Do adults with stroke have altered interhemispheric inhibition? A systematic review with meta-analysis.

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Declaration of interest statement

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Keywords

Transcallosal inhibition, interhemispheric inhibition, primary motor cortex, ipsilateral silent period, neurological conditions.

Abstract:

Objective Interhemispheric inhibition is an important cortical mechanism to support motor control. Altered interhemispheric inhibition has been the target of neuromodulation interventions. This systematic review investigated the evidence for altered interhemispheric inhibition in adults with unilateral neurological conditions: stroke, amyotrophic lateral sclerosis, cerebral palsy, complex regional pain syndrome, traumatic brain injury, and cerebral palsy

Methods We pre-registered the protocol and followed PRISMA guidelines. Five databases were systematically searched to identify studies reporting interhemispheric inhibition measures in unilateral neurological conditions and healthy controls. Data were grouped according to the measure (ipsilateral silent period and dual-coil), stimulated hemisphere, and stage of the condition (subacute and chronic).

Results 1372 studies were identified, of which 14 were included (n=226 adults with stroke and 161 age-matched controls). Ipsilateral silent period-duration was longer in people with stroke than in controls (stimulation of dominant hemisphere) regardless of stroke stage. Motor evoked potential was less suppressed in people with sub-acute stroke (stimulation of the unaffected hemisphere) than controls (stimulation of dominant hemisphere) and this reversed in chronic stroke.

Conclusion Detection of altered interhemispheric inhibition appears to be dependent on the measure of interhemispheric inhibition and the stage of recovery.

Significance Rebalancing interhemispheric inhibition using neuromodulation is considered a promising line of treatment for stroke rehabilitation. Our results did not find compelling evidence to support consistent alterations in interhemispheric inhibition in adults with stroke.

1. Background

Transcallosal pathways are the primary white matter projections connecting the two brain hemispheres (Caleo, 2018). One of the functional roles of the transcallosal pathways is to convey inhibitory influences between the primary motor cortices (M1s), a process known as interhemispheric inhibition (IHI). M1 is involved in the execution of skilled motor movements, and IHI is thought to be responsible for preventing involuntary activation of the non-active upper limb during unimanual motor tasks in healthy adults (Hübers et al., 2008).

People with unilateral neurological conditions, including stroke, amyotrophic lateral sclerosis, cerebral palsy, and complex regional pain syndrome, present with altered physiological activity not only in the affected hemisphere but also in the unaffected hemisphere (Di Pietro et al., 2013, Di Pietro et al., 2015, Emackey et al., 2014, Hubers et al., 2020, Stinear et al., 2008, Wittstock et al., 2007). Whether bilateral brain changes are the result of behavioural modifications caused by unilateral impairment or reflect functional changes in brain regions connected anatomically via transcallosal pathways is not clear.The effect of chronic asymmetric upper limb use in unilateral neurological conditions on cortical physiology is difficult to establish, in part due to the difficulty in identifying and quantifying upper limb use. Nonetheless, 10 hours of “non-use” of the right-hand and “free use” of the left hand has been associated with lower excitability of the left M1 and decreased IHI from the left to the right hemisphere (Avanzino et al., 2011). Similarly, greater excitability of right M1 and greater IHI from the right onto the left hemisphere were evident when participants were allowed to freely use the left hand but not when this hand use was limited (Avanzino et al., 2011). Within a healthy population, this suggests that modification of M1 cortical physiology may be driven by increasing or decreasing the use of the contralateral hand. As a result, an imbalance in IHI might indicate a behaviourally relevant physiological marker in people with unilateral neurological conditions. Indeed, IHI imbalance has been linked to motor impairment in several

unilateral neurological conditions (Emackey et al., 2014, Karandreas et al., 2007, Pantano et al., 2002, Takechi et al., 2014).

To date, many therapeutic interventions in unilateral neurological conditions such as stroke have targeted IHI imbalance. Studies investigating neurophysiological brain changes in people post-stroke proposed the IHI imbalance model (Duque et al., 2005, Murase et al., 2004). This model suggests the presence of a lesion reduces excitability of M1 of the affected hemisphere, thus reducing its neural output, which includes diminished IHI towards M1 of the unaffected hemisphere. This results in a relative increase in excitability for M1 of the unaffected hemisphere, increasing neural output – thereby increasing IHI from the M1 of the unaffected hemisphere to M1 of the affected hemisphere and further suppressing the excitability of M1 of the affected hemisphere. In an attempt to improve motor outcomes, several studies have evaluated neuromodulation treatments to drive inhibitory influences between M1s towards a more balanced level (Ansado et al., 2019, Fang et al., 2013, Wang et al., 2014). This is often achieved by either suppressing the unaffected hemisphere M1 excitability and/or increasing the affected hemisphere excitability. However, current evidence from neuromodulation treatments based on this model is mixed, bringing into question whether this proposed imbalance model in IHI is accurate.

Several methodological challenges might have hindered the current understanding of the IHI imbalance in unilateral neurological conditions. First, the two common transcranial magnetic stimulation (TMS) measures of IHI, ipsilateral silent period (ISP) and dual-coil, can be influenced by several factors. For example, higher stimulation intensity was associated with greater ISP and dual-coil measures, and the direction of TMS current affected dual-coil but not ISP measures (Chen et al., 2003). Brain state (e.g. level of arousal or attention) has also been shown to influence cortical excitability (Coombes et al., 2009; Mars et al., 2007). For example, viewing unpleasant images was associated with larger motor evoked potentials compared to viewing pleasant and neutral images

(Coombes et al., 2009). Furthermore, measuring IHI from unaffected to affected hemisphere has proven more challenging than measuring IHI from the affected to unaffected hemisphere, particularly in people with cortical but not subcortical lesions (Butefisch et al., 2008; Niehaus et al., 2003). This is because it is not always possible to evoke a recordable motor evoked potential from the affected hemisphere due to structural damage following a brain injury. A recent review by Carson (2020) suggested that TMS measures of IHI might not reflect the complex physiology of transcallosal interactions between M1s. This may be due to the reduced spatial definition of TMS and the high stimulation intensities required to measure IHI. The combination may lead to unwanted activation of neuronal circuits beyond those required for natural IHI to occur (Carson, 2020). Furthermore, it was postulated that IHI might facilitate contrast-enhancing and integrative roles between hemispheres via a crossed surround inhibition mechanism rather than resulting in undifferentiated inhibition of the contralateral hemisphere (Carson, 2020). Second, despite the evidence that both hemispheres (affected and unaffected) undergo physiological changes, most studies have compared IHI between hemispheres, possibly giving an inaccurate account of the magnitude of inhibitory influence (Hubers et al., 2020, Karandreas et al., 2007, McDonnell and Stinear, 2017). A more appropriate comparator might be healthy controls. Third, there is evidence for neurophysiological changes over time from subacute (post-condition duration < six months) to the chronic stage (post-condition duration ≥ six months) in people post-stroke (Swayne et al., 2008). However, the evidence for IHI imbalance comes mainly from studies investigating people in the chronic stage only (Bertolucci et al., 2018, Fang et al., 2013, Takechi et al., 2014). A deeper understanding of IHI underlying physiology and how IHI changes over time is required to deepen the understanding of causal relationships between IHI imbalance and motor function.

The purpose of this systematic review was to determine the neurophysiological evidence for altered IHI in adults with unilateral neurological conditions compared to healthy controls. The outcomes we

were interested in are two measures of IHI using TMSparadigms, 1. ISP and 2. dual-coil. A secondary aim was to investigate the effect of the duration of the presenting condition on IHI.

2. Methods

2.1 Protocol registration

A protocol for this systematic review was registered with Open Science Framework (OSF) on February 26th 2020, accessible via the link https://osf.io/jf4uq.

2.2 Type of Studies

This review included observational (case-control, cross-sectional, prospective longitudinal cohort), and interventional (pre-post) studies. For interventional studies, only baseline measures were included. The included studies must have recruited both patients and healthy controls and reported a neurophysiological measure of IHI.

2.3 Participants

Adults aged 18 years or older, diagnosed with a unilateral neurological condition: stroke, traumatic brain injury, cerebral palsy, amyotrophic lateral sclerosis, or complex regional pain syndrome, and a control group of neurologically intact healthy adults were included. Data were only included if the authors clearly showed that the participants had unilateral impairments i.e. the study has clearly stated that the neurological condition was unilateral (e.g., unilateral stroke), and/or the study stated that only one side of the participant's body was affected (e.g., left/right hemiplegia or left/right-sided weakness)

2.4 Measures of IHI

Included studies needed to have a well-documented neurophysiological measure of IHI. The TMS paradigms, ISP and dual-coil are neurophysiological measures of IHI and are often used

interchangeably (Chen, 2003, Perez and Cohen, 2009). In the dual-coil technique, a TMS conditioning stimulus (CS) delivered to M1 of one hemisphere precedes a test stimulus (TS) delivered to M1 of the opposite hemisphere. Delivery of the CS inhibits corticospinal excitability of the opposite hemisphere via IHI. As a result, the motor evoked potentials (MEPs) recorded during the CS+TS application are smaller than the MEPs evoked from application of TS alone. The suppression in the magnitude of 'test MEP' is used as a measure of IHI (Ferbert et al., 1992). For the ISP, a single TMS pulse applied to the M1 ipsilateral to a pre-activated voluntary hand muscle contraction inhibits ongoing electromyographic (EMG) activity (Chen, 2003) being recorded from the hand. The level of IHI can be quantified by the duration, latency or amplitude of EMG activity; a longer ISP-duration, increased latency, or greater magnitude of EMG suppression is thought to represent greater IHI. The two paradigms are represented by the cartoons presented in Figure 1.

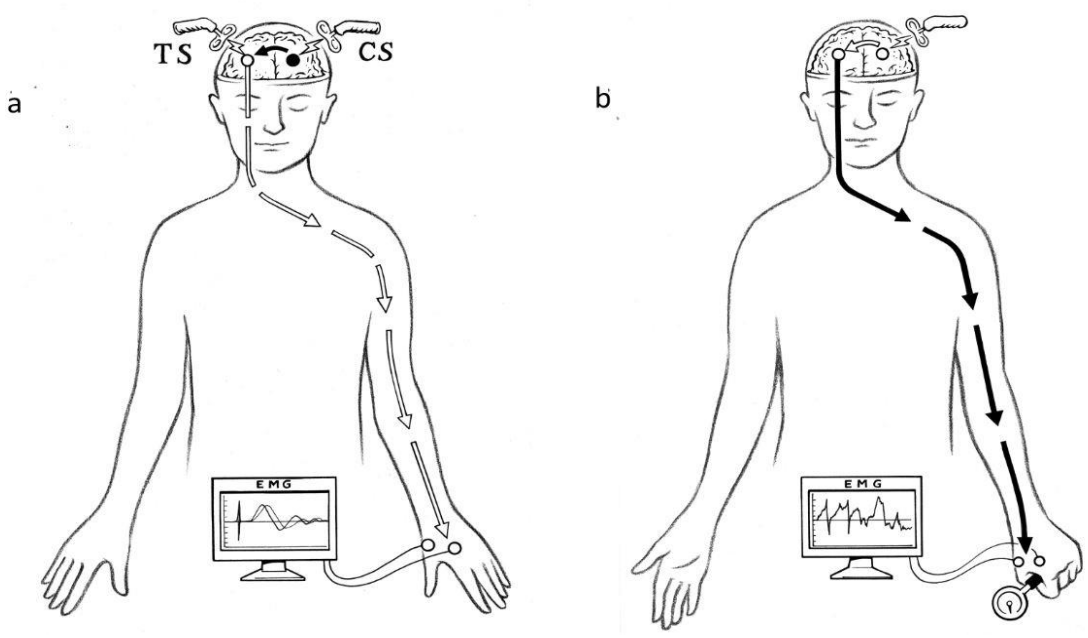

Figure 1. a) A schematic representation of the dual-coil paradigm. **b)** A schematic representation of the ipsilateral silent period paradigm.

2.5 Search strategy

The search strategy was developed in consultation with a librarian who was an expert in systematically searching the literature. Five databases were systematically searched (Medline,

Cochrane Library, EMBASE, EMCARE, and Scopus) from inception until November 3rd, 2021 without setting language limits on the search. The Medline search strategy is available in Supplementary File 1 (see page 31).

2.6 Exclusion criteria

Studies were excluded if they were case studies, case series, conference abstracts, non-peer-reviewed studies, or only used a structural measure of brain interhemispheric connectivity, e.g., diffusion tensor imaging or magnetic resonance imaging.

2.7 Study selection

One researcher (AG) ran the search in each database. The search results were imported into Endnote software and then uploaded into Covidence online software, where duplicates were removed automatically (The EndNote Team, 2013, Veritas Health Innovation, 2019). Two researchers (AG and either BH or CB) independently screened the titles and abstracts of all search studies for eligibility. Following the title and abstract screening, author pairs independently completed a full-text screening of included studies. When there was a disagreement between the two researchers, a third researcher determined study eligibility.

2.8 Data extraction and management

Two researchers (AG and either CB or BH) independently extracted the data from eligible studies utilising a customised data extraction form. The data obtained were the participants' demographics (diagnosis, age, gender, handedness, affected side, and duration post-diagnosis), the study aim and design, the neurophysiological technique used, the sample size, and the IHI measures (mean and standard deviation). When data were missing, the corresponding authors were contacted two times. Data that could not be pooled were summarised narratively. Where data of interest were reported predominantly as charts, and

we were unable to obtain the raw data, an online software was used to extract values from the chart (Rohatgi, 2019).

2.9 Risk of bias assessment

Two independent researchers (AG and either CB or BH) assessed the quality of each study using a standardised tool, the Joanna Briggs Institute Critical Appraisal tool: Checklist for Case-Control Studies (Ma et al. 2020; The Joanna Briggs Institute, 2017; Vardell and Malloy 2013). The assessment results were compared between the researchers, who resolved discrepancies through discussion, and consulted a third reviewer if agreement was not reached.

2.10 Data analysis

IHI data were grouped according to the hemisphere measured (affected or unaffected, dominant or non-dominant), the measure of IHI (dual-coil TMS and ISP), and time post-condition (subacute stage < 6 months and chronic stage ≥ 6 months). Where data could be pooled, data were analysed using the random effects estimate/size (ES) and the standardized mean differences (SMD). Data were reported with 95% confidence intervals (CIs). Heterogeneity between studies was assessed using I^2 statistic; heterogeneity greater than 50% was considered substantial. Where studies reported two or more time points (i.e., longitudinal study of IHI), we included all time points in the meta-analysis but divided the sample size by the number of time points, e.g., 30 participants tested at 3-time points resulted in an adjusted sample size of 10 participants for each time point). IHI measures of healthy controls were also included in the analyses.

3. Results

3.1 Study selection

A systematic search identified 1372 unique studies. Titles and abstracts were screened for eligibility, and 49 studies were retained for full-text screening. A further 35 studies were excluded after the full-text screening, leaving a total of 14 studies included within this review. Although the systematic review aimed to investigate IHI in several unilateral neurological conditions, all studies that met the inclusion criteria reported data for people post-stroke. The flowchart of all studies screened, reviewed in full-text, and included or excluded is presented in Figure 2.

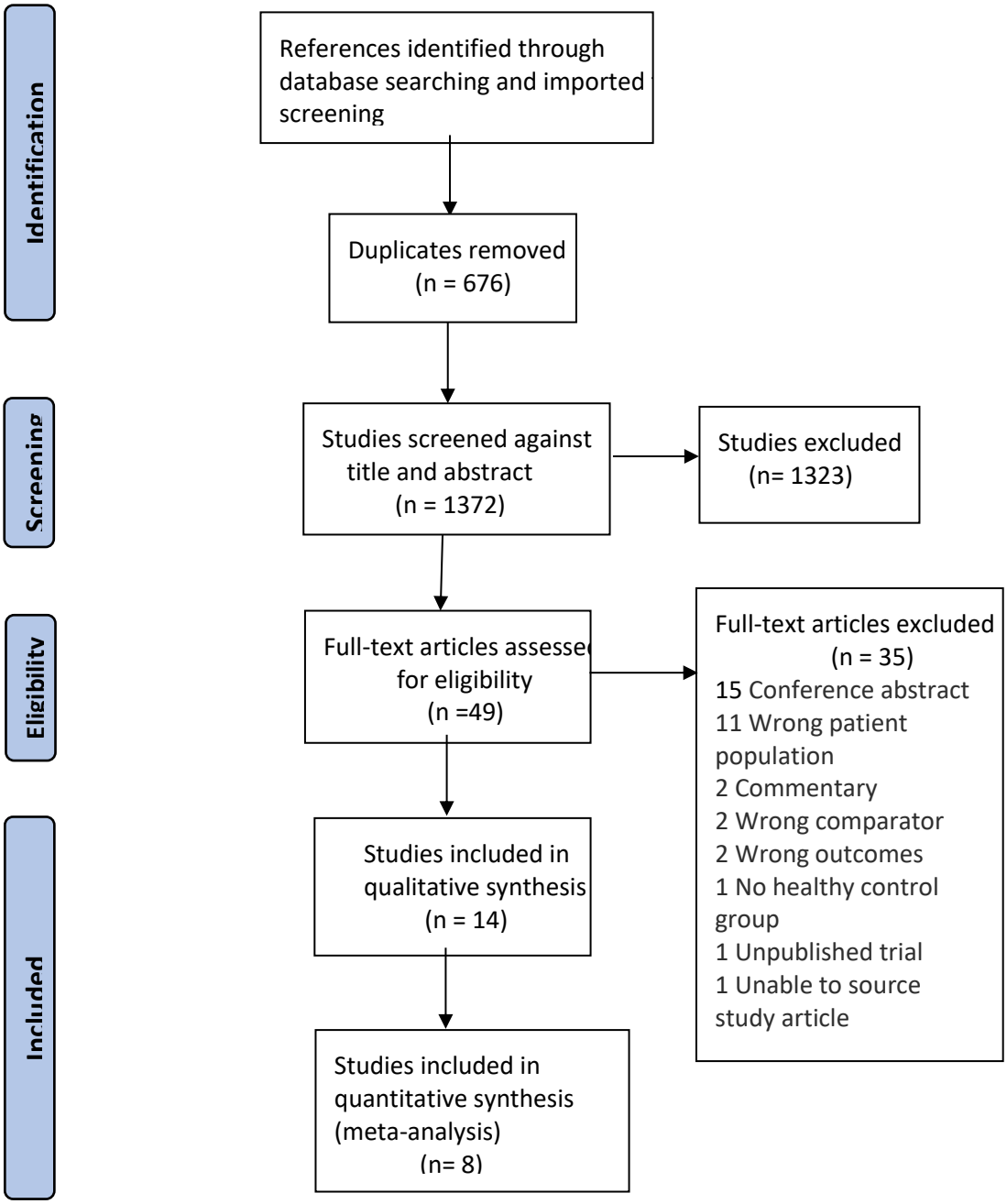

Figure 2. PRISMA Study Flow Diagram.

3.2 Study characteristics

The review included a total of 226 people poststroke (153 males) and 161 age-matched, neurologically intact healthy controls (82 males). The mean ages of participants reported in the included studies ranged from 54 to 66 years for people post-stroke and 49 to 64 years for healthy adults. Thirteen studies were observational, and one was interventional (Urbin et al., 2015). Eight of the included studies investigated the chronic stage only (total n = 124, duration post-stroke: 0.5 to 10 years) (Borich et al., 2015, Dimyan et al., 2014, Lewis and Perreault, 2007, Lin et al., 2020, Mang et al., 2015, Murase et al., 2004, Palmer et al., 2019, Urbin et al., 2015), two studies investigated subacute stage only (n = 35, duration post-stroke: 1 to 6 weeks) (Butefisch et al., 2008, Niehaus et al., 2003), two longitudinal studies tested patients from subacute to chronic stage (n = 46, duration post-stroke: 2 to 52 weeks) (Takechi et al., 2014, Xu et al., 2019), and one cross-sectional study investigated both subacute and chronic stage (n = 21, duration post-stroke: 0.5 to 12.9 months) (Shimizu et al., 2002). Three of the included studies recruited people with either hemorrhagic or ischemic stroke (Lin et al., 2020, Takechi et al., 2014, Urbin et al., 2015), seven included people with ischemic stroke only (Borich et al., 2015, Butefisch et al., 2008, Dimyan et al., 2014, Duque et al., 2005, Niehaus et al., 2003, Palmer et al., 2019, Xu et al., 2019), and three did not specify stroke pathology (Lewis and Perreault, 2007, Mang et al., 2015, Shimizu et al., 2002). Detailed study characteristics are available in Table 1 (see page 29).

3.3 Study quality assessment

Most studies included in this review had a small sample size and performed poorly on the selection of a representative sample. About 50% of the included studies did not indicate what criteria they used to identify healthy controls. All studies used a neurophysiological measure of IHI (dual-coil or ISP). About 30 percent of studies did not report controlling for other confounding factors such as the hemisphere (dominant and non-dominant), lesion location, or

severity. A summary of the quality assessment of the included studies is provided in Table 2 (see page 30).

3.4 **IHI measures**

Seven of the included studies used the dual-coil TMS measure of IHI, and seven used ISP (five measured ISP-duration, one measured ISP-latency, and one measured the percentage of decrease in EMG amplitude during ISP). All included studies measured IHI by recording from intrinsic hand muscles (e.g., first dorsal interosseous muscle). In people post-stroke, nine studies measured IHI in both directions: affected to unaffected hemisphere M1 and unaffected to affected hemisphere M1 ((Borich et al., 2015, Butefisch et al., 2008, Dimyan et al., 2014, Lewis and Perreault, 2007, Mang et al., 2015, Murase et al., 2004, Niehaus et al., 2003, Palmer et al., 2019, Takechi et al., 2014), three measured IHI from unaffected to affected hemisphere M1 only (Lin et al., 2020, Shimizu et al., 2002, Xu et al., 2019), and the remaining two measured IHI from the affected to unaffected hemisphere only (Lewis and Perreault, 2007, Urbin et al., 2015). In healthy controls, six studies measured IHI in both directions, i.e., from the non-dominant hemisphere to the dominant hemisphere and from the dominant to the non-dominant hemisphere (Borich et al., 2015, Butefisch et al., 2008, Lewis and Perreault, 2007, Mang et al., 2015, Murase et al., 2004, Palmer et al., 2019). Eight studies measured IHI from the dominant to the non-dominant hemisphere only (Dimyan et al., 2014, Duque et al., 2005, Lin et al., 2020, Niehaus et al., 2003, Shimizu et al., 2002, Takechi et al., 2014, Urbin et al., 2015, Xu et al., 2019). The extracted data can be viewed in tabular form via this Open Science Framework link: http://osf.io/2b9nt/.

Five of the seven dual-coil TMS studies provided IHI measures (mean and standard deviation) which allowed for data pooling (Butefisch et al., 2008, Duque et al., 2005, Lewis and Perreault, 2007, Murase et al., 2004, Xu et al., 2019). However, the results from Murase et al. (2004)

were omitted from the meta-analysis and included only in the descriptive analyses because some of the data were subsequently reported by Duque et al. (2005). Two studies provided only a descriptive summary of their IHI results (Dimyan et al., 2014, Shimizu et al., 2002). Four of the included ISP studies reported ISP-duration (mean and SD), which allowed for data pooling (Borich et al., 2015, Mang et al., 2015, Palmer et al., 2019, Takechi et al., 2014). One study only reported a descriptive summary of their ISP-duration results (Urbin et al., 2015), one study reported the ISP-latency (Niehaus et al., 2003) and one study reported the percentage of decrease in EMG amplitude during ISP (Lin et al., 2020).

3.5 IHI from the affected to unaffected hemisphere M1

3.5.1 Dual-coil TMS measure

Pooled results from three studies that measured the effect of affected on unaffected hemisphere M1 showed no difference between dual-coil TMS measure in people post-stroke and healthy controls (effect of M1 of non-dominant on M1 of dominant hemisphere) when the subacute and chronic stage data were combined (ES = -0.17, 95% CI [-1.27, 0.93], p = 0.77 (Butefisch et al., 2008, Duque et al., 2005, Lewis and Perreault, 2007; see Figure 3). Subgroup analysis showed MEP suppression was greater in the chronic stroke group than the control group (ES = -0.71, 95% CI [-1.36, -0.06], p = 0.03) and weaker in subacute stroke compared to the control group (ES = 0.96, 95%CI [0.02, 1.90], p = 0.05). Substantial heterogeneity was detected for the dual-coil measure ($\chi^2 = 8.34$, P = 0.02, $I^2 = 76\%$). There were two additional studies with insufficient data to include in the forest plot. Shimizu et al. (2002) investigated people in the subacute stage of stroke (n = 21) and reported that the dual-coil TMS measure showed no suppression of the MEP in people with cortical lesions. In contrast, both people with subcortical lesions and healthy controls showed visible suppression of the MEP. Murase et al. (2004) found no difference in the dual-coil TMS measures between people with chronic stage stroke (n = 9) and healthy controls.

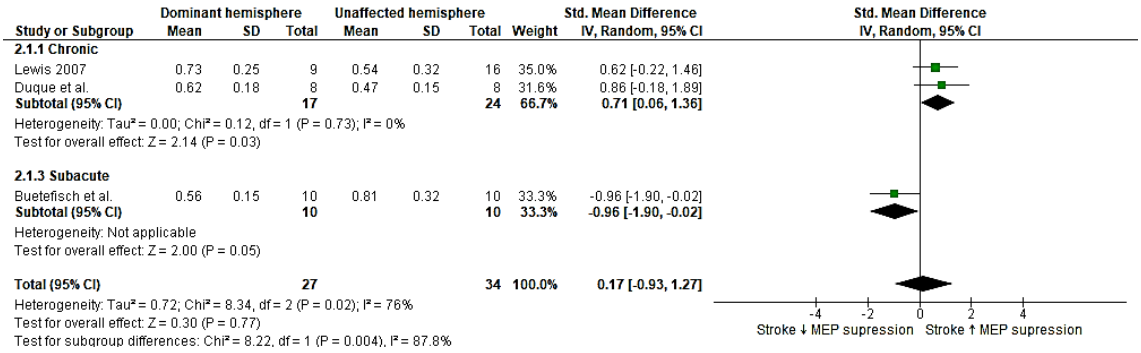

Figure 3. Dual-coil TMS measure representing IHI from the affected to the unaffected hemisphere M1 in people with stroke compared to the non-dominant to dominant hemisphere M1 in healthy controls. ↑= greater suppression ↓ = less suppression, MEP = motor evoked potential.

3.5.2 ISP

Data were pooled in two comparisons from four studies of the effect of the affected hemisphere M1 on the unaffected hemisphere M1 using ISP-duration in people post-stroke compared to healthy controls (effect of non-dominant hemisphere M1 on dominant hemisphere M1) (Borich et al., 2015, Mang et al., 2015, Palmer et al., 2019, Takechi et al., 2014). ISP-duration was longer in people post-stroke when the subacute and chronic stage data were combined compared to healthy adults (ES = -0.58, 95% CI [-0.97, - 0.19], $p < 0.01$; Figure 4). Subgroups for duration of condition showed ISP-duration was longer in the subacute stage than in healthy controls ($p = 0.01$), while there was no difference between ISP-duration in the chronic stage and healthy controls ($p = 0.06$). Data were pooled from three studies of the effect of M1 of affected hemisphere on M1 of unaffected hemisphere using ISP-duration in people post-stroke compared to healthy controls (effect of dominant on none-dominant hemisphere) (Borich et al., 2015, Mang et al., 2015, Palmer et al., 2019). ISP-duration did not differ between people post-stroke and healthy controls (ES -0.03, 95% CI [-0.9, 0.83], $p = 0.94$; Figure 5). In addition, Niehaus et al. (2003), not included in the meta-analysis, measured the ISP-latency in 25 people with acute stroke and 25 healthy controls. They found no difference between those with subcortical lesions and healthy controls, while ISP was non-detectable in people with cortical lesions.

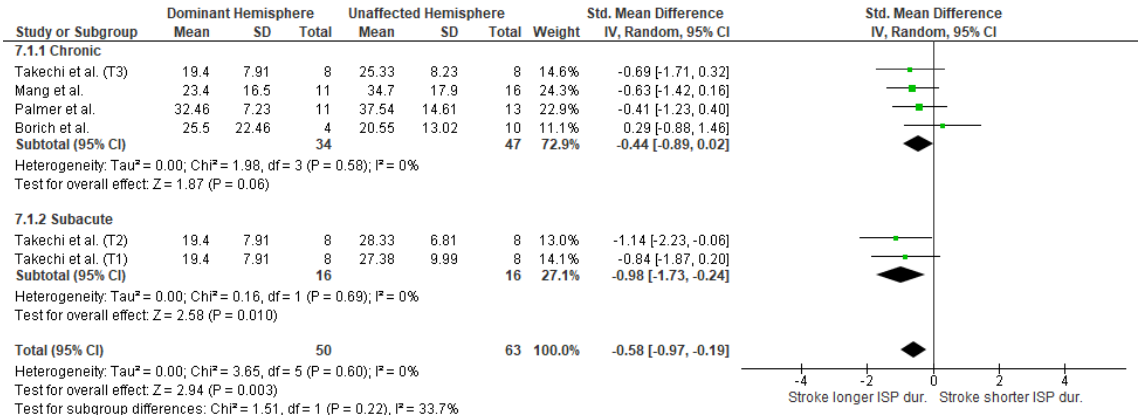

Figure 4. ISP-duration representing IHI from the affected to the unaffected hemisphere M1 in people with stroke compared to the non-dominant to dominant hemisphere M1 in healthy controls. Dur = duration.

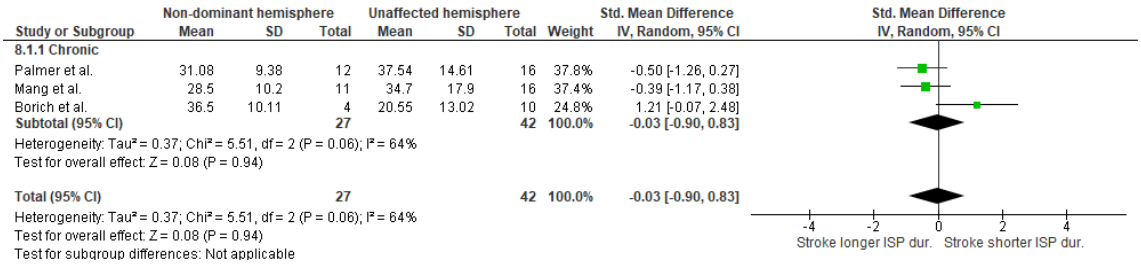

Figure 5. ISP-duration representing IHI from the affected to the unaffected hemisphere M1 in people with stroke compared to the dominant to non-dominant hemisphere M1 in healthy controls. Dur = duration.

3.6 IHI from the unaffected to affected hemisphere M1

3.6.1 Dual-coil TMS measure

Data were pooled from four studies, including a longitudinal study with measures at 1, 4, 12, 24, and 52 post-stroke, of the effect of the unaffected hemisphere M1 on the affected hemisphere M1 using dual-coil TMS measure in people post-stroke and healthy controls (effect of M1 of non-dominant on M1 of dominant hemisphere). No difference was shown between the groups (ES 0.29, 95% CI [-0.23, 0.82], p = 0.27; Figure 6) (Butefisch et al., 2008, Duque et al., 2005, Lewis and Perreault, 2007, Xu et al., 2019). Subgroups for duration of condition showed no difference between either chronic stage (p = 0.74) or subacute stage (p = 0.10) and

healthy controls. There were two additional studies that did not meet the data criteria to be included in the forest plot. Murase et al. (2004) found that the dual-coil TMS measure did not significantly differ between people post-stroke and healthy controls. Dimyan et al. (2014) used dual-coil TMS measure during rest and activity of the non-paretic hand (matched with non-dominant hand in healthy controls) and found lower suppression of the MEP within the stroke group, reflecting reduced inhibition from unaffected to affected hemisphere M1. Notably, the statistical analysis did not directly compare the results between groups at rest or during activity.

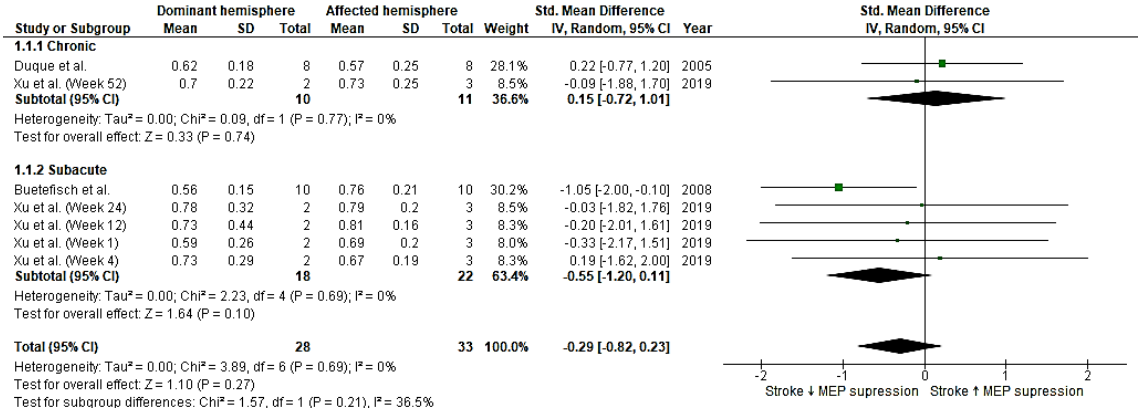

Figure 6. Dual-coil TMS measure representing IHI from the unaffected to affected hemisphere M1 in people with stroke compared to the non-dominant to dominant hemisphere M1 in healthy controls. ↑= greater suppression ↓ = less suppression, MEP = motor evoked potential.

3.6.2 ISP measures

Data were pooled in two comparisons from four studies of the effect of M1 of unaffected hemisphere on M1 of the affected hemisphere using ISP-duration in people post-stroke compared to healthy controls (M1 of non-dominant to M1 of dominant hemisphere; Figure 7 and from M1 of dominant to M1 of non-dominant hemisphere; Figure 8). ISP-duration in people post-stroke was longer than healthy controls (M1 of non-dominant to M1 of dominant hemisphere) when data from subacute and chronic stages were combined (ES = 0.65, 95% CI [-1.12, 0.19], $p < 0.01$; Figure 7). Subgrouping showed that ISP-duration in the chronic stage of stroke was no different from that in

healthy controls (p = 0.07). In contrast, ISP-duration was longer in the subacute-stage than in healthy controls (p < 0.01). Pooled results from three studies where ISP-duration in people post-stroke was compared to ISP-duration representing IHI from M1 of dominant to M1 of non-dominant hemisphere showed no difference between the two groups (ES = 0.06, 95% CI [-1.18, 1.30], p = 0.92; Figure 8). In addition, Lin et al. (2020),not included in the meta-analysis found no significant difference between IHI in people with chronic stroke and healthy control.

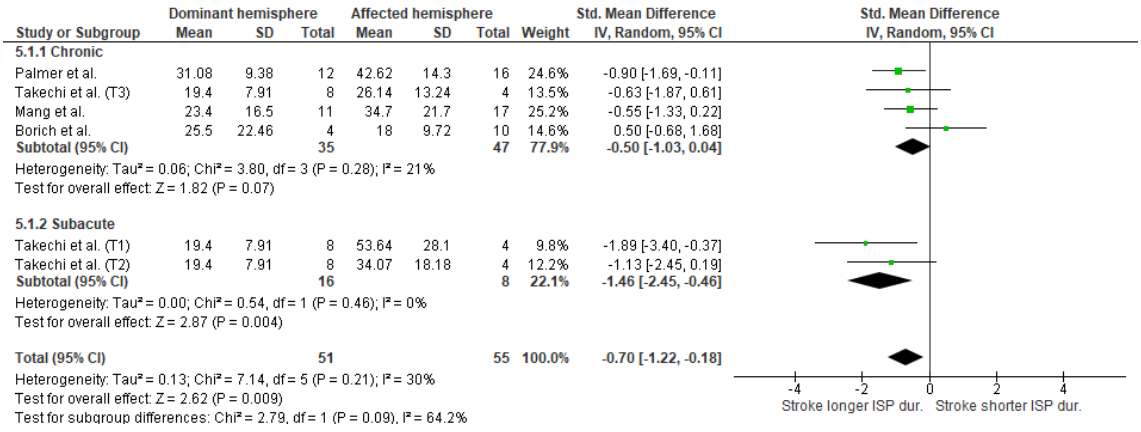

Figure 7. ISP-duration representing IHI from the unaffected to the affected hemisphere M1 in people with stroke compared to the non-dominant to dominant hemisphere M1 in healthy controls. Dur = duration.

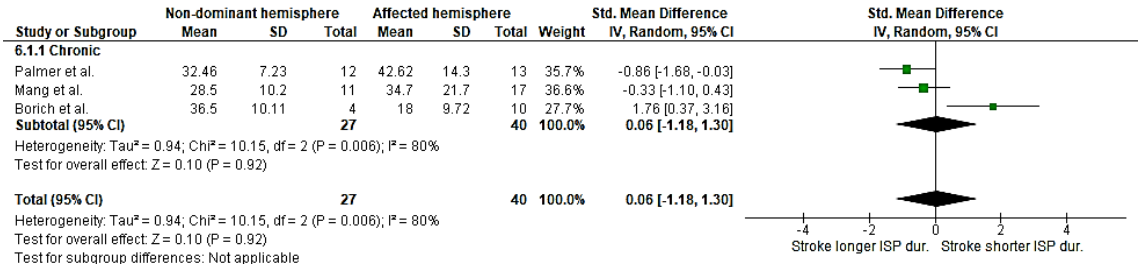

Figure 8. ISP-duration representing IHI from the unaffected to the affected hemisphere M1 in people with stroke compared to the dominant to non-dominant hemisphere in healthy controls. Dur = duration.

4. Discussion

The primary aim of this review was to determine the evidence for altered IHI in people with unilateral neurological conditions compared to healthy controls. The only studies that met the inclusion

criteria, however, enrolled people post-stroke. We found some limited, but inconsistent, evidence to support a difference in IHI between people with stroke and healthy controls. The outcome appears to be dependent on the TMS measure (dual-coil and ISP), duration post-stroke (subacute and chronic), and the direction the effect is measured including that of the comparison group. Both greater MEP-suppression (with dual-coil) and a prolonged ISP-duration (with ISP) are thought to represent stronger IHI (Chen, 2003). For IHI in both directions, affected to unaffected hemisphere M1 and unaffected to affected hemisphere M1, the dual-coil TMS measure did not differ between people with stroke and healthy controls, regardless of the direction measured in the healthy controls. ISP-duration in contrast was prolonged in people with stroke regardless of the direction in which it was measured, but only when compared to IHI from non-dominant to dominant hemisphere M1 direction in healthy controls. In a sub-group analysis of the data, dual-coil TMS measures indicated lower IHI from the affected to unaffected hemisphere M1 in the subacute stage, compared to healthy controls (IHI from non-dominant to dominant hemisphere M1), and higher IHI under the same conditions in the chronic stage. ISP-duration did not show differences between these subgroups.

The assessment of IHI appeared to differ between ISP and dual-coil assessment techniques, with ISP detecting a bilateral increase in IHI in people with stroke compared to healthy control. In contrast, dual-coil detected no overall difference between the two groups. It appears that for a unilateral neurological condition such as stroke, the ISP assessment indicated bilateral cortical changes. Although ISPand dual-coil TMS techniques are often used interchangeably to measure IHI between M1s, they appear to be mediated by different physiological mechanisms (Chen, 2003, Perez and Cohen, 2009). First, the dual-coil TMS measure, which is often undertaken at rest, with a conditioned stimulus preceding a test stimulus with an interstimulus interval of around 7-10ms, is thought to be underpinned by post-synaptic GABA-A receptors (Chen, 2003, Irlbacher et al., 2007). Conversely, ISP is thought to be mediated by post-synaptic GABA-B receptors and is measured in a pre-activated muscle. Along with differences in GABA receptor subunits, the role of muscle activation (rest vs.

active) is important to acknowledge. IHI is typically released during movement initiation and execution and serves to prevent unwanted movement in the non-active limb during a unimanual task. It is likely that measurement of IHI with the hand muscle either at rest using dual-coil or while the muscle is contracted (without visible movement) using ISP may not provide a complete understanding of this complex physiological mechanism, but at least provide a proxy physiological assessment to gain some insight to IHI. The results suggest that people post-stroke exhibit greater GABA-B mediated IHI, but similar GABA-A mediated IHI compared to controls. However, these differences in ISP held only for comparison to IHI from the non-dominant to dominant hemisphere M1 in healthy controls. When compared to IHI from the dominant to non-dominant hemisphere M1 in healthy controls, differences with people post-stroke were not observed. A possible explanation is that IHI from the non-dominant to dominant hemisphere in healthy controls is weaker (due to hemispheric dominance) than IHI from the dominant to non-dominant hemisphere, making it easier to observe the greater ISP duration in people with stroke. Interhemispheric inhibitory drive is indeed stronger in a dominant to non-dominant direction in healthy individuals (Bäumer et al., 2007). This IHI asymmetry seems more pronounced and defined in right-handed individuals, i.e. the left hemisphere's dominance over the right, whereas the asymmetry in left-handed individuals is more heterogeneous, i.e. it is not as defined (Reid and Serrien 2012). Furthermore, these inhibitory processes differed according to the nature of the task (e.g. bimanual tasks versus unimanual) in right-handed individuals, but it seems the interhemispheric mechanisms were less affected by the nature of task in left-handed individuals. Hence, to appreciate the significance of the difference in ISP measures between patients and healthy controls we have provided comparisons to both directions in the healthy controls (dominant to non-dominant and non-dominant to dominant) to check for the effect of direction of inhibition.

Cortical neurophysiology is known to change over time from acute/subacute to chronic stage after a stroke (Takechi et al., 2014, Takeuchi et al., 2012). This systematic review found some

evidence to suggest IHI does change from sub-acute to chronic phases of stroke recovery when measured with dual-coil technique, but not ISP. Specifically, there was a lower IHI from M1 of the affected to M1 of the unaffected hemisphere in the subacute stage, which reversed in the chronic stage (Butefisch et al., 2008, Takechi et al., 2014, Xu et al., 2019). The reduction in IHI in the subacute stage is consistent with current evidence for reduced excitability of the affected hemisphere in people with subacute stroke, likely resulting in the reduced IHI (McDonnell and Stinear, 2017). Moreover, IHI from the affected to unaffected hemisphere M1 was not detectable in people with cortical lesions in the subacute stage but detectable in the chronic stage, also suggesting a change in IHI over time (Niehaus et al., 2003). It is not clear whether this pattern is due to reduced excitability in the lesioned hemisphere, also reducing IHI from M1 or the affected hemisphere to M1 of the unaffected hemisphere. The relationship between cortical excitability and IHI is complex and a change in cortical excitability does not always correlate with change in IHI. For example, in healthy adults, transcranial direct current stimulation modulated cortical excitability but did not influence IHI (Lang et al., 2004). This suggests a perturbation of cortical excitability of one hemisphere might not induce equal (or correlated) responses in hemispheric excitability and interhemispheric excitability. In stroke, the lesion size and location might further complicate the relationship between interhemispheric and interhemispheric measures of cortical excitability. For example, Butefisch et al. (2008) showed less IHI from ipsilesional M1 to contralesional M1 than in the opposite direction, but the correlation with an intracortical excitability measure (short-latency intracortical inhibition) only held for participants with cortical but not subcortical lesions.

The results of this systematic review are not consistent with the IHI imbalance model (Bertolucci et al., 2018, Takechi et al., 2014). This is important because the model has underpinned the development of brain-based therapies that aim to improve motor function in people post-stroke (Boddington and Reynolds, 2017, Nicolo et al., 2018, Stinear et al., 2008).

First, the model's suggestion of an overall decreased inhibition from the affected to unaffected hemisphere M1 was not supported by dual-coil TMS measures of IHI and was contradicted by ISP measures of IHI. Second, although the model's suggestion of increased IHI from the unaffected to affected hemisphere M1 was supported by the prolonged ISP-duration, this suggestion was not supported by the dual-coil TMS measures. A systematic review by McDonnell et al. (2017) was also inconclusive about the balance of IHI in people post-stroke compared to healthy adults due to the limited number of studies included with small sample sizes. Besides, the authors found no evidence for increased excitability in M1 of the unaffected hemisphere in either subacute or chronic stage stroke, questioning the model's suggestions that increased excitability in M1 of the unaffected hemisphere drives greater IHI towards M1 of the affected hemisphere. However, a more recent systematic review by Bertolucci et al. (2018) supported IHI imbalance model. The authors suggested that IHI may depend on the residual motor function, with a suggestion that rebalancing IHI might be more beneficial for people with good residual motor function than for those with poor residual motor function.

Limitations

This work should be considered with regard to some limitations. First, although our search strategy was broad, the only studies that satisfied our a priori criteria for inclusion involved people with stroke, which limits the generalisability of our results beyond that group. Second, only four studies included participants with subacute stroke (three of them were included in the meta-analysis), while the remaining studies included only people with chronic stroke. Hence definitive conclusions cannot be made on the effect of duration post-stroke on IHI. Third, there was high heterogeneity between studies, possibly due to the diversity of stroke lesion type (ischemic vs. haemorrhagic), severity and, most importantly, lesion location. There is evidence that the lesion location (cortical or subcortical) affects neural reorganisation after stroke (Bertolucci et al., 2018).

Future research recommendations

Several recommendations emerge from this systematic review. First, to investigate mechanisms of IHI recovery a deeper understanding of the processes that occur throughout recovery is required. This will help to tailor treatment for effectiveness at each stage of recovery. Second, using both dual-coil and ISP to measure IHI may be needed for a better understanding of neurophysiology, as the two techniques seem to provide different insights into mechanisms of IHI. This can be done in conjunction with measuring IHI during movement initiation and/or execution using the dual-coil paradigm to better interrogate this complex neurophysiological mechanism. Third, with further supporting evidence it may be pertinent for clinicians to consider the nature of manual tasks used in physical therapy (for instance bimanual or unimanual, use of affected or unaffected hand) according to, or informed by post-stroke stage of recovery because evidence suggests that the relationship between IHI and bimanual coordination might be context-dependent (Kuo and Fisher, 2020). Therefore, future research may apply a more ecologically designed testing paradigm to unravel the complexity of IHI physiology. Lastly, future research should consider stratifying participants with stroke according to the lesion location (cortical and subcortical) and duration post-stroke to deepen understanding of these covariates' effects on brain physiological changes. Lastly, these insights from stroke may prove valuable to guiding research in other unilateral neurological conditions.

Conclusion

There is limited and inconsistent evidence for a difference in IHI between people post-stroke and healthy controls. The differences in IHI were dependent on the duration post-stroke, which supports consideration of the interaction between recovery stage and IHI when designing clinical trials to guide clinical decision-making. That the measures used (ISP and dual coil) did not provide identical results confirms previous evidence that they may be measuring

different aspects of IHI. The findings of this systematic review do not support the IHI imbalance model, which raises the possibility that the model may benefit from a deeper understanding of the neurophysiological processes underpinning IHI.

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Table 1. Study Characteristics

Author	Study design	Characteristics of stroke participants								Characteristics of healthy controls		
		Stage of stroke	Type of stroke	Lesion location C: Sc	Lesioned hemisphere Left: Right	N	Duration post-stroke (SD)	Gender M: F	Mean age (SD)	N	Gender M: F	Mean age (SD)
Borich et al. 2016	CC	Chronic	Ischemic	2: 8	5:5	10	75 (47) M	10:0	66.6 (4.1)	4	3:1	62.5 (8.1)
Butefisch et al. 2008	CC	Sub-Acute	Ischemic	6:4	4:6	10	1-6 W	5:5	54.9 (12.3)	10	6:4	49.47 (17.89)
Dimyan et al. 2014	CC	Chronic	Ischemic	NS	5:4	9	8 (8.7) Y	5:4	62.7 (9.8)	8	4:4	66
Duque et al. 2005	CC	Chronic	Ischemic	0:8	4:4	8	3 (2.1) Y	3:5	65 (14.2)	8	5:3	62 (12.6)
Lewis et al. 2007	CC	Chronic	NS	NS	10:6	16	10 (6) Y	11:5	59 (10)	9	NS	62 (8)
Lin et al. 2020	CC	Chronic	Ischemic or haemorrhagic	NS	7:16	23	45.6 (45.4) months	18:5	61.7 (8.9)	11	10:1	63.8 (11.7)
Mang et al. 2015	CC	Chronic	NS	8:16	12:12	24	71.0 (60.5) M	19:5	65.0 (8.6)	11	6:5	62.8 (9.6)
Murase et al. 2004	CC	Chronic	Ischemic	0:9	6:3	9	4.8 (3.3) Y	5:4	65 (13)	8	5:3	62 (13)
Niehaus et al. 2003	CC	Sub-Acute	Ischemic	12:13	NS	25	8 (5) D	17:8	60	25	13:12	51
Palmer et al. 2019	CS	Chronic	Ischemic	5:14	8:11	19	45 (36) M	11:8	66 (11)	14	8:6	53 (14)
Shimizu et al. 2002	CC	Sub-Acute and chronic	NS	12:9	10:11	21	C: 3.82 (3.61) M Sc: 1.78 ± 0.88 M	14:7	63.7 (7.6)	10	6:4	58
Takechi et al. 2014	PLC	Sub-Acute to chronic	Ischemic (n=14) or haemorrhagic (n=10)	0:24	18:6	24	2 -52 W	16:8	63.6	25	17:8	63
Urbin et al. 2015	PP	Chronic	Ischemic (n=5) or Haemorrhagic (n=1)	2:4	4:2	6	9.16 (6.24) M	4:2	54 (14)	7	2:5	50 (11.8)
Xu et al. 2019	PLC	Sub-Acute to chronic	Ischemic	NS	10:12	22	W1: 12 (3) D W4: 34 (5) D W12: 93 (8) D W24: 184 (12) D W52: 369 (10) D	15:7	57.5 (16)	11	7:4	64 (9)

Legend CC = Case-Control; CS = Cross-Sectional; PLC = Prospective Longitudinal Cohort; C= Cortical; SC = Subcortical; NS = Not Specified; D/W/M/Y = Days/Weeks/Months/Years; M = Male, F = Female, SD = standard deviation; Y = Yes; N = No.

Table 2. Summary of study quality assessment using the Joanna Briggs Institute Critical Appraisal tools: Checklist for Case-Control Studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Were cases and controls matched appropriately?	Were the same criteria used for identification of cases and controls?	Was exposure measured in a standard, valid, and reliable way?	Was exposure measured in the same way for cases and controls?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were outcomes assessed in a standard, valid, and reliable way for cases and controls?	Was the exposure period of interest long enough to be meaningful?	Was appropriate statistical analysis used?
Borich et al. 2016	+	?	+	+	+	-	-	+	+	+
Butefisch et al. 2008	+	+	+	+	+	+	+	+	+	+
Dimyan et al. 2014	+	+	+	+	+	+	+	+	+	+
Duque et al. 2005	+	+	+	+	+	?	?	+	+	+
Lewis et al. 2007	?	?	+	+	+	+	+	+	+	+
Lin et al. 2020	+	+	+	+	+	+	+	+	+	+
Mang et al. 2015	+	+	+	+	+	+	+	+	+	+
Murase et al. 2004	+	+	+	+	+	+	+	+	+	-
Niehaus et al. 2003	?	-	-	+	+	?	?	+	+	+
Palmer et al. 2019	+	+	-	+	+	+	-	+	+	+
Shimizu et al. 2002	+	+	-	+	+	+	+	+	+	+
Takechi et al. 2014	-	-	-	+	+	-	-	+	+	+
Urbin et al. 2015	+	?	?	+	+	+	+	+	+	+
Xu et al. 2019	?	?	-	+	+	+	+	+	+	+

Legend: + : Yes , - : No, ? : Unclear

Supplemental File 1. Medline Search Strategy

#	Searches
1	(cerebrovascular accident? or stroke? or brain? vascular accident? or CVA or CVAS or cerebral circulation infarction? or brain infarction? or brain? Venous infarction? or brain? circulation infarction? or cerebral infarction? or aca infarctions or cerebral arter* infarction? or mca infarction? or cerebral arter* circulation infarction? or cerebral arter* infarction? or brain? injur* or brain? laceration? or brain? H?emorrahage? or cerebellar h?emorrhage? or brain? trauma? or TBI or Cerebral Pals* or Reflex Sympathetic Dystroph* or Complex Regional Pain Syndrome? or CRPS or Algodystroph* or RSD or Sympathetic Reflex Dystroph* or Causalgia? or Deafferentation Pain? or neurological condition? or neurological disease? or unilateral neurological condition? or unilateral neurological disease? or Hemipleg* or monopleg* or Hemiparesis or mono?paresis or amyotrophic lateral scleros?s or ALS or bulbar palsies or bulbar pulsy or bulbar paralys?s or motor neuron disease?).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2	exp Stroke/
3	Brain Injuries/
4	Brain injuries, traumatic/
5	Brain injury, chronic/
6	Brain hemorrhage, traumatic/
7	Cerebral Palsy/
8	Reflex Sympathetic Dystrophy/
9	Complex Regional Pain Syndromes/
10	Causalgia/
11	CRPS.mp.
12	Hemiplegia/
13	Paresis/
14	Motor Neuron Disease/
15	Bulbar Palsy, Progressive/
16	Amyotrophic Lateral Sclerosis/
17	or/1-16
18	Corpus Callosum/
19	(inter?hemispher* or cross?hemispher* or transcallosal or IHI or IHI or corpus callosum?).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
20	18 or 19
21	interaction.mp.
22	inhibition.mp.
23	connectivity.mp.
24	21 or 22 or 23
25	17 and 20 and 24