2004) demonstrated a suppressive effect on the contralateral M1 during rest when stimulating PMd. During left finger contraction, conditioning stimuli over M1 had a larger suppressive effect than PMd stimulation. IHI decreased from left PMd to right M1 just before left but increased before right hand movement onset (Koch et al., 2006). The latter study included the suggestion that PMd is involved in facilitating a specific unimanual movement and in suppressing other (mirror) movements. Note that IHI from left PMd to right M1 was not entirely supported in a later study of this research group (Kroeger et al., 2010). There, left PMd exerted an inhibitory effect onto the right M1 during early stage of movement preparation (increase in IHI), but this interaction was facilitated when a stimulus was presented just prior to left finger movement onset (decrease in IHI). Conditioning of the left M1 consistently led to inhibition and slower reaction times for right hand movements and inhibition for left hand movements. This finding found support by Liuzzi et al. (2010) who investigated the interaction between left M1 and both right PMd and right M1.

Taken together, IHI appears always present but whether it increases or decreases seems to depend on both the targeted area (M1 vis-à-vis PMd) and on the motor task. Especially the latter renders a clear-cut comparison a challenge.

3.2.2. Task dependency

We grouped the aforementioned and several other studies into those containing ‘real’ movements, in particular rhythmic ones, and compared them with tonic, isometric contractions. Regarding the latter, we considered ‘simple’ finger abductions and keypresses as isometric whenever the finger was lying on the key and/or no major transfer movement was made.

The vast majority of studies in the isometric group reported an increase of IHI from the active to passive hemisphere (Hinder et al., 2010a; Mochizuki et al., 2004; Mooney et al., 2018; Sharples and Kalmar, 2012; Talelli et al., 2008b; Tazoe and Perez, 2013; Uehara et al., 2014; Vercauteren et al., 2008). A few exceptions reported a decrease (Hortobagyi et al., 2011; Nelson et al., 2009; Sattler et al., 2012) or no difference (Morishita et al., 2014, 2012) in IHI while performing isometric contractions compared to rest. Interestingly, findings appeared to be fairly consistent when varying force levels of isometric contractions: IHI from contra- to ipsilateral M1 decreases significantly with increasing force (Howatson et al., 2011; Liang et al., 2014; Perez and Cohen, 2008; Uehara et al., 2014). A likewise consistent finding seems to be the change in IHI during the preparatory phase prior to isometric contractions. There, IHI is reduced from the ipsilateral to the contralateral hemisphere; this effect was observed in reaction tasks and from left PMd to right M1 (Duque et al., 2007; Hinder et al., 2012, 2018; Koch et al., 2006; Kroeger et al., 2010; Liuzzi et al., 2010; Perez et al., 2007). More recent, Chye et al. (2018) argued that preparing a unimanual task may lead to an increase in excitability of ipsilateral M1 reflecting the state of the active limb, rather than the motor planning of the passive limb.

Studies on unimanual movements typically extend to intrahemispheric connectivity in the presence of additional timing requirements. For rhythmic movements, Uehara et al. (2013) suggested PMd-M1 connectivity to differentially modulate ipsilateral M1 excitability dependent of movement frequency. In this experiment, however, the IHI acting simultaneously with the PMd-M1 connectivity from the active to passive M1 was not linearly associated with the movement frequency. Similar to effects in the aforementioned reaction task, IHI did decrease in the preparatory phase of a Fitts's task, i.e. a target selection task, especially when the task became more complex by decreasing the target size in a pointing task (Wischnewski et al., 2016). Here, IHI was again directed from the passive to the active hemisphere. As such, findings on isometric force production and real movements appear similar.

A few studies contrasted (fine) movements and isometric force production directly. Morishita et al. (2012, 2014), reported a significantly larger IHI from active to resting M1 in a fine motor task compared to performing isometric contractions. It seems that IHI is particularly pronounced when movements are challenging. This finds support in several rTMS studies. Buetefisch et al. (2011) stimulated left M1 during a pointing task with varying difficulty levels. rTMS improved performance in both hands for the most demanding task. Chen et al. (1997) reported the ipsilateral hemisphere to be more involved in complex compared to simple finger sequence movements because in the first more errors were present with ipsilateral (left) M1 stimulation. Similarly, Dafotakis et al. (2008) reported a stronger bilateral effect after rTMS over left M1 than over the right one, suggesting stronger interhemispheric influences exerted from the dominant (left) hemisphere.

3.3. EEG and MEG

3.3.1. Bilateral interaction

The bulk of EEG/MEG studies indicates a decrease in both the alpha- and beta-frequency power (i.e. desynchronization) when contrasting unimanual motor tasks with rest, while the coherence between bilateral premotor and sensorimotor areas appears to increase (Calmels et al., 2008, 2006; Farber and Anisimova, 2000; Ford et al., 1986; Gerloff et al., 1998b; Lange et al., 2006; Man'kovskaya, 2006; Manganotti et al., 1998; Mima et al., 2000; Serrien, 2008; Shibata et al., 1998; Svoboda et al., 2002; Van Wijk et al., 2012a; Vecchio et al., 2014; Wang et al., 2017).

In right-handed participants, the left-hand movements seem to induce greater coupling than right-hand (or bimanual) ones (Serrien and Spapé, 2009b), including the preparatory phase (Bai et al., 2005). On this account, Serrien and Spapé (2009b) suggested activity in the left hemisphere to be essential for controlling complex movements. Interestingly, this does not seem to be a function of handedness since even in left-handed participants the left PM has been shown to be involved in both left- and right-hand unimanual finger tapping (Pollok et al., 2006). That is, left PM has an important role in the control of complex movements, be they uni- or bimanual.

3.3.2. Task dependency

In contrast to the diversity in TMS results, EEG/MEG studies reported more steady findings when it comes to task dependency. Overall, experimentally induced increases in task complexity, again especially higher demands in motor timing, are consistently accompanied by increased bilateral activations with – as said – left PM being a key player. This seems to apply for both isometric and 'real' movements. However, activation patterns discriminate between static and dynamic isometric unimanual force productions (Van Wijk et al., 2012a). There, the corresponding MEG source-reconstructed signals revealed significant ipsilateral beta desynchronization during the dynamic isometric force production but not during the static condition. Event-related desynchronization was bilaterally modulated, while event-related synchronization appeared only to be present in contralateral M1. Van Wijk et al. (2012a) suggested that ipsilateral activity does not solely reflect interhemispheric crosstalk, but may contain additional mechanisms that contribute to 'proper' motor control.

Bilateral coupling quantified through interhemispheric coherence always increases with increasing task complexity within a study protocol as well as with the formation of new motor programs (Farber and Anisimova, 2000; Salmelin et al., 1995; Serrien, 2009; Serrien and Spapé, 2009a, b). Based on these and other findings, Serrien (2009) suggested the increase of bilateral information processing with increasing timing requirements, or more generally, "when exigencies on the motor system increase". In an earlier study, she already reported a strengthening of the interhemispheric connections when unimanual tasks were performed following bimanual pacing (Serrien, 2008), implying the relevance of task history for motor execution.

Internally paced movements show greater functional coupling of cortical premotor and sensorimotor areas than externally paced ones (Gerloff et al., 1998b; Wang et al., 2017). The most significant increase was found in task-related coherence in the beta-frequency band between left and right regions (M1 and S1) and between left central and mesial frontocentral regions, including pre-SMA and SMA proper, both involved in pre-movement activation. By subsequently looking at the information flow between hemispheres, Lange et al. (2006) revealed that this is mostly increased by the modification of extrinsic coordinates (in this study performing a mirror task with the opposite hand) compared to intrinsic coordinates.

3.4. fMRI

3.4.1. Bilateral interaction

When contrasting unimanual movements to rest, BOLD activation is present in the contralateral and BOLD deactivation in the ipsilateral sensorimotor cortex (Allison et al., 2000; Amann et al., 2009; Grefkes et al., 2008; Hamzei et al., 2002; Langan et al., 2010; Volz et al., 2015). As for the TMS and EEG/MEG studies, premotor areas were often targeted using fMRI during unimanual movements. BOLD changes in premotor areas appear strongly correlated with each other, as well as with the M1 contralateral to the moving hand (Gabitov et al., 2016; Grefkes et al., 2008; Volz et al., 2015). Dynamic causal modeling (DCM) estimates of interregional interactions at the neural level for endogenous (movement-dependent) coupling suggested ipsilateral M1 to be strongly inhibited by both bilateral PMs (Volz et al., 2015) and contralateral SMA (Grefkes et al., 2008). In a more recent study, Bonstrup et al. (2016) compared these fMRI-based models with induced responses assessed through EEG. Again, a grip-dependent interhemispheric inhibition between bilateral M1 was found by DCM-fMRI, but not by DCM-EEG.

Langan et al. (2010) reported a decreased size of the CC (estimated from anatomical scans) and an increased activation in the right (ipsilateral) sensorimotor cortex in older compared to younger adults. These age-related changes were associated with longer reaction times, leading to the suggestion that a reduced structural interhemispheric connectivity hampers inhibition of the non-dominant hemisphere yielding deteriorated motor timing. Along these lines, Stančák et al. (2003) suggested that a correlation between the size of the CC and fMRI activation during unimanual movements only occurs in the mesial frontal cortex including SMA, which is – as said – believed to be involved in pre-movement activation.

3.4.2. Task dependency

The effect of handedness and hemispheric dominance was recently reported by, e.g., Diwadkar et al. (2018) and Begliomini et al. (2018) who found strong interhemispheric influences exerted from the left hemisphere for both left- and right-hand movements. Tettamanti et al. (2002) assessed the interhemispheric transfer with Poffenberger's paradigm: participants had to perform a visual manual RT task in a crossed (visual stimuli presented to the hemifield contralateral to the moving hand) and uncrossed (visual stimuli presented to the hemifield ipsilateral to the moving hand) condition. Comparing these revealed that the crossed conditions activated an extended network involving mainly visuomotor and premotor components, as well as the genu of the CC.

3.5. Combining results of different modalities

3.5.1. TMS and fMRI

Combining IHI and BOLD results seems a natural next step in the search for an in-depth understanding of the role of bilateral connectivity during unimanual movement. Sarfeld et al. (2012) found a positive correlation between the strength of IHI targeting the right (ipsilateral) hemisphere and movement-related BOLD activity in left M1 during rhythmic right-wrist movements. Similar results have been reported for isometric handgrip movements (Talelli et al., 2008a), where also an increased task-related BOLD activation in the ipsilateral M1 was found to be negatively associated with IHI targeting the ipsilateral hemisphere. This might indeed be a muscle-dependent effect, since the IHI targeting the ipsilateral hemisphere also decreases when a homologous muscle was contracting (Chiou et al., 2013). This muscle-dependent effect was also found within the ipsilateral M1 that displayed less intracortical inhibition and more corticospinal output during homologous muscle contraction. Under the same conditions, BOLD activation of bilateral M1s was present during unimanual movements with the right hand. (Chiou et al., 2013; Kobayashi et al., 2003). This bilateral activity was, however, only seen for half of the participants when moving their left (non-dominant) index finger in the study of Kobayashi et al. (2003). None of these participants showed significant activation of the ipsilateral M1/S1 during right (dominant) finger movements, in line with the corresponding IHI results: While all showed strong inhibition targeting the right hemisphere, only those that also showed ipsilateral BOLD activity displayed significant IHI targeting the left hemisphere. Arguably, that indicates a suppression of the dominant hemisphere by the non-dominant hemisphere. The activation contralateral to the hand movement was located more anterior in the group with ipsilateral activation compared to the others, which according to the authors might include PM.

Combining TMS and fMRI also underscored that left M1 and PM play a key role when moving with just one hand (Bestmann et al., 2008; Callaert et al., 2011; Verstynen and Ivry, 2011). Left PM appeared strongly activated during movements with either the left or right hand, and even increased with more complex movements (Callaert et al., 2011; Verstynen and Ivry, 2011). The ipsilateral response was weaker in right PM and not modulated by task complexity (Verstynen and Ivry, 2011). Callaert et al. (2011) argued that the left hemisphere might be more capable than the right one to support motor execution of both hands. Following stimulation of the left PM with rTMS during rest, BOLD activation of the stimulated region was reduced which led to an increased correlation between activity levels in the two M1s (Verstynen and Ivry, 2011). Bestmann et al. (2008) investigated this further by applying high intensity TMS to left PM during an isometric left-hand grip task. Relative to low intensity TMS, activity was increased in contralateral motor regions (M1 and PM). By contrast, when the stimulus was applied during the no-grip condition, relative activity was decreased when compared to low TMS. Similar results were found when applying inhibitory cathodal stimulation to the contralateral M1 while performing a reaction time task (Stagg et al., 2009). That yielded increased motor-related activations in the interconnected regions of the opposite M1 and PM and the functional connectivity between these areas and the stimulated M1.

3.5.2. Structural MRI combined with functional and behavioral measures

As said, the CC is the major passage for interhemispheric communication, such as IHI (Meyer et al., 1998). Several studies confirmed this and showed that bilateral M1 are interconnected through the posterior half of the CC, the isthmus and posterior midbody (Hofer and Frahm, 2006; Zarei et al., 2006). Kurth et al. (2013) found significant correlations between the callosal thickness in these areas and the hand motor performance of the dominant hand in right-handed children and adolescents. This correlation appeared to be also present when using both hands albeit less pronounced. By contrast, it was completely absent during non-dominant hand performance. Sehm et al. (2016) reported an asymmetry between the movements of the dominant compared to the non-dominant hand, namely mirror activity was more pronounced when the dominant hand was moving, which positively correlated with FA from M1 fiber tracts. A higher radial diffusivity, meaning a poorer structural connectivity, has been found in older compared to younger adults leading to a higher functional connectivity and poorer unimanual motor performance (Fling et al., 2012; Sullivan et al., 2010). Fling et al. (2012) suggested that this higher functional connectivity might be indicative for a shift from the normally predominant inhibitory to more excitatory/faciliatory interhemispheric communication.

By combining TMS, fMRI and DTI, Chiou et al. (2014) identified a significant association between the white matter microstructure of the callosal motor fibers – indicated by FA – and functional changes in the ipsilateral M1 when performing a unimanual motor task: Higher FA values led to greater facilitation in ipsilateral M1 during unimanual movement with the homologous muscle. Higher values of FA were found to correlate with the magnitude of IHI between the M1 hand areas in the two hemispheres (Wahl et al., 2007). It seems that a stronger structural connectivity between two hemispheres can lead to a more 'effective' non-mirroring network, which suppresses unwanted motor spill-over during unimanual movement (Ruddy et al., 2017), in line with our outline in the introduction section.

Stančák et al. (2002) performed EEG coherence measures (as sketched in Section 1.2.2) and correlated them with the sizes the cross-sectional surface areas of the CC and seven other callosal regions. Bilateral sensorimotor coherence in the lower alpha band after movement onset turned out to be correlated positively with the size of the callosal body during a brisk flexion and elevation of the right index finger. No correlations were found between the bilateral parietal electrodes and the size of the callosal body, supporting the idea that the bilateral sensorimotor cortices are the main connectors during movement.

4. Discussion

The question whether unimanual movements have a bilateral neural representation comes with quite some history. For many years it has been considered textbook knowledge that movement execution with one hand is characterized by largely – if not entirely – contralateral activation in the brain. This idea dates back to the nineteenth century and is based on early studies on animal brains and/or human pathology using invasive electrical stimulation (Jackson et al., 1870; Schiff, 1859). Gustav Fritsch together with Eduard Hitzig (1870) and, independently, David Ferrier (1873) stimulated the cortex surface of different (anesthetized) mammals and evoked movements in different parts of the contralateral side of the body. These studies allowed researchers to identify ordered motor maps within this contralateral hemisphere, in particular by Clinton Woolsey and Wilder Penfield in non-human mammals and in humans, respectively (Penfield and Boldrey, 1937; Woolsey and Fairman, 1946). In fact, Penfield and Boldrey (1937) identified the human motor homunculus just anterior to central sulcus (M1), i.e. the representation of body parts in brain areas containing an ensemble of neurons that, when activated, result in motor output. Especially in finely controlled limb muscles (fingers, hands, arms, legs), but also in the tongue, are these areas relatively large. These seminal studies were followed by studies on the SMA, where muscle activation on the contralateral side of the body could be evoked through electrical stimulation, much like stimulation of M1 (Woolsey, 1952).

4.1. Crossed and uncrossed fibers

By now, pyramidal tracts are the best-studied efferent pathways of the cortical motor system (Davidoff, 1990; Nyberg-Hansen and Rinvik, 1963; Woolsey et al., 1972). Most of these tracts are bilaterally symmetrical and the bulk of fibers cross over to the opposite side at the pyramidal decussation – figures vary between about 70%–90% that undergo this crossing but the majority of studies tend towards higher percentages though this depends on the end-effector under study. For example, primates' hand and finger muscles seem to have more uncrossed fibers (Al Masri, 2011; Hong et al., 2010; Nathan et al., 1990)). The remaining fibers (~10-30 %) do not cross before they reach the spinal cord (Carson, 2005). The presence of these non-crossing fibers underlies the appealing idea that the ipsilateral hemisphere is involved in movements not only at the contralateral side of the body, but also at the ipsilateral side as extensively outlined here. An example for a possible model including ipsilateral control, i.e. an alternative to the combination of interhemispheric excitation and intrahemispheric inhibition, is shown in Fig. 1, panel A. Interestingly, in a very recent paper Bundy and Leuthardt (2019) discussed the functional role of the ipsilateral hemisphere in motor control. They argued that the descending pathways primarily elicit movements and speculated about how the interaction through the CC may facilitate unimanual movements. And, they concluded that a balance between the excitatory and inhibitory function of interhemispheric interactions is mandatory for proper motor function. Our systematic review confirms these suggestions but also highlights that the story is not that simple. Our reading of the literature has identified three key findings that seem to underlie the hypothesized excitatory and inhibitory bilateral neural interactions, namely (a) the increase in task complexity of the unimanual task under investigation requires more efficient communication between hemispheres, (b) the anatomical properties of transcallosal fiber tracts enable this interhemispheric information exchange, and (c) the left (pre) motor areas play a key role when performing more complex motor tasks, irrespective of whether the left or right hand is being used.

In Fig. 1, we also depict another alternative, namely possible inhibitory cortico-cortical projections from S1 to M1 within a hemisphere (panel C). We added this model because of culminating evidence for synchronized or fine-tuned interactions between the periphery and S1 via feedback afferent pathways (see, e.g., Baker (2007) and references therein). Discussing this and other related animal studies in more detail is, however, beyond the scope of the current review.

4.2. Bilateral interaction

When executing a unimanual movement the human motor network shows consistent bilateral activation. This finding has been confirmed with all neuroimaging modalities reviewed here. It hence seems likely that inhibitory and faciliatory processes are needed to suppress the outflow of activity in the ipsilateral hemisphere to avoid bimanual motor (co-) activation.

TMS studies have revealed both an increase and a decrease in IHI. These conflicting IHI patterns might be explained by differences in experimental settings, especially the type of conditioning stimuli. The intensity of the stimuli could be adjusted to compensate for the increased MEP amplitude induced at the stimulus side because of the unimanual movements (Nelson et al., 2009; Sattler et al., 2012) and may hence yield a reduced IHI. By contrast, when conditioning stimuli are not adjusted to compensate for the stimulus-induced increase in MEP amplitude, IHI may increase (Hinder et al., 2010a, b; Liang et al., 2014; Uehara et al., 2014; Vercauteren et al., 2008). According to Brocke et al. (2008) these inhibitory processes are accompanied by measurable changes in the local neurovascular signal. As we summarized, unimanual movements are associated with BOLD activation in the contralateral and deactivation in the ipsilateral sensorimotor cortices. It has been suggested that this deactivation in the ipsilateral hemisphere could be caused by transcallosal inhibition involving GABAergic interneurons (Matsumura et al., 1992), an idea that might deserve future exploration.

BOLD changes of bilateral premotor areas seem strongly correlated with each other, as well as with the changes in M1 contralateral to the moving hand. This agrees with EEG and MEG assessments that revealed a decrease in both alpha and beta power, and an increase in coherence between bilateral premotor and sensorimotor cortices when performing unimanual movements. This bilateral coupling becomes more pronounced with increasing task complexity. There, symmetry appears broken in that left PM is especially active during both left- and right-hand complex movements. This is particularly interesting in view of the so-called 'motor dominance theory' that suggests that the left hemisphere is more capable than the right one to support motor activity; it hence might always be involved in motor execution, be that with the right or the left hand (Callaert et al., 2011; Ziemann and Hallett, 2001).

4.3. Task dependency

The direction and location of both inhibition and facilitation appears to depend on the motor task that is performed. Overall, an experimentally induced increase in task complexity, in particularly an increase in motor timing requirements, seems to be accompanied with more (efficient) communication between hemispheres. For unimanual movements we envision the following scenario when task complexity increases: Inhibition of the ipsilateral hemisphere likely increases, while inhibition of the contralateral hemisphere likely reverses into facilitation when the motor task becomes more challenging. Several research groups forwarded the idea that activation patterns of complex motor control operate at a 'high level' (Donoghue and Sanes, 1994; Gerloff et al., 1998a; Hummel et al., 2003; Manganotti et al., 1998; Sadato et al., 1996), but this level remains ill defined. Hummel et al. (2003) suggested that a task-complexity related increase in ipsilateral activation is not caused by motor memory load but by processing increasingly difficult transitions between movements. Interestingly, however, task-dependent activations, both excitatory and inhibitory, are not restricted to bilateral M1s, but are also present in other parts of the motor network, in particular in SMA and PM (Andres and Gerloff, 1999). The role of SMA in the preparation and performance of sequential movements has been demonstrated by, e.g., Gerloff et al. (1997), where stimulation with rTMS over SMA induced errors in motor performance in the more complex sequences. And, the role of left PM has been discussed above.

4.4. Outlook

4.4.1. Multimodal approaches

As highlighted in the *Introduction*, the CC is the main gateway for interhemispheric communication. A positive correlation was reported between the callosal thickness of the CC and the hand performance of the (right) dominant hand, but not of the (left) non-dominant hand (Kurth et al., 2013; Sehm et al., 2016). According to the aforementioned motor dominance theory one might speculate that this pattern of results will also be observed with left-handed participants. One could then assume that the left hemisphere is more involved in the support of motor activity and that the thickness of the CC is mainly related to the passage from left to right M1.

Stronger structural connectivity (higher FA) is associated with the reduction of unwanted mirror movements. Likewise, age-related atrophy implies weaker structural connectivity yielding stronger functional connectivity and poorer performance (Fling et al., 2012; Langan et al., 2010; Sullivan et al., 2010).

Earlier work investigated whether the CC exerts an inhibitory or excitatory role in the interhemispheric communication and concluded that there is evidence in the literature for both outcomes, although most studies support the excitatory function of the CC in interhemispheric communication (Bloom and Hynd, 2005; Carson, 2005; van der Knaap and van der Ham, 2011). As likewise hypothesized in the introduction, if transcallosal pathways are primarily excitatory and if the motor network shows (almost) symmetric, bilateral activation patterns while moving unimanually, then this indicates some type of intrahemispheric inhibition mediated through intrahemispheric pathways probably involving the premotor areas (Daffertshofer et al., 2005; Stinear and Byblow, 2002).

Combining the findings of multimodal approaches to study unimanual movements may help indeed to better understand how the brain enables the fine-tuned motor coordination that we are capable of. Still, several questions concerning the control of unilateral hand movements remain unanswered. Based on this review, we suggest that future research should investigate the role of the left hemisphere in greater detail, in particular the left PM. There is some evidence that this area plays a key role in the control of unimanual movements, but more research is needed, specifically with both left- and right-handed participants, to confirm this.

Only a few studies linked structural and functional connectivity in one experiment while performing unimanual movements (cf. *Supplementary Material S2*, Table 5). This is unfortunate because – as we outlined here – unimanual movements are likely to rely on the interhemispheric cross-talk through transcallosal tracts. We do suggest to intensify the research that combines different modalities as this may be key to unravel all the factors involved in unimanual motor control.

4.4.2. Integrating other populations

Our main aim was to specify the determinants and functional role of the often reported, bilateral activation patterns in the cortex during normal unimanual motor control in healthy humans. For this review we only included non-invasive studies, since invasive approaches may alter the normally functioning brain and, by this, the normal control of unimanual behavior. Yet, there is much to learn by combining our finding with the plenitude of studies in non-human primates, let alone studies on impaired motor control as observed in, e.g., stroke patients. For instance, Grefkes and Ward (2014) identified that lesions in M1 can lead to proportional changes in ventral PM activity. In fact, they argued that inactivation of either ipsi- or contralateral M1 or contralateral ventral PM deteriorates hand function recovery post stroke (there experimentally induced macaque monkeys). Interestingly, studies on partly hemiparetic stroke patients revealed unimanual movement of the affected (contralesional) side to display clearly bilateral neural activity. While this may indicate the 'emergence' of ipsilateral control to compensate motor impairment post stroke, one has to realize that motor learning of the non-affected side can limit the recovery of the affected one (Boddington and Reynolds, 2017; Dodd et al., 2017), which arguably speaks for a (dis-)balance of interhemispheric excitation versus intrahemispheric inhibition (Grefkes and Ward, 2014; Koch et al., 2016), as advocated here.

4.5. Conclusion

Unimanual movements appear to rely on a highly coordinated pattern of neural activation, consisting of both inhibition and excitation across the bilateral motor network, in contrast to the complete contralateral activation as reported in the classical textbooks. Generative brain network models that consider individual structural connectivity and dynamics of inhibitory and excitatory neurons may allow for inferring local and global neuronal interactions underlying the various multimodal observations. Based on this systematic literature review, we are inclined to argue that unimanual movements have a bilateral neural origin, with the transcallosal tracts, in general, and the corpus callosum, in particular, as important communication instrument. The degree to which this bilateral activation is present depends on the motor task performed. For more complex motor tasks, the left (pre)motor areas are key controllers irrespective of whether the task is executed with the left or the right hand.

Declaration of Competing Interest

None.

Acknowledgements

This research received financial support by the following funding sources: H2020 Research and Innovation Action grants 826421 and 650003, 720270 and 785907, and ERC683049; German Research Foundation CRC 1315 and 936, and RI 2073/6-1; Berlin Institute of Health and Foundation Charité, Johanna Quandt Excellence Initiative.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.03.002.

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