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Neural Mechanisms Mediating the Cross Education of Motor Function: Implications for Healthy Older Adults

A dissertation submitted to the University of Dublin, Trinity College, for the degree of Doctor of Philosophy (Ph.D.)

By

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Declaration

I, Glenn H. M. Calvert, declare that this thesis has not been submitted as an exercise for a degree at this or any other university and is entirely my own work.

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Summary

Cross education (CE) is the process whereby a regimen of unilateral limb training engenders bilateral improvements in motor function. It is widely held that the contralateral gains thus derived may impart therapeutic benefits for patients with unilateral deficits arising from orthopaedic injury or stroke. Despite this prospective therapeutic utility, there exists remarkably little consensus concerning the mechanistic basis of this interlimb effect. The precise means through which the neuroanatomical structures and cellular processes that mediate CE may be influenced by age-related neurodegeneration are also almost entirely unknown. Notwithstanding the increased incidence of unilateral impairment in later life, age-related variations in the expression of CE have been examined only infrequently. In seeking to address these lacunae, the aim of this thesis was twofold: i) to examine age-related variations in the extent to which the phenomenon of CE is manifested, and ii) to devise novel methods of non-invasive brain stimulation with which to elucidate the physiological mechanisms which mediate this effect.

In Chapter 1, an extensive review of the literature was presented that detailed several pathways that exhibit the potential to mediate the neural adaptations that underlie the expression of CE. A specific emphasis was placed upon the extent to which associated brain structures and networks may be affected by the neurodegenerative processes that are a feature of ageing. Although various mechanisms were proposed, a particular emphasis was assigned to the potential functional contributions of interhemispheric interactions subserved by transcallosal projections between dorsal premotor cortex (PMd) and primary motor cortex (M1).

In Chapters 2 and 3, two novel methods of non-invasive brain stimulation were developed and refined, with the view of probing excitatory and inhibitory interhemispheric interactions between these brain regions. The intent was to apply these methods subsequently in an investigation of CE that formed the basis of Chapter 4.

In the first experimental study (Chapter 2), we assessed the feasibility of applying a short duration burst (6-500 ms) of transcranial alternating current stimulation (tACS) or transcranial random-noise stimulation (tRNS) unilaterally to M1, in order to potentiate the amplitudes of motor-evoked potentials (MEPs) elicited 6 ms later by transcranial magnetic stimulation (TMS) applied to the opposite M1. The aim of this approach was to devise a novel assay of interhemispheric facilitation (IHF) – a notoriously capricious measure of interhemispheric function that is obtained classically with dual-coil TMS. As this effect has been examined only sparingly with magnetic conditioning of non-primary motor regions (and elicited with even greater scarcity), we decided that in seeking to establish proof of principle, and to facilitate comparisons with effects reported by dual-coil TMS studies, it was necessary to apply conditioning stimulation only to M1. In applying this methodology, IHF was obtained by conditioning M1 with a 30 ms (but not 100 or 500 ms) duration burst of 140 Hz tACS. The magnitude of this effect was within the range of values reported previously by dual-coil TMS studies. In circumstances in which 6-500 ms duration bursts of 670 Hz tACS or 100-640 Hz tRNS were applied, this effect was not however obtained. Although these findings suggest that conditioning M1 with short duration tACS may provide a means of eliciting IHF, the inconsistency with which the effect was observed across conditions (and indeed

participants) indicates that more research is required to optimise fully the stimulation parameters with which this effect may be obtained. Consequently, the tACS-based methodology developed in Chapter 2 was not applied as an index of IHF in the investigation of CE undertaken in Chapter 4.

In the second experimental study (Chapter 3), a novel method of eliciting interhemispheric inhibition (IHI) was devised, that incorporated a fully automated dual-coil adaptive threshold hunting (ATH) paradigm. Although by convention IHI is expressed as a percentage change in MEP amplitude when a test stimulus of fixed intensity is applied in the presence of conditioning stimulation, the ATH method quantifies IHI as the percentage change in stimulation intensity required to elicit a MEP of a pre-specified amplitude. The objective of this study was to define a range of stimulation parameters (i.e., conditioning stimulus intensities, interstimulus intervals, and test coil orientations) that can be used reliably to elicit PMd-M1 IHI. In applying these methods, PMd-M1 IHI was obtained with test stimuli that induced current flow in the posteroanterior (PA) direction but was conspicuously absent when anteroposterior stimuli were applied instead. The magnitude of IHI obtained with PA test stimuli tended to increase with conditioning stimulus intensity (90%, 110%, 130% of resting motor threshold) but did not vary by interstimulus interval (8, 10, 40 ms). In seeking to demonstrate that the ATH method yields outcomes similar to those obtained with conventional MEP-derived measures, we also collected measures of M1-M1 IHI. In doing so, we showed that the pattern of outcomes obtained with ATH-based measures of M1-M1 IHI was consistent with that obtained with classical IHI approaches. These measures of (PMd-M1) IHI were applied subsequently in the study of CE that formed the basis of Chapter 4.

In the third (and final) experimental study (Chapter 4), a unimanual ballistic wrist extension paradigm was employed, in which young and older adults completed a single session of non-dominant limb training. The intent was to examine potential differences in the levels of CE attained by young and older adults both immediately and one-week following the initial training session. Consistent with previous studies, we found that following a single session of unimanual ballistic wrist extension training undertaken with the non-dominant limb, similar levels of CE (expressed in terms of relative improvement and interlimb transfer) were present in young and older adults. Somewhat surprisingly, and in contrast to previous studies, the raw accelerations exhibited by older volunteers tended to exceed, and in some cases were appreciably greater than, those exhibited by young adults. It is therefore possible that the sample of older adults recruited in the present study was not representative of older adults generally. Using methods developed in Chapter 3, we also sought to establish whether training-related changes in short- and long-latency PMd-M1 IHI were related to interindividual variations in CE. Due to substantial fluctuations in the amplitudes of "control" MEPs (i.e., those obtained in the absence of conditioning stimulation) during the course of each IHI measurement, which deviated appreciably from the expected threshold hunting target (200 μV), it was not however possible to ascribe any functional significance to the ostensive changes in IHI that were observed. More specifically, as it was not known whether equivalent populations of neurons were being stimulated by the test stimulus at each point of measurement (due to fluctuations in control MEP amplitude), we could not discern whether the observed changes in IHI were driven by training-related changes in the excitability of corticospinal projections from the untrained M1, or alterations in the level of

inhibitory drive engendered by the contralateral PMd. As a consequence, an interpretation of the observed changes in IHI could not be provided.

The thesis concludes with a discussion of the main findings and limitations of the works thus presented and offers recommendations that may inform the basis of future studies of CE.

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This thesis is dedicated to my dear friend, Jerome Carr, and mother-in-law, Linda McDonald, who sadly passed away during the course of its completion.

Glossary of Abbreviations

ACL	Anterior cruciate ligament
aMT	Active motor threshold
AP	Anteroposterior / anterior-to-posterior
ATH	Adaptive threshold hunting
BA	Brodmann area
BCa	Bias-corrected-and-accelerated (95% confidence interval)
BOLD	Blood-oxygen-level-dependent
CC	Corpus callosum
CE	Cross education
CNS	Central nervous system
CRST	Corticoreticulospinal tract
CS	Conditioning stimulus
CSE	Corticospinal excitability
cSP	Contralateral silent period
CST	Corticospinal tract
DBS	Deep brain stimulation
DLF	Dorsolateral funiculus
dlPFC	Dorsolateral prefrontal cortex
d_R	Robust variant of Cohen's *d*
DWI	Diffusion weighted imaging
ECR	Extensor carpi radialis (longus)
EMG	Electromyography
FA	Fractional anisotropy
FCR	Flexor carpi radialis
FDI	First dorsal interosseus
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
GABA	γ-aminobutyric acid
HAROLD	Hemispheric asymmetry reduction in older adults

HF-tRNS	High-frequency transcranial random-noise stimulation
ICF	Intracortical facilitation
IHF	Interhemispheric facilitation
IHI	Interhemispheric inhibition
ISI	Interstimulus interval
iSP	Ipsilateral silent period
LICI	Long-interval intracortical inhibition
LM	Lateromedial / lateral-to-medial
M1	Primary motor cortex
M1a	Anterior division of primary motor cortex
M1p	Posterior division of primary motor cortex
MD	Mean diffusivity
MEP	Motor-evoked potential
MRI	Magnetic resonance imaging
MSO	Maximum stimulator output
NMDA	*N*-methyl-$_D$-aspartate
PA	Posteroanterior / posterior-to-anterior
PEST	Parameter estimation by sequential testing
PFC	Prefrontal cortex
PMd	Dorsal premotor cortex
PMRF	Pontomedullary reticular formation
PMv	Ventral premotor cortex
RFD	Rate of force development
rms	Root mean square
rMT	Resting motor threshold
rTOST	Robust two one-sided t-test
r_{pb}	Percentage bend correlation coefficient
rTMS	Repetitive transcranial magnetic stimulation
$SD_{(w)}$	(Winsorized) standard deviation
SICF	Short-interval intracortical facilitation
SICI	Short-interval intracortical inhibition
SMA	Supplementary motor area

SRTT	Serial reaction time task
STN	Subthalamic nucleus
tACS	Transcranial alternating current stimulation
TB	Training block
THT	Threshold hunting target
TMS	Transcranial magnetic stimulation
tRNS	Transcranial random-noise stimulation
TS	Test stimulus
VLa	Anterior ventrolateral thalamic nucleus
VLp	Posterior ventrolateral thalamic nucleus
VMF	Ventromedial funiculus

List of Publications

Published Articles

Chapter 1

Calvert, GHM., & Carson, RG. (2022). Neural mechanisms mediating cross education: With additional considerations for the ageing brain. *Neurosci Biobehav Rev.*, 132, 260-288. https://doi.org/10.1016/j.neubiorev.2021.11.025

Chapter 3

Calvert, GHM., McMackin, R., & Carson, RG. (2020). Probing interhemispheric dorsal premotor-primary motor cortex interactions with threshold hunting transcranial magnetic stimulation. *Clin Neurophysiol.*, 131 (11), 2551-2560. https://doi.org/10.1016/j.clinph.2020.07.020

Published Abstracts

Chapter 2

Calvert, GHM., & Carson, RG. (2018). Interhemispheric facilitation of corticospinal pathways induced by short duration tACS. *XXII Congress of the International Society of Electrophysiology and Kinesiology (ISEK)*, Dublin, Ireland. (Prize awarded for best student poster presentation)

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Chapter 1

Neural Mechanisms Mediating Cross Education: With Additional Considerations for the Ageing Brain

1.1 Introduction

1.1.1 General context

Among the many challenges encountered by older people, unilateral injuries arising from falls are among the most debilitating. In persons aged 65 years or older, the risk of sustaining a fall at least once annually is between 30-40% (Cumming et al., 2008; Tinetti et al., 1994). In those admitted to hospital consequently, approximately three-quarters will have sustained a fracture, with the upper limbs affected in more than half of cases (Balasegaram et al., 2000; Hoff et al., 2016; Nordell et al., 2000). While the injured limb is typically stabilised with plaster or external fixation to facilitate orthopaedic recovery, little attention is typically given to the loss of functional capacity that may occur during the immobilisation period. Indeed, even in healthy young adults with extensive

functional reserves, three weeks of immobilisation engenders decreases in muscle strength of up to 50% of initial capacity (Hortobagyi et al., 2000). These effects are exacerbated markedly in older people (Hvid et al., 2010).

The most significant risk arising from protracted periods of disuse in older adults is that the corresponding loss of function may leave the individual below the frailty threshold and unable to perform activities of daily living (Barry & Carson, 2004; Booth & Zwetsloot, 2010; Carson, 2015). The unilateral deficits thus incurred may persist for more than 12 months following the initial injury and lead to an irreversible loss of independence (Carson, 2015; Chung et al., 2007; Roh et al., 2017). If, however, the opposite limb is trained during the period of immobilisation, the loss of functional capacity (i.e., in the immobilised effector) is attenuated markedly (for a meta-analysis, see Haggert et al., 2020). The benefits derived through training of the opposite limb may also have therapeutic significance for patients with unilateral deficits arising from stroke, in whom the loss of function is often so severe that approaches such as constraint-induced movement therapy are beyond practical consideration (for reviews, see Farthing & Zehr, 2014; Sun & Zehr, 2019).

Despite this prospective therapeutic utility, there is remarkably little consensus concerning the mechanistic basis of the function enhancing, sustaining, and restoring properties of contralateral limb training. The precise means through which the neuroanatomical structures and cellular mechanisms that mediate their expression may be influenced by age-related neurodegeneration are also almost entirely unknown. Notwithstanding the increased incidence of unilateral impairment in later life (e.g., following stroke, e.g., Bejot et al., 2016), age-related

variations in the magnitude of gain derived by the contralateral limb – for which the term cross education (CE) was coined, have been examined only infrequently. On the basis of the limited number of studies that have been conducted, the contemporary view is that the capacity to augment the performance of the untrained effector through training of its homologue is preserved in later life, although the magnitude of such benefits may be smaller than those exhibited by young adults (Barss et al., 2016). A better understanding of any age-related changes in the mechanisms that mediate CE appears necessary therefore, in order to advance the therapeutic exploitation of this phenomenon.

1.1.2 Scope and structure of the review

The review commences with a primer on CE. This encompasses a brief history and conceptual overview of the behavioural phenomenon, along with notes concerning its potential therapeutic utility. The manner by which the expression of CE may change with advancing age is also considered. In the sections that follow, we examine several pathways that exhibit the potential to mediate the expression of neural adaptations that provide a basis for CE. We begin with an appraisal of accounts that emphasise the role of non-decussated projections that descend ipsilaterally from the 'untrained' primary motor cortex (M1), as well as 'redecussated' projections (i.e., decussated fibres that recross the neuraxis via the spinal commissure) that have hitherto escaped detailed attention. A discussion of corticoreticulospinal projections is also provided. The supposition that CE is mediated by adaptations within M1 is then considered. A detailed discussion of

interhemispheric transcallosal connectivity is included in this context. In the sections which follow, we attend to other (i.e., non-primary motor) elements of the cortical motor network (namely prefrontal and premotor areas) which may play an instrumental role in CE. The review concludes with a discussion of thalamocortical projections. Each section includes a survey of age-related variations in the characteristics of the specific pathways/structures under consideration.

1.2 A PRIMER ON CROSS-EDUCATION

1.2.1 PHENOMENOLOGY

The capacity for the experience of one limb to alter the performance of its opposite counterpart was first reported by Volkmann in 1858. Following the repeated administration of a two-point discrimination task – applied unilaterally to the distal phalanx, Volkmann reported increases in tactile acuity for stimuli applied to homotopic regions of the corresponding finger on the opposite hand (Volkmann, 1858). It was almost forty years later that Edward Scripture and colleagues obtained analogous effects in the motor domain (Scripture et al., 1894). Using a simple manometer to derive a rudimentary measure of grip strength, Scripture's group reported bilateral gains in compressive force following a two-week regimen of unimanual rubber bulb compression training. Similar effects were obtained in the context of a 'skill training' paradigm in which a participant was tasked with placing a needle through a series of holes of decreasing diameter (~5.8-1.0 mm) on a twist-drill gauge with the aim of avoiding contact with the

sides. Numerous expressions of this phenomenon have since been elicited in a multitude of studies conducted over the course of the past 120 years (for reviews, see Hortobagyi, 2005; Lee & Carroll, 2007; Ruddy & Carson, 2013).

While not given prominence in all contexts in which CE has been studied, its estimation necessarily requires that a transfer test be conducted. More generally, transfer tests are those in which an individual is assessed in a different situation or context (e.g., using the opposite limb), or on a novel variant of the training/practice task (e.g., Schmidt et al., 2018). The goal in most instances is to gauge the generalisation of an acquired capability. Such generalisation is, along with the retention of that capability, considered to be demonstrative of effectual learning (e.g., Magill, 2010). A further intent of transfer testing is to aid in the understanding of that which has been learned and to define the characteristics of the associated processes of memory formation (Schmidt & Young, 1987) – whereby memory is conceived of in terms of the capability for performance (Schmidt et al., 2018). It is important to recognise however that empirical findings (e.g., derived from brain imaging) that bear upon neural processes which mediate changes in performance during training/practice, are not necessarily relevant in elucidating the mechanisms that underpin CE, i.e., as it presents as a manifestation of learning and memory formation. These can only be determined by employing methods (e.g., tests of transfer and retention) sufficient to permit the inference that learning has occurred. This is a matter to which we will return in the sections that follow.

In the present review, we use the term “cross education” (CE) to describe the behavioural phenomenon by which a regimen of unilateral limb training

engenders bilateral improvements in motor function (Carson et al., 2016). In recent years, such terms as bilateral transfer (Land et al., 2016), cross-limb transfer (Hinder et al., 2011), interlimb transfer (Ruddy et al., 2016), and intermanual transfer (Ossmy & Mukamel, 2016), have also been applied. In presenting previous empirical findings, however, we use the terms "absolute improvement", "relative improvement", and "interlimb transfer" as distinct quantitative indices of CE, in order to distinguish the outcome measures that have been used sometimes interchangeably (and often ambiguously) in the literature. In this context, absolute improvement is defined as the change in performance attained by the untrained limb expressed in 'raw' units, e.g., an increase in wrist acceleration of x ° s^{-2}. In contrast, relative improvement is defined as the change in performance attained by the untrained limb expressed as a percentage of pre-training capacity, e.g., an increase in wrist acceleration of 50%. Lastly, interlimb transfer is defined as the relative gain in performance attained by the untrained limb, expressed as a percentage of that attained by the training limb (i.e., a ratio of 'untrained' to 'trained' relative improvement).

Although meta-analytic estimates vary appreciably – due to the considerable heterogeneity that exists between study training protocols (Manca et al., 2018), the magnitude of interlimb transfer is generally in the order of 52-80% (Green & Gabriel, 2018). In terms of relative improvement, this corresponds to an increase of 8-18% of initial (i.e., pre-training) capacity for the untrained limb (Carroll et al., 2006; Cirer-Sastre et al., 2017; Green & Gabriel, 2018; Manca et al., 2017b; Munn et al., 2004). The contralateral benefits conferred by unilateral training are generally most prominent when the homologues of muscles that act

as principal agonists in the training task are engaged in the transfer task (Andrushko et al., 2018; Enoka, 1988; Hortobagyi, 2005; Hortobágyi et al., 1999; Lee & Carroll, 2007; Zhou, 2000). The greatest increases are typically observed following the use of training protocols that require eccentric contractions, as well as those that emphasise the maximal engagement of muscles in the training limb (e.g., ballistic movement protocols) (Cirer-Sastre et al., 2017; Hortobágyi et al., 1997; Manca et al., 2017b; Tseng et al., 2020; Valdes et al., 2021). The magnitude of the effect (whether expressed in terms of relative improvement or interlimb transfer) is ostensibly equivalent for the upper and lower limbs (Green & Gabriel, 2018).

Although in recent years there has been some debate as to whether cross education is affected by training limb dominance (e.g., Adamson et al., 2008; Coombs et al., 2016; Toca-Herrera et al., 2008; Farthing, 2009) – whereby "dominance" is conceived of in terms of stated limb preference (i.e., handedness or footedness), this conceptualisation of motor lateralisation neglects an important observation. Just as different facets of language may be lateralised to either the right or left hemispheres (e.g., Grimshaw, 1998), it has been suggested that different aspects of movement control may be similarly localised (Sainburg, 2002). In the present context, Sainburg's notion of "dynamic dominance" implies that transfer asymmetries (i.e., where one task transfers preferentially following training of one limb rather than the other – irrespective of which limb is considered classically "dominant") may reflect the hemispheric lateralisation of specific control processes, rather than the subject's handedness or footedness. It has been demonstrated previously that in right-handed participants, prior training of the

right hand in a single-joint targeted reaching task was associated with increased dependence on initial acceleration amplitudes (shown previously to rely upon left hemispheric mechanisms) to increase the velocity of movements made by the left hand. By contrast, prior training of the left hand was associated with increased dependence upon the modulation of acceleration duration (shown previously to rely upon right hemispheric mechanisms) to increase the velocity of movements made by the right hand (Sainburg et al., 2016). This effect, for which the term "control asymmetries" is often applied, is frequently overlooked in studies of CE.

1.2.2 THERAPEUTIC UTILITY

The therapeutic applications of CE apply most readily to circumstances in which the primary objective of rehabilitation is concerned with: i) the attenuation of functional deficits that arise *during* the course of unilateral limb immobilisation, and ii) the promotion of functional recovery *following* unilateral injury of the CNS (e.g., stroke) or periphery (e.g., joint reconstruction surgery) (for reviews, see Farthing & Zehr, 2014; Haggert et al., 2020; Hendy et al., 2012; Sun & Zehr, 2019). While the base of evidence remains relatively meagre, CE interventions have thus far shown promise in preserving, promoting, and/or restoring motor function in: i) patients with unilateral limb fractures (Magnus et al., 2013), ii) post-surgical patients recovering from unilateral musculo-ligamentous injuries (Harput et al., 2019; Zult et al., 2018a, 2018b) or arthroplasty procedures (Jacksteit et al., 2021), iii) hemiplegic stroke survivors (Ausenda & Carnovali, 2011; Ausenda et al., 2014; De Luca et al., 2017; Dehno et al., 2021; Ehrensberger et al., 2019;

Simpson et al., 2019; Sun et al., 2018; Urbin et al., 2015), iv) below-elbow amputees instrumented with an upper limb prosthesis (de Boer et al., 2016), and v) muscle weakness in patients with multiple sclerosis (Manca et al., 2017a) and osteoarthritis (Onigbinde et al., 2017).

1.2.3 AGE-RELATED VARIATIONS IN CROSS EDUCATION

While at first glance it would appear that older adults are the group most likely to derive practical benefits from the phenomenon of CE, it is notable (and somewhat paradoxical) that age-related variations in its expression have been examined only infrequently. Indeed, much of the evidence upon which the therapeutic applications of CE are based has been derived almost exclusively from studies conducted in younger adults. Why is this matter of more general significance? In the first instance, it is well established that the brains of humans undergo profound age-related changes in functional and structural connectivity that manifest most prominently in later life (e.g., Cox et al., 2016; Seidler et al., 2010). It is also recognised that the adaptations that occur in response to a training impetus may vary substantially across the lifespan (Barry & Carson, 2004). An obvious question thus arises. Are there age-related variations in the degree to which the phenomenon of CE is manifested? And relatedly, do the neural mechanisms that mediate the expression of this phenomenon change with age?

The first question has been addressed in a limited number of studies. There remain however many gaps in our knowledge. While the conclusion has on occasion been drawn that the contralateral gains engendered by unilateral training

are preserved in later life (Barss et al., 2016; Tracy et al., 1999), several caveats necessarily apply. In adhering to resistance training protocols, older adults exhibit performance gains for the untrained limb that are lower in absolute terms than those of their younger counterparts, and yet equivalent in relative terms, i.e., when expressed with respect to pre-training capacity (Bemben & Murphy, 2001; Ehsani et al., 2014; Hester et al., 2019a; Hester et al., 2019b). There may well exist an element of task specificity in this regard. In following ballistic training protocols – which typically have as their goal the maximum realisable velocity/acceleration of a joint or limb segment, it has been demonstrated consistently that older adults exhibit smaller gains in the performance of the untrained limb, when expressed in both absolute and relative terms, as well as lower levels of interlimb transfer, compared to younger subjects (Dickins et al., 2015a; Hinder et al., 2011; Parikh & Cole, 2013; *cf.* Hinder et al., 2013). In circumstances in which the training task imposes greater demands for precision and dexterity (e.g., grip-and-lift, two-ball rotation), there exists a small body of evidence which suggests that older adults may exhibit similar levels of CE (expressed in terms of absolute improvement, relative improvement, and interlimb transfer) as their younger counterparts (Dickens et al., 2015; Nuzum et al., 2021; Parikh & Cole, 2013; Reissig et al., 2015). As discussed previously, these putative "task-specific" effects may be understood by consideration of the "dynamic dominance" hypothesis (Sainburg, 2002). It has been demonstrated previously that following unimanual practice, older adults exhibit smaller asymmetries in performance during unilateral movements compared to younger subjects (e.g., Przybyla et al., 2011). This effect is also apparent in respect of transfer. For example, whereas young adults may

exhibit transfer (i.e., in respect of some facet of motor skill) from the dominant to non-dominant limb only, older adults may exhibit transfer in both directions (i.e., from the non-dominant to dominant limb and vice versa) (Wang et al., 2011). Viewed in this light, it is conceivable that the degree to which age-related effects in CE paradigms are expressed, may depend on the relative preservation of mechanisms that contribute to hemispheric lateralisation of motor control.

It is the second question: "do the neural mechanisms that mediate the expression of this phenomenon change with age?" that is the primary focus of the present review. To date, it has largely escaped direct empirical study (*cf.* Nuzum et al., 2021; Veldman et al., 2021). In the sections that follow therefore, the inferences that we make are sometimes indirect. On the one hand, they are based upon appraisal of the extent to which specific neuroanatomical structures (e.g., the corticospinal tract, corticoreticulospinal projections, transcallosal fibres, and thalamocortical radiations) exhibit the potential to mediate the expression of CE. On the other, they are derived from current knowledge concerning the manner in which these structures and their associated cellular processes are influenced by the neurodegenerative processes that are a feature of ageing.

1.3 IPSILATERAL DESCENDING PROJECTIONS

1.3.1 THEORETICAL CONTEXT

As early as 1934, Hoff and Hoff demonstrated that unilateral extirpation of Brodmann area 4 (BA4), i.e., the cytoarchitecturally defined region that

encompasses M1, engendered bilateral degeneration of terminal boutons in the dorsal and ventral horns of the rhesus macaque (Hoff & Hoff, 1934). Since this time, high-resolution anatomical tracer studies in non-human primates have confirmed extensive ipsilateral innervation arising from pyramidal tract projections (Lacroix et al., 2004; Rosenzweig et al., 2009; Soteropoulos et al., 2011; Yoshino-Saito et al., 2010). These fibres comprise corticofugal projections that fail to cross at the pyramidal decussation, and also those that decussate and later recross the midline through lamina X in the spinal grey matter ('redecussated fibres'). It has been widely supposed that during actions that are unilateral by intention, a corollary of the 'descending set' of motor commands may alter the excitability of spinal motoneurons that innervate the muscles of the opposite limb – by means of these ipsilateral projections (for reviews, see Bundy & Leuthardt, 2019; Carson, 2005; Chettouf et al., 2020; Cleland & Madhavan, 2021). When considered specifically in relation to CE, there have been corresponding proposals that alterations in the excitability of ipsilateral projections to homologous motor pools (i.e., that occur during (unilateral) training movements) may provide a basis for functional adaptations that increase the performance of the untrained limb (Hellebrandt, 1951; Hortobagyi, 2005).

The supposition that CE is mediated, at least in part, by alterations in the excitability of ipsilateral projections (or in the states of neurons which they innervate) invokes a number of considerations, including: i) the rostrocaudal trajectory of the ipsilateral projection, ii) the spinal laminae in which terminal arbours are formed, and iii) the spinal segments in which arborisation occurs. With these considerations in mind, we assess three pathways through which descending

corticofugal projections may synapse with spinal motor nuclei in the ipsilateral hemicord: i) non-decussated pyramidal tract projections, ii) redecussated ('recrossed') pyramidal tract projections, and iii) (cortico)-reticulospinal projections.

1.3.2 NON-DECUSSATED PYRAMIDAL TRACT PROJECTIONS

The fascicular arrangement of the corticospinal tract is such that most fibres decussate in the anterior median fissure of the medulla oblongata. Yet there exists a small proportion of corticofugal fibres that fail to cross at the pyramidal decussation (Glees & Cole, 1952; Nyberg-Hansen & Rinvik, 1963) (see Figure 1.1). In the Lewis rat, sagittal slices of the caudal medulla have revealed little evidence of axonal branching in pyramidal tract projections, suggesting that 'uncrossed' fibres do not simply collateralise from decussated projections (Alawieh et al., 2017; Brosamle & Schwab, 1997). Indeed, intralaminar injections of hydroxystilbamidine (a retrograde tracer) at the level of the thoracolumbar juncture have revealed that non-decussated fibres rather emanate from large-diameter corticospinal neurons situated near the hindlimb representation in layer V of rat sensory-motor cortex (Brosamle & Schwab, 1997). Notably, these cells are indistinguishable in terms of size and spatial distribution from corticospinal neurons whose axons fasciculate into crossed projections (Brosamle & Schwab, 1997). Similar findings have been reported in other mammalian species (Stanfield, 1992), and it has been suggested that a corresponding pattern of innervation (or remnants thereof) may also exist in humans (Alawieh et al., 2017). The notion

follows that during early development, the corticospinal tract (CST) consists of bilateral projections that become refined as limb dominance is established. In human neonates, ipsilateral responses to transcranial magnetic stimulation (TMS) have shorter onset latencies, and similar amplitudes and thresholds, as motor-evoked potentials (MEPs) elicited in the homologous muscle of the opposite limb (Eyre et al., 2001). By twelve months of age however, and indeed onwards into adulthood (Cincotta & Ziemann, 2008), the ipsilateral response to TMS is associated with a longer onset latency and higher threshold than its contralateral counterpart (Eyre et al., 2001).

In several species of non-human primate (e.g., macaque, marmoset), non-decussated corticospinal fibres, upon exiting the caudal medulla, descend in the dorsolateral and ventromedial funiculi of the ipsilateral hemicord. Altogether, they constitute less than 12% of the total pyramidal tract projection (Baker et al., 2015; Kondo et al., 2015; Rosenzweig et al., 2009). In the dorsolateral funiculus (DLF) of the rhesus macaque (*macaca mulatta*), the uncrossed projection may extend from the rostral cervical segments to the caudal lumbar cord (Lacroix et al., 2004; Rosenzweig et al., 2009; Yoshino-Saito et al., 2010). Remarkably, while these fibres appear to descend ipsilaterally, they do not terminate or collateralise on the same side from which they emanate. At least insofar as the cervical spine is concerned, non-decussated DLF fibres tend to project to the contralateral grey matter through lamina X – a region of grey matter that surrounds the central canal (Baker et al., 2015; Yoshino-Saito et al., 2010). The spinal laminae in which arborisation occurs (i.e., in the contralateral hemicord) appear to be the same as those in which the crossed (i.e., decussated) projection terminates. Consequently,

it has been suggested that uncrossed DLF fibres may reflect errors of axonal guidance that have been corrected at the segmental level, such that if the axon had crossed the medulla, the laminar target would be the same (Baker et al., 2015). To the extent that an ipsilateral projection is defined as any fibre that *terminates* ipsilateral to its origin, non-decussated DLF fibres may be better conceptualised as contralateral projections that undergo a segmental rather than medullary decussation.

This pattern of innervation is not however ubiquitous throughout the spinal cord. In macaque, serial reconstructions of DLF projections to lumbar segments have revealed bouton-like swellings in lamina IX, in close proximity to Nissl-counterstained motoneuronal somata in the lateral motor nuclei (Lacroix et al., 2004). It has been suggested that uncrossed fibres that terminate in these segments may synapse onto ipsilateral motoneurons that innervate the distal extremities of the lower limbs (Lacroix et al., 2004). Indeed, in several species of non-human primate, it has been demonstrated that following spinal hemisection and total callosotomy, ipsilateral responses to cortical stimulation are elicited preferentially in lower limb muscles (Bucy & Fulton, 1933). It is beyond the scope of the present analysis to consider the selection pressures that may have promoted an organisation whereby non-decussated DLF projections undergo segmental 'correction' in the cervical spine, and yet terminate upon ipsilateral motor pools in the lumbar cord. That which is clear however, is that based on evidence derived from studies in non-human primates, the DLF may constitute a potential path by which a corollary of a descending (unimanual) motor command may terminate

upon ipsilateral motor pools at the level of the lumbar (but not necessarily cervical) cord.

In macaque, the ventromedial funiculus (VMF) comprises a much smaller proportion of non-decussated fibres (~2 vs. ~10% of corticospinal projections) than its dorsolateral counterpart (Baker et al., 2015; Brinkman & Kuypers, 1973; Rosenzweig et al., 2009; Soteropoulos et al., 2011; Yoshino-Saito et al., 2010). These fibres are most pervasive in the rostral cervical cord (C2-C4) but may descend as far caudal as the upper thoracic (T1-T2) segments (Yoshino-Saito et al., 2010). While terminal arbours are typically elaborated in lamina VIII of the ventral grey matter, a small number of *en passant* and bouton-like swellings have also been observed in the intermediate zone (Dum & Strick, 1996; Lacroix et al., 2004; Morecraft et al., 2013; Rosenzweig et al., 2009; Satomi et al., 1988; Soteropoulos et al., 2013; Yoshino-Saito et al., 2010). In both cat and monkey, spinal interneurons in these regions are involved in the control of axial and proximal muscles (Dum & Strick, 2002; Harrison et al., 1986; Soteropoulos et al., 2013; Sterling & Kuypers, 1968). As the vast majority of cells in lamina VIII are commissural interneurons, it is however the *contra*- rather than *ipsi*-lateral musculature that is principally affected (Baker et al., 2015; Jankowska & Edgley, 2006; Jankowska & Stecina, 2007). Indeed, as with DLF projections that terminate in the cervical cord, non-decussated fibres in the VMF – whilst ipsilateral in their descent, appear to terminate upon spinal motor nuclei that exert effects contralateral to their origin.

In summary, most non-decussated corticospinal projections tend to terminate upon spinal motor nuclei that directly (i.e., by recrossing the midline

through lamina X, *viz*. DLF) or indirectly (i.e., through commissural interneurons in lamina VIII, *viz.* VMF) affect the contralateral hemicord. Non-decussated DLF projections that terminate ipsilaterally at the level of the lumbar spine appear to be one exception. In respect of the conjecture that CE is mediated (at least in part) by functional adaptations engendered by an ipsilateral corollary of the descending motor command, non-decussated projections in the DLF may constitute a candidate mechanism. This possibility applies only however to motor pools which innervate lower limb muscles. On solely anatomical grounds therefore, the supposition that CE is mediated by non-decussated ipsilateral projections may only be excluded for circumstances in which the upper (but not lower) limb is trained. This does not however constitute *prima facie* evidence that ipsilateral projections (i.e., fibres that *terminate* on the same side as which they emanate) are not instrumentally involved in CE – even in circumstances in which the upper limb is trained. Indeed, as we will see in the sections below, the vast majority of ipsilateral projections arise not from non-decussated fibres, but from axon collaterals of those that cross at the pyramidal decussation and later traverse the spinal commissure (Baker et al., 2015).

1.3.3 REDECUSSATED PYRAMIDAL TRACT PROJECTIONS

In the middle of the 19th Century, Charles-Édouard Brown-Séquard described in his seminal work, a rare neurological syndrome that arose following spinal hemisection (Brown-Séquard, 1868). This condition – for which the term "Brown-Séquard syndrome" was eponymously coined, is characterised (at all

levels at and caudal to the lesion) by an ipsilesional hemiparaplegia (unilateral weakness). Remarkably, the loss of motor function that occurs in the ipsilesional limb is rarely permanent. Indeed, within 1-6 of months of sustaining injury, many patients –particularly those with an upper limb paresis (e.g., following cervical hemisection), experience a marked recovery of gross motor function (Little & Halar, 1985; Roth et al., 1991). It has long been suspected that the recovery of ipsilesional motor function is mediated by corticospinal projections whose axons decussate in the caudal medulla only to 'recross' the neuraxis below the lesion site, thereby bypassing the lesion altogether. These projections have been described as "latent" as they are not believed to contribute to motor function in the presence of intact corticospinal projections, i.e., their functional contribution is manifest only following CNS injury (Alawieh et al., 2017; Gerloff et al., 2006). Often, such 'redecussation' is conceptualized as a functional adaptation that arises following spinal cord injury, e.g., collateral sprouting. It should however be noted that spinal redecussation is a ubiquitous characteristic of the intact primate nervous system (Lacroix et al., 2004; Rosenzweig et al., 2009; Yoshino-Saito et al., 2010).

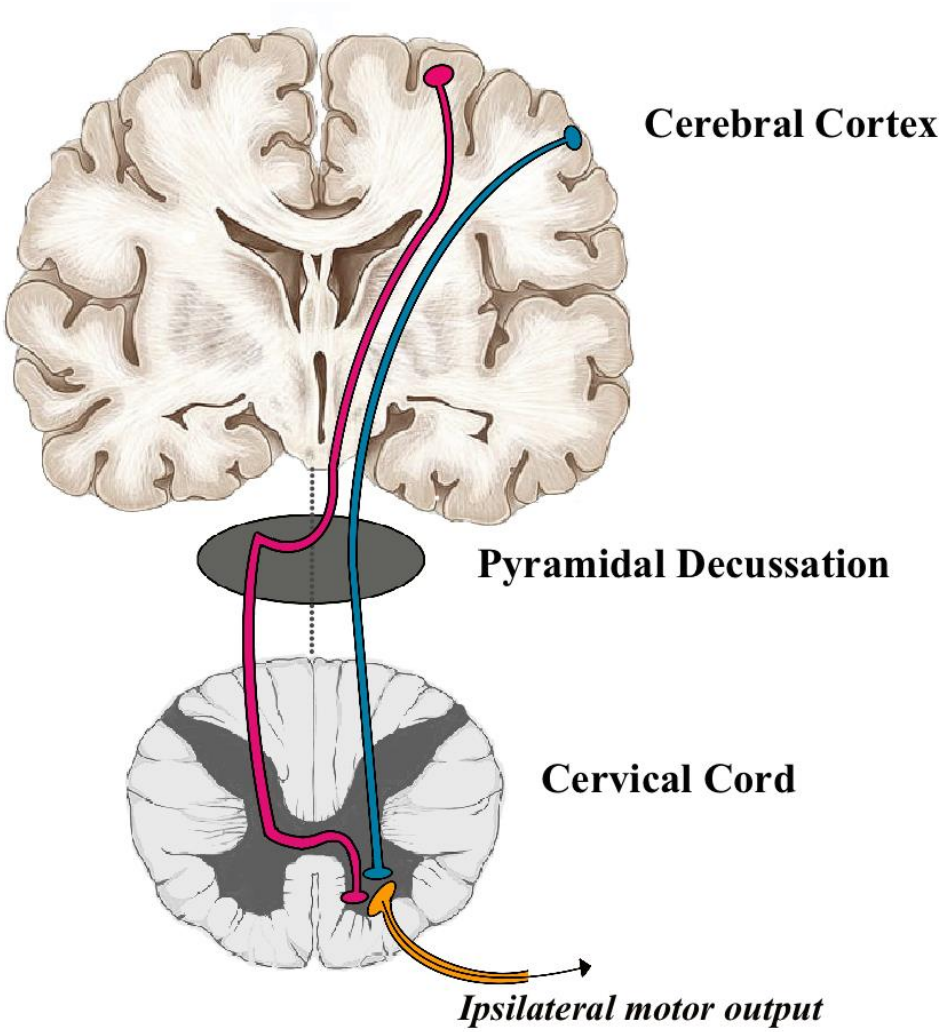


Figure 1.1: Non-decussated and uniformly redecussated ipsilateral pathways. The non-decussated projection (blue solid line) originates from cortex and terminates upon spinal motor nuclei (bottom image, shown in cross section) that project to ipsilateral muscle groups (orange solid line). By definition, the non-decussated projection fails to cross the midline (grey dashed line) via the pyramidal decussation (grey ellipse). The uniformly redecussated projection (red solid line) originates from cortex and crosses the midline (grey dashed line) twice: firstly, via the pyramidal decussation (grey ellipse), and secondly,

via the spinal commissure of the cervical cord (bottom image, shown in cross section). Thereafter, the redecussated projection terminates upon spinal motor nuclei that project to ipsilateral muscle groups (orange solid line).

On the basis of high-resolution anatomical tracer studies conducted in non-human primates, it has been established that there occurs extensive redecussation of pyramidal tract projections both within the cervical and lumbar cords (Lacroix et al., 2004; Rosenzweig et al., 2009; Yoshino-Saito et al., 2010). In the cervical enlargement alone, almost twice as many corticospinal projections cross the spinal commissure compared to those which descend in the DLF alone (Rosenzweig et al., 2009). These fibres tend to arborise in mid-cervical segments (C4-C7) and give rise to collaterals that branch orthogonally to their descent (Yoshino-Saito et al., 2010). In circumstances in which axonal arbours are formed prior to the midline traversal, axon collaterals that branch from a single fibre may uniformly decussate across the spinal commissure (i.e., to the side ipsilateral to their origin) or descend bilaterally to homo- or hetero-topic regions of spinal cord (Rosenzweig et al., 2009). Upon reaching their terminal destinations, terminal arbours are elaborated in lamina VIII, to a lesser extent in the intermediate zone, and sparsely so in the ventromedial nuclei of lamina IX (Rosenzweig et al., 2009; Yoshino-Saito et al., 2010). Consequently, it is conceivable that redecussated projections (and their collaterals) may act upon ipsilateral spinal motor nuclei through a multitude of pathways. In the sections below, we consider only three of several possible mechanisms by which 'redecussated fibres' may promote functional adaptations in the ipsilateral hemicord: i) redecussated fibres whose axons

terminate uniformly upon ipsilateral motor pools, i.e., by recrossing the neuraxis entirely (Figure 1.1); ii) redecussated fibres that descend bilaterally and engender 'common drive' to homologous motor pools (Figure 1.2); and iii) redecussated fibres that descend bilaterally and terminate upon heterologous motor pools, i.e., at different spinal segments (Figure 1.3).

In respect of the 'common drive' hypothesis (Figure 1.2), it has been established that in both axial and truncal muscles (e.g., rectus abdominis), the cross-correlograms of multi-unit electromyographic (EMG) recordings of homologous muscle pairs are characterised by the presence of short-duration central peaks that may be considered indicative of common drive to homologous motor pools (Carr et al., 1994; for methodological concerns related to this approach, see Kline & De Luca, 2015). In proximal (e.g., deltoid, biceps brachii) and distal muscles (e.g., first dorsal interosseous), i.e., those that serve as functional agonists in the majority of training tasks for which CE effects have been obtained, the expressions of such peaks are however rarely observed (Carr et al., 1994; Farmer et al., 1990; Marsden et al., 1999; Mayston et al., 1999). These findings are consistent with those derived from coherence analyses of motor unit spiking in homologues of paraspinal and intrinsic hand muscles, whereby inter-muscular coupling has been detected in the former but not latter muscle groups (Marsden et al., 1999). Studies of cortico-muscular coupling (e.g., in the rhesus macaque) have likewise demonstrated that during the hold phase of a precision grip task, local field potentials derived from intracranial recordings of M1 exhibit strong evidence of β-band synchronisation with EMG recordings of intrinsic hand muscles in the contralateral limb (Nishimura et al., 2009). In contrast, no such

coupling is evident in respect of EMG activity recorded from the ipsilateral homologue (Nishimura et al., 2009). These findings are consistent with those derived from earlier magnetoencephalographic studies (Conway et al., 1995; Kilner et al., 2003) and suggest that insofar as the electrophysiological literature is concerned, there is little evidence of common drive to homologous motor pools during unilateral contractions of upper limb muscles in the distal extremities.

It remains conceivable that a small proportion of redecussated fibres – which uniformly traverse the spinal commissure (Figure 1.1), or which collateralise bilaterally and arborise heterotopically (Figure 1.3), may terminate upon spinal motor nuclei within the ipsilateral hemicord. Indeed, while bilateral responses to TMS applied unilaterally to M1 are rarely observed (at least in 'healthy' human subjects), it is possible (though challenging in practice) to evoke ipsilateral responses to TMS in muscles as far distal as the first dorsal interosseus and thenar eminence group (Benecke et al., 1991; Netz et al., 1997). An obvious question thus arises. Through which pathway is the ipsilateral response to TMS produced? Is it equivalent to that which mediates the contralateral response? And how do the characteristics of the ipsilateral MEP differ from those of its contralateral counterpart? In the sections below, we provide a brief overview of TMS – the primary method by which ipsilateral motor responses are obtained, followed by a discussion of the characteristics and possible origins of the ipsilateral MEP.

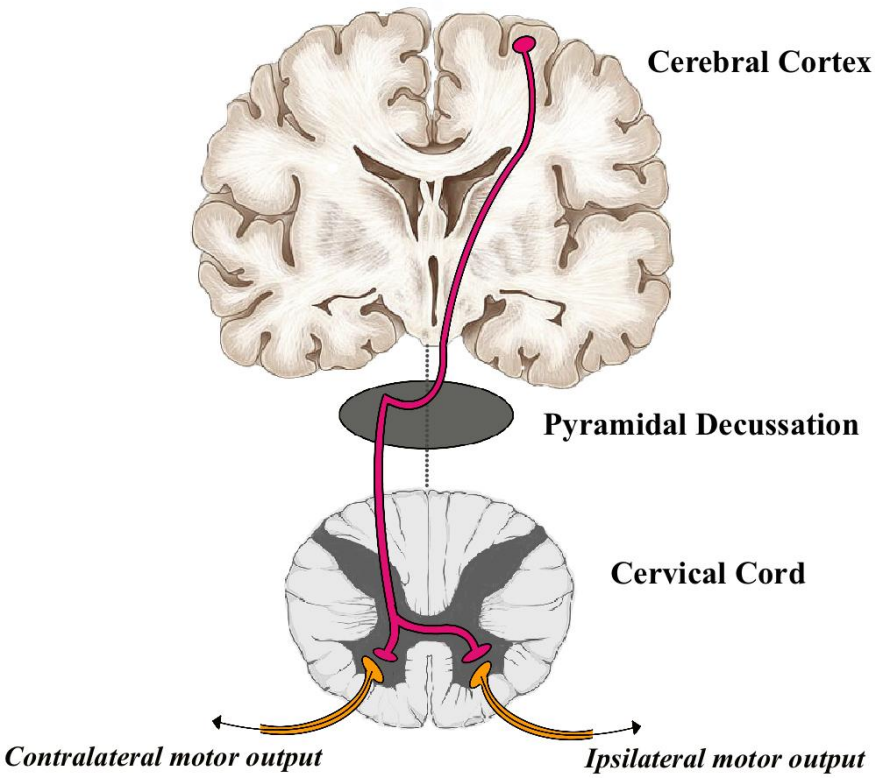


Figure 1.2: Redecussated projections that descend bilaterally and terminate homotopically. The descending decussated projection (red solid line) originates from cortex and crosses the midline (grey dashed line) via the pyramidal decussation (grey ellipse). Within the contralateral hemicord (left of image), the descending projection gives rise to two collaterals. One collateral remains within the contralateral hemicord (left of image). The other recrosses the midline via the spinal commissure of the cervical cord (right of image). Each collateral terminates upon homotopic spinal motor nuclei that project to homologous motor pools, i.e., at the same spinal segment (orange solid lines).

The essence of TMS is that a brief high-voltage current is passed through a conducting coil that is positioned tangential to the scalp. As the current passes through the coil, a transient magnetic field (~200 μs, ~1.5-3.0 T) is produced perpendicular to the plane of the coil that passes unimpeded through the periencephalic tissue (i.e., scalp, skull, meninges). As the magnetic field vector varies in magnitude, an eddy current is induced in the underlying tissue that flows parallel to the plane of the coil. Depending on the orientation of the coil with respect to the region of brain that encompasses M1, which determines the direction of the induced cortical eddy current, pyramidal tract neurons may be activated directly or indirectly (i.e., mono- or poly-synaptically). At sufficient intensities, a series of high-frequency (~670 Hz) descending volleys are characteristically evoked. The first volley, which constitutes the "D-wave", is held to arise from *direct* activation of corticospinal neurons at the level of the initial axon segment or proximal internodes (Terao & Ugawa, 2002). The train of volleys arising subsequently – for which the term "I-waves" is most commonly applied, is held to reflect *indirect* (presumably trans-synaptic) activation of corticospinal neurons (Terao & Ugawa, 2002). Each volley is transmitted to α-motoneurons (i.e., via the CST) in the ventral horn of the spinal cord, whereupon they summate to generate MEPs which may be registered by EMG recordings (Terao & Ugawa, 2002). In general, variations in MEP amplitude (i.e., in 'single-pulse' TMS paradigms) are held to reflect changes in the 'excitability' or 'states' of short- and long-range projections that synapse upon large-diameter corticospinal neurons with cell bodies in M1 and fast-conducting axons that innervate spinal motoneurons (Lemon et al., 2002). In contrast, variations in MEP latency are held to reflect the

synaptic characteristics of the interceding pathway, with longer latency responses considered characteristic of oligo-/poly-synaptic transmission.

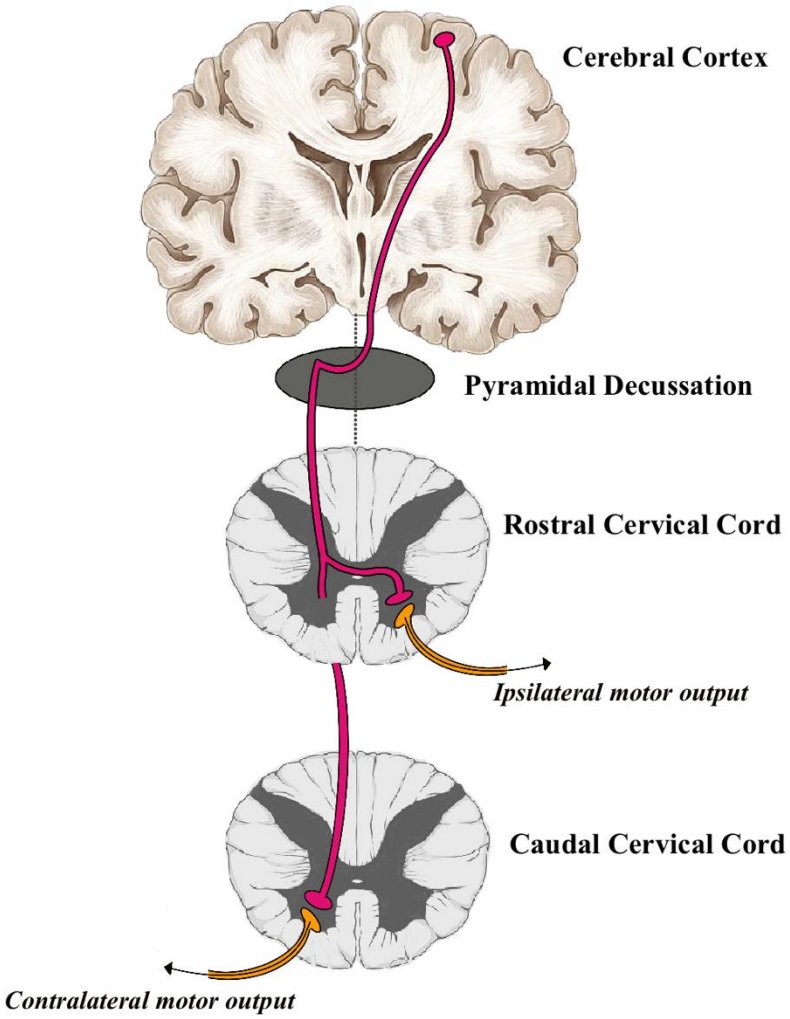


Figure 1.3: Redecussated projections that descend bilaterally and terminate heterotopically. The descending projection (red solid line) originates from cortex and crosses the midline (grey dashed line) via the pyramidal decussation (grey ellipse). Within the contralateral hemicord (left of image), the descending projection gives rise to two collaterals. One collateral recrosses the midline (grey dashed line) via the spinal commissure and

terminates upon spinal motor nuclei that project to ipsilateral muscle groups which receive their innervation from the rostral cervical cord (orange solid line, right). The second collateral passes through the rostral cervical cord and descends to, and terminates upon, spinal motor nuclei that project to contralateral muscle groups which receive their innervation from the caudal cervical cord (orange solid line, left). Note that each collateral terminates upon heterotopic motor pools (i.e., at different spinal segments) on opposite sides of cord.

In healthy human subjects, the characteristics of the ipsilateral MEP differ strikingly from those of its contralateral counterpart. In the first instance, it has been established that the ipsilateral MEP is elicited most readily via magnetic stimulation applied over the lateral third of M1 in a region that corticobulbar neurons most likely predominate (Caramia et al., 2000; Keizer & Kuypers, 1989; Wassermann et al., 1994; Ziemann et al., 1999). The latency to onset of the ipsilateral response is also approximately 3.5-13.0 ms longer than that elicited in the contralateral limb (Alagona et al., 2001; Kim et al., 2004; MacKinnon et al., 2004; Netz et al., 1997; Turton et al., 1996). Based on these findings, it has been suggested that the ipsilateral MEP may be mediated by a slow-conducting (presumably monosynaptic) corticospinal pathway (Netz et al., 1997). There is however another possibility. During lateral head rotation, it has been shown that the ipsilateral MEP elicited by TMS in a wrist extensor muscle is facilitated in a manner consistent with the asymmetric tonic neck reflex (Tazoe & Perez, 2014; Ziemann et al., 1999). As neck afferents project onto reticulospinal and

propriospinal neurons (Pompeiano et al., 1984; Srivastava et al., 1984; Wilson & Peterson, 1981), it has been suggested that the same pathway which mediates the ipsilateral response may receive convergent input from tonic neck afferents. Ziemann et al. (1999) postulated that such convergence must occur upstream of the spinal motoneuron pool because facilitation of the ipsilateral MEP was associated with a shortening (~2.1 ms) of its onset latency. On this basis, the supposition that the ipsilateral MEP is mediated by an oligosynaptic pathway, and in particular one that comprises a reticulospinal component, has gained increasing prominence (MacKinnon et al., 2004; Maitland & Baker, 2021; Netz et al., 1997; Staudt et al., 2002; Ziemann et al., 1999).

Although it is possible to elicit ipsilateral responses to TMS in the distal musculature, the interceding pathway – at least in healthy adults – does not appear to mirror that which mediates the contralateral MEP. Indeed, at least insofar as the upper limbs are concerned, there does not appear to exist any pathway – non-decussated or redecussated – through which a *direct* (i.e., monosynaptic) corollary of the efferent motor command may descend to the ipsilateral hemicord. Consequently, the supposition that CE is mediated by adaptations subserved by ipsilateral (monosynaptic) corticospinal pathways – at least in circumstances in which the upper limb is trained, cannot be sustained. This does not however preclude the possibility that oligosynaptic pathways may provide a potential means by which the ipsilateral corollary may descend. Among the most prominent candidates in this regard are corticoreticulospinal projections, which originate in cortex and project bilaterally to spinal cord from a triad of nuclei in the reticular formation (Sakai et al., 2009). Notwithstanding its role in mediating such facets

of ‘gross’ motor function as locomotor control (Mori et al., 2001) and postural adjustment (Deliagina et al., 2008), which often require bilateral engagement of axial and proximal muscles, there exists an emerging recognition that the (cortico-) reticulospinal tract may possess the capacity to exert (at least partial) control over upper limb muscles in the distal extremities.

1.3.4 CORTICORETICULOSPINAL PROJECTIONS

The reticulospinal tract (RST) emanates from a group of three structures within the pontomedullary reticular formation (PMRF), namely the caudal pontine, gigantocellular, and oral pontine reticular nuclei (Sakai et al., 2009). Cells within these regions are characterised by an extensive network of arbours that function as the main targets for descending corticofugal fibres (Rossi & Brodal, 1956; Scheibel et al., 1973). In several species of non-human primate (e.g., *macaca fascicularis, macaca mulatta*), the descending projection is ostensibly bilateral with a moderate predominance of ipsilateral fibres (Kneisley et al., 1978; Sakai et al., 2009). This ‘ipsilateral bias’ appears to be conserved across several mammalian species, including cat (Matsuyama et al., 1993), monkey (Kneisley et al., 1978), opossum (Beran & Martin, 1971), and rat (Newman, 1985).

In both cat and monkey, reticulospinal fibres project to all segments of spinal cord and tend to terminate in the internuncial layer of the ventral horn (i.e., laminae VII and VIII), and to a lesser extent, upon spinal motoneurons in lamina IX (Kuypers et al., 1962; Matsuyama et al., 1999; Peterson et al., 1975; Riddle et al., 2009). While the distributions of contra- and ipsi-lateral reticulospinal

projections are somewhat uneven, it has been demonstrated in the crab-eating macaque (*macaca fascicularis*) that microstimulation of the PMRF engenders a relatively 'balanced' degree of bilateral activation in upper limb muscles (Davidson & Buford, 2006). It has been suggested that the contralateral activation (i.e., arising from PMRF stimulation) may be mediated by commissural interneurons in the spinal cord (e.g., in lamina VIII) – upon which a significant proportion of reticulospinal fibres are known to terminate (Jankowska et al., 2003), or interneuronal relays within the PMRF itself (Figure 1.4).

Although spinal motoneurons are perhaps the most well-known targets of corticofugal fibres, the vast majority of these fibres actually terminate at the level of the brainstem (Scheibel et al., 1973). It has been established that the application of TMS over the region of brain that encompasses M1 engenders short-latency bilateral responses in antidromically-identified reticulospinal neurons in the primate PMRF (Fisher et al., 2012). The consensus view is that these (mesencephalic) terminations arise from axon collaterals of corticospinal projections to the spinal cord, as well as corticofugal fibres that project directly to the PMRF (Keizer & Kuypers, 1989; Newman et al., 1989; Rho et al., 1997). In both cat and monkey, the bulk of corticoreticular projections arise not from M1, but from non-primary motor regions including dorsal premotor cortex (PMd) and supplementary motor area (SMA) (Keizer & Kuypers, 1984, 1989). This is consistent with evidence derived from diffusion tensor modelling studies conducted in humans (for a brief review, see Jang & Lee, 2019). While most M1-PMRF projections are believed to collateralise from the CST, those that arise from PMd and SMA tend to emanate directly from the cortex itself (Kably & Drew,

1998; Keizer & Kuypers, 1984, 1989). It is thus conceivable that corticoreticular projections from M1 – which collateralise from the CST, may enact efferent drive to the ipsilateral hemicord via interneuronal relays within the PMRF. This possibility likewise applies to corticoreticular fibres that arise from frontal motor areas (i.e., PMd, SMA), which are more numerous than those which arise from M1.

While the CST is known to mediate the control of fractionated movements of the upper and lower limbs (Buys et al., 1986), the phylogenetically older RST is generally considered to play a specific role in the coordination of whole body and orienting movements (for a review, see Lemon, 2008). This differentiation has often been inferred on the basis of the respective laminar targets upon which cortico- and reticulo-spinal fibres terminate, as well as the numbers and distribution of motor units innervated by the fibre. For example, it is well established that corticospinal projections tend to terminate in the lateral motor nuclei of lamina IX upon a small number of (local) motor units that innervate the distal extremities (Buys et al., 1986) – a pattern of innervation that is held to facilitate fine fractionated control of the digits (Schieber, 2001; van Duinen & Gandevia, 2011). In contrast, reticulospinal fibres project to a large number of motor pools – sometimes spanning the entire length of cord (e.g., in cat, Matsuyama et al., 1999), and were once believed to terminate almost exclusively upon 'medial' motoneurons in lamina VII that innervate axial and proximal muscles (Holstege & Kuypers, 1987; Jones & Yang, 1985). In recent years, it has however been demonstrated that motoneurons which innervate wrist and digit muscles receive both mono- and di-synaptic reticulospinal inputs, including

monosynaptic excitatory projections to motoneurons which innervate the muscles of the hand (Riddle et al., 2009). It is also known that microstimulation of the PMRF engenders bilateral activation of upper limb muscles as far distal as the wrist (Davidson & Buford, 2004; Davidson & Buford, 2006; Davidson et al., 2007).

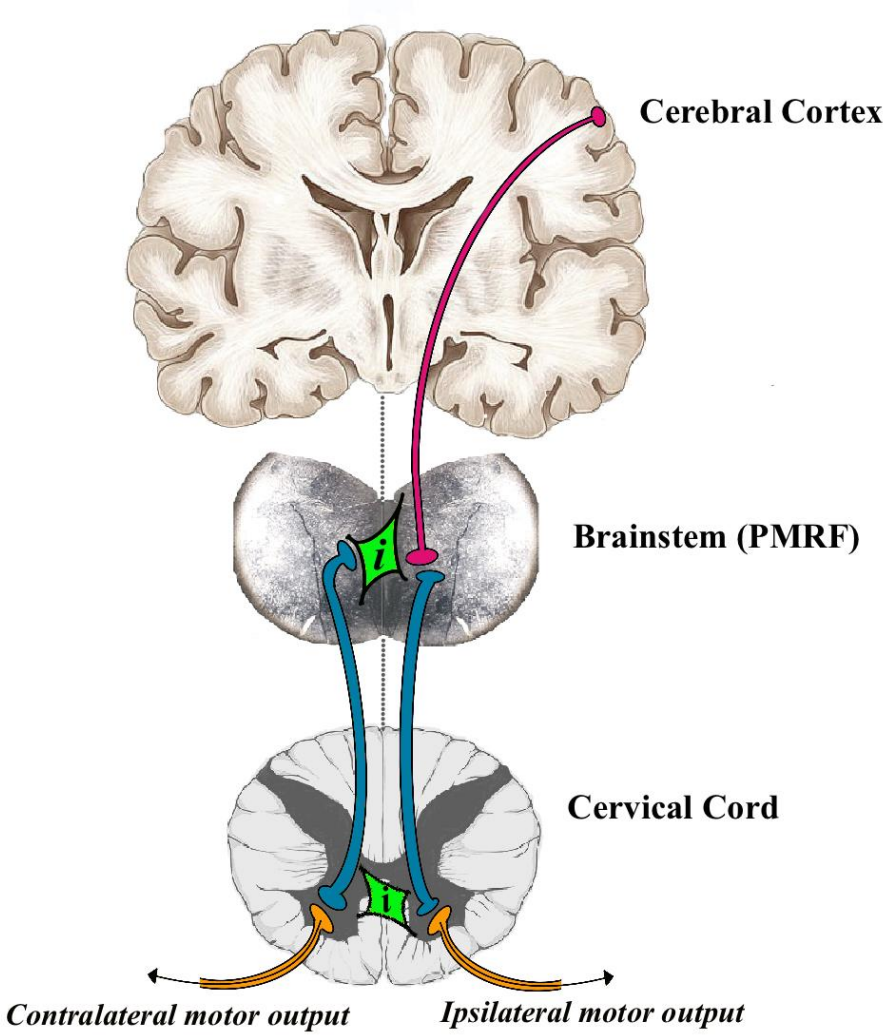


Figure 1.4: Corticoreticulospinal projections. The descending projection (red solid line) originates from cortex and terminates upon the pontomedullary reticular formation (PMRF) of the brainstem. The PMRF projects bilaterally

to the cervical cord via reticulospinal projections (blue solid lines) which terminate upon spinal motor nuclei that innervate contra- and ipsi-lateral muscle groups (orange solid lines). Interneuronal interactions (green quadrilaterals, denoted '*i*') may occur within the PMRF and/or cervical cord. These interactions serve ultimately to augment reticulospinal drive to the spinal cord.

The role of extrapyramidal pathways in the recovery of strength following CNS injury has been recognised for some time. It was more than fifty years ago that Lawrence and Kuypers (1968) demonstrated that, following the induction of pyramidal tract lesions in the rhesus macaque, there occurs a striking increase in strength (or more accurately, a recovery thereof) within four to six weeks of the initial operation (Lawrence & Kuypers, 1968). Since this time, it has been established that following lesions of the CST, the amplitudes of mono- and di-synaptic excitatory postsynaptic potentials elicited by stimulation of the medial longitudinal fasciculus are enhanced significantly, consistent with a strengthening of reticulospinal output (Zaaimi et al., 2012). These changes are accompanied by increases in the firing rates of neurons in the PMRF (Zaaimi et al., 2018). In humans, it has been proposed that the RST may constitute one of two independent systems (the other being the CST) that mediates motor recovery (namely of strength) in stroke survivors (Xu et al., 2017). To what extent therefore might the (cortico-) RST be implicated in the processes which mediate CE? In macaque, it has been demonstrated that during the course of a nine-week unimanual strength training intervention, the amplitudes of MEPs elicited by stimulation of M1 and

the RST are increased significantly (Glover & Baker, 2020). These changes are not however accompanied by alterations in the amplitudes of MEPs elicited by stimulation of the CST at the level of the cervico-medullary junction. Following a wash-out period of two weeks and a further three months of training, the level of spinal gain registered within the intermediate zone and motor nuclei of the 'trained' hemicord was elevated markedly and exceeded that registered by intraspinal recordings of the 'untrained' side (Glover & Baker, 2020). Notably, these effects were obtained by stimulation of the RST only (and notably not by stimulation of the CST) and arose irrespective of whether stimuli were applied contra- or ipsi-laterally (i.e., to the PMRF). Taken together, these findings are consistent with the view that following unimanual training, there occurs a bilateral increase in reticulospinal output that is manifest most prominently in spinal circuits of the 'trained' hemicord.

In considering the supposition that CE is mediated, at least in part, by an ipsilateral corollary of a descending set of 'unimanual' motor commands, the corticoreticulospinal tract (CRST) appears to represent a candidate mechanism. There are however caveats. In the first instance, while the CRST may afford the coverage that ipsilateral CST projections do not – insofar that its constituent fibres terminate (i.e., ipsilaterally) over a broader range of segments, the degree of innervation elaborated at each segment is relatively sparse. A further issue pertains to a lack of focality. It has been demonstrated previously that a single RST fibre may act upon nuclei located within both the cervical and lumbar spine (Matsuyama et al., 1999; Matsuyama et al., 1997; Peterson et al., 1975). While this pattern of innervation may give rise to sets of functionally meaningful

synergists, the point has been raised previously (e.g., Baker, 2011) that the extent of divergence may come at the expense of fine fractionated control. This is notable for several reasons. In the first instance, fractionated movement is an essential feature of many training tasks in which CE effects have been obtained. Secondly, it is unclear how the lack of focality afforded by CRST projections can be reconciled with the observation that the gains in performance realised by the untrained limb (i.e., following unimanual training) tend to be homologue specific. It is therefore difficult to ascribe any more than a partial role to CRST projections in the expression of CE.

1.3.5 AGE-RELATED VARIATIONS IN CORTICOSPINAL STRUCTURE

We are not aware of any research concerned specifically with age-related variations in the microstructure of the ipsilateral cortico- and/or reticulo-spinal tracts. Indeed, since there has been little work examining microstructural integrity with a view to assessing potential variations across the hemicords, laminae, or spinal segments within or upon which descending projections terminate, it is possible only to provide an overview of age-related changes in the microstructural integrity of the entire CST.

In humans, the most common method of examining white matter tracts *in vivo* is that of diffusion weighted imaging (DWI). The essence of the technique is that based upon differences in the Brownian motion of specific moieties along an axon's length (e.g., water) – whose diffusion is constrained by such factors as lipidic cover and interstitial volume, it is possible to derive quantitative estimates

of several microstructural properties (for a primer, see Le Bihan, 2014). Although the streamlines defined via DWI tractography do not equate to anatomical fibres per se, they are frequently used as a basis upon which to define white matter tracts, with respect to which the quantitative estimates are referred. Among these estimates, fractional anisotropy (FA) – a measure that encapsulates the directionally-dependent diffusion of water molecules along a fibre bundle, is regarded as a general index of microstructural status (Billiet et al., 2015) due to its sensitivity to alterations in axonal density (Friedrich et al., 2020), integrity (Basser & Pierpaoli, 1996), and myelination (Beaulieu, 2002). A related measure is that of mean diffusivity (MD) – a composite measure of axial and radial diffusion (which may be considered indices of axonal degeneration (Sun et al., 2006) and demyelination (Song et al., 2005) respectively), which is held to reflect white matter tract integrity (Power et al., 2019).

The CST originates from a swathe of cortical divisions including cingulate motor area, M1, premotor cortex, and SMA (for a review, see Lemon, 2008). In spite of the wide-ranging and seemingly disparate functions subserved by each of these regions, age-related changes in the microstructural characteristics of the CST are frequently examined at the whole-tract level. In this regard, it has been reported widely that measures of FA derived for the CST as a whole are typically much lower in older adults compared to younger subjects (Jang et al., 2011; Lebel et al., 2012; Sala et al., 2012). This is consistent with the supposition that the microstructural integrity of the CST diminishes with age. Converging evidence is provided by the observation that MD – a measure for which larger values are indicative of diminishing microstructure, is elevated to a greater degree in older

subjects (Molloy et al., 2021; Sala et al., 2012). If, however, the CST is reconstructed on the basis of streamlines that arise from specific regions of cortex, a different pattern of outcomes emerges altogether.

In circumstances in which the CST is reconstructed from Brodmann area 6 (BA6) – a region which lies just rostral of M1 that encompasses premotor cortex laterally and SMA medially, it has been noted that the volume of the CST is lower in older subjects (mean age = 73.6 years) compared to healthy adults aged ≤ 50 years (Jang & Seo, 2015). Unlike whole-tract measures, however, there is no accompanying evidence of age-related differences in measures of FA or MD. If instead the CST is reconstructed from BA4 (i.e., the region encompassing M1), age-related differences in CST volume, FA, and MD are not obtained (Jang & Seo, 2015). Overall, these findings are consistent with the supposition that projection fibres in general (Cox et al., 2016), and the CST in particular (Chad et al., 2018; Jang & Seo, 2015), are relatively resistant to age-related decline.

1.3.6 Summary: Ipsilateral descending projections

In recognition of the sparse nature of the ipsilateral projections that arise from corticofugal neurons, there appears to be limited scope for these projections to act upon spinal motoneurons that innervate the muscles of the upper and lower limbs. Indeed, with the exception of non-decussated DLF projections to lumbar cord, there is no evidence that there exists a direct pathway between corticofugal neurons and ipsilateral spinal motoneurons. Although it is not possible to dismiss the role of indirect (polysynaptic) ipsilateral projections in mediating CE, the

extant evidence is consistent with the view that ipsilateral (monosynaptic) corticospinal pathways are unlikely to constitute a basis for the relevant adaptations to occur, at least in circumstances in which the upper limb is trained. The (C)RST represents a viable (albeit oligosynaptic) alternative; however, the similarly sparse, afocal innervation it affords is likely to restrict the extent of its functional contribution.

As the structure of the CST appears relatively robust to the neurodegenerative processes that are a feature of ageing, a causal role in mediating age-related variations in the mechanisms which mediate CE – at least on the basis of the existing neuroimaging evidence, cannot be sustained. Considerable circumspection is however required. The current conclusions are based on studies in which the CST was examined as a whole or delineated by cortical origin. In no instance of which we are aware has the CST been partitioned on the basis of whether its constituent fibres terminate in the contra- or ipsi-lateral hemicord. As ipsilateral fibres account for only a small proportion of descending projections, it is conceivable that any age-related microstructural and/or volumetric changes that affect those fibres specifically may have been masked by the relative preservation of other projections. Nevertheless, based on the anatomical considerations discussed previously, our analyses indicate that there is little evidence – beyond a (potential) partial role for (cortico-) reticulospinal fibres – to support the view that CE, in either young or older adults, is mediated by ipsilateral projections.

1.4 ON THE ROLE OF PRIMARY MOTOR CORTEX

1.4.1 THEORETICAL CONTEXT

In seeking to elucidate the neural mechanisms which mediate CE, a major focus has hitherto been placed upon those brain regions most prominently engaged in generating motor output. In particular, many investigations appear predicated on the assumption that CE is mediated by changes in the states of circuits within the M1 ipsilateral to the training limb. At first glance, an emphasis upon the role of M1 appears to be sufficiently motivated. Perhaps most obviously, the expression of the interlimb effect would not be possible without corticospinal output, which arises predominately from the activation of corticofugal neurons with cell bodies in the caudal sector of M1 (Lemon et al., 2002). It is necessary therefore to consider the potential mediating role of adaptations that modulate the states of circuits within M1, or which influence the excitability of corticospinal projections descending from it. In this regard, it is relevant to first consider the material substrate through which such changes might arise, i.e., during or following the repeated execution of training movements by the ipsilateral limb. The most obvious candidate anatomical structure is that of the corpus callosum (CC) – the largest white matter bundle in the human brain.

A case has been made that the CC should be considered a key element in the early phases of neurodegenerative disease and in the preservation of functional capacity in the course of healthy aging (Di Paola et al., 2011). The DWI variant of magnetic resonance imaging (MRI) yields measures that have the potential to characterize age-related changes in the microstructural organisation of the CC.

The diffusion tensor model (Basser et al., 1994) is the mathematical framework that has been used most frequently to make inferences that relate diffusion-weighted images to local white matter tissue microstructure. It has however been shown that this model is inadequate when applied to regions such as the lateral cortical projections of the CC (Jeurissen et al., 2011) that contain complex architectures such as crossing fibres (Alexander et al., 2002; Jeurissen et al., 2013; Tuch et al., 2002). In the summary of age-related changes in the structural integrity of the CC that follows therefore, we largely restrict our coverage to investigations in which more sophisticated biophysical modelling of CC microstructure has been undertaken (e.g., based on high angular resolution DWI sequences).

Estimates have been obtained for sub-divisions of the CC defined by interrogating the functional connectivity of white matter networks (e.g., Wang et al., 2020), as well as via traditional histological methods (e.g., de Lacoste et al., 1985). In such schemes, (sensori-) motor functions are typically ascribed to the body and isthmus subdivisions of the CC. A negative association between age and estimates of white matter structural integrity has been reported for the body of the CC (Liu et al., 2018b; Vien et al., 2016). This is held to manifest most prominently after forty years of age (Wang et al., 2019a). It is also possible to delineate specific interhemispheric tracts of interest following whole brain tractography (e.g., Ruddy et al., 2017a). On this basis, age-related variations in estimates of structural integrity have been observed for CC fibres projecting to M1 (Kuhn et al., 2019). To date, longitudinal assessments have been conducted primarily using low angular resolution DWI sequences. In one such example, Sexton et al. (2014) reported that, in a cohort of 215 individuals assessed twice over a period ranging

between 2.7 and 4.7 years, annual decreases in FA, as well as increases in axial diffusivity, radial diffusivity, and MD – perhaps representing myelin disruption or degeneration, were detected for the body of the CC. The start of this decline was estimated to occur in the fifth decade (see also Bender et al., 2016). Important caveats (e.g., Jones et al., 2013) relating to the interpretation of DWI-based modelling notwithstanding, it appears reasonable to suppose that there occur age-related decreases in the structural integrity of callosal fibres that connect various nodes of the cortical motor network, including M1. By extension, such changes may underpin lifespan variations in the means through which gains in performance are derived through training of the opposite limb.

In contemporary mechanistic accounts of the CE phenomenon, the emphasis upon brain regions – especially M1, which play a fundamental role in generating motor output, and their interhemispheric (i.e., callosal) projections, can be traced to the influence of the "cross activation" hypothesis (Parlow & Kinsbourne, 1989) (Figure 1.5). This model encapsulates the notion that bilateral motor activity which occurs during unimanual actions induces "parallel" adaptations in motor circuits on both sides of the neuraxis, and that such adaptations serve to augment the functional capacity of the trained limb, and also the untrained limb. Although not necessarily implied in the original formulations (e.g., Hellebrandt, 1951), the "cross activation" hypothesis has frequently come to be interpreted in terms of direct (inter-hemispheric) interactions between the primary motor cortices (e.g., Dickins et al., 2015a; Hinder et al., 2011; Reissig et al., 2015). In order to appreciate the pervasive influence of this hypothesis, it is

first necessary to describe the nature of the experimental phenomena from which it was first derived.

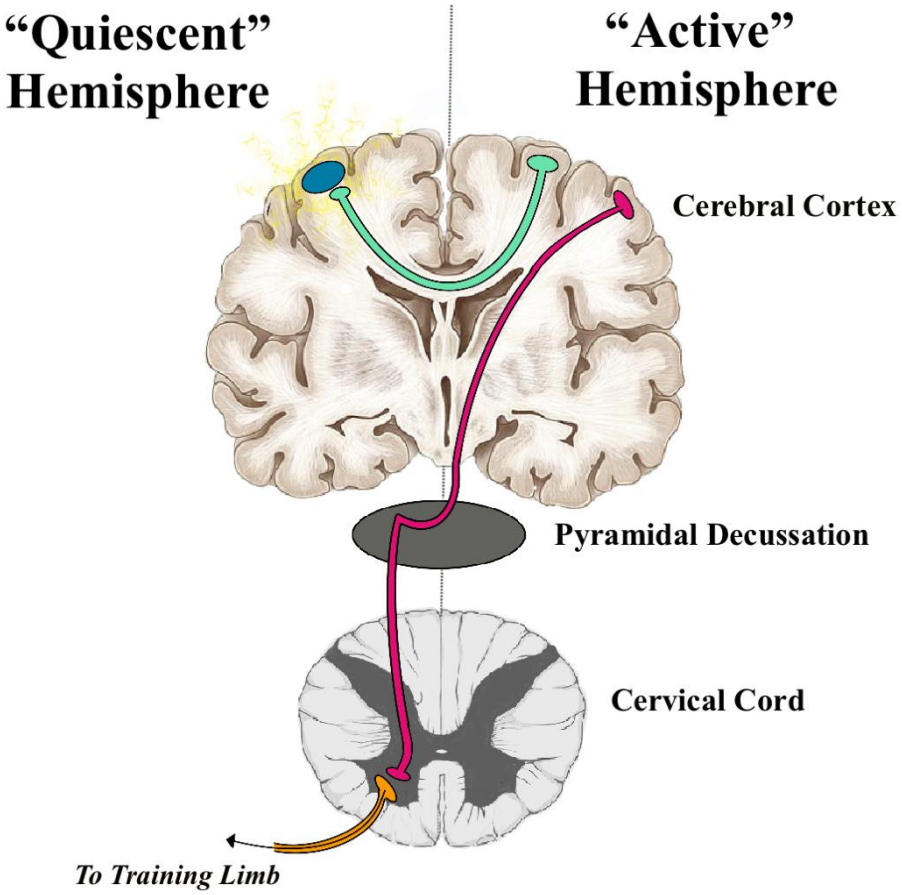


Figure 1.5: Cross activation model of cross education. The unimanual motor command, which arises from the 'active' hemisphere (right of image), is transmitted to the contralateral hemicord (left of image) via corticofugal projections (red solid line). These projections terminate upon spinal motor nuclei which innervate task-agonist muscles in the training limb (orange solid line). Concurrent functional adaptations are expressed in the motor circuits of the 'quiescent' hemisphere (left of image) that augment the functional capacity of the untrained limb (blue ellipse with yellow highlight). These adaptations are mediated via transcallosal projections that arise from the

'active' hemisphere (green solid line). In other words, the repeated execution of unimanual movements induces parallel adaptations in motor circuits that control effectors on both sides of the body, which serve ultimately to enhance the functional capacity of the trained and untrained effectors.

1.4.2 CROSSED FACILITATION AND MOTOR IRRADIATION

In 1898, Welch was among the first to observe that rhythmic contractions undertaken in squeezing a rubber bulb held in one hand, give rise to corresponding fluctuations in the isometric force generated by the other hand (Welch, 1898). It was more than fifty years later that Hellebrandt (1951) proposed that that this phenomenon of 'motor irradiation' may be instrumentally related to CE. Since the advent of TMS in the 1980s, and following the widespread adoption of the motor-evoked potential (MEP) as an assay, it has been demonstrated consistently that focal contractions that are unilateral by intention engender bilateral elevations in corticospinal excitability (CSE) (Hess et al., 1986; Muellbacher et al., 2000; Stedman et al., 1998). This has been termed "crossed facilitation". As this effect is generally obtained by stimulation over the region of brain that encompasses M1, but not when stimulation is applied at the level of the cervico-medullary junction (Carson et al., 2004; Hortobagyi et al., 2003; *cf.* Carson et al., 2007), it has been surmised that the bilateral changes in CSE that are evident during unimanual actions are mediated primarily by supraspinal (and it has been presumed transcallosal) mechanisms. It should however be noted that potentiation of the cortically elicited EMG response (and a decrease in MEP onset latency) during forceful contractions of the opposite limb is also obtained in patients with agenesis

of the anterior trunk of the CC (Meyer et al., 1995). Although the impact of atypical development in such cases is difficult to gauge, it is nonetheless important to recognise that the CC is not the only pathway exhibiting the potential to mediate crossed facilitation (or indeed CE, Tilsley et al., 2021).

It is well established that, as with motor irradiation (Cernacek, 1961; Hopf et al., 1974), the magnitude of crossed facilitation increases with the level of neural drive that is directed to the muscles of the 'active' limb. During isometric contractions, the amplitudes of MEPs elicited by TMS in otherwise quiescent muscles of a static limb increase with the level of tension generated by the contralateral homologue (Bunday & Perez, 2012; Hortobagyi et al., 2003; Perez & Cohen, 2008). In the case of rhythmic contractions, the MEP is maximally potentiated during the phase of motion in which the contralateral homologue is maximally engaged (Carson et al., 1999; Carson et al., 2004; Stinear & Byblow, 2002). It should however be emphasised that, in a CE context, the magnitude of gain realised by the non-training limb is not dependent on the intensity of contraction generated by its homologue (for a review, see Cirer-Sastre et al., 2017). This finding alone should be sufficient to prompt caution in seeking to relate the processes that mediate the expression of crossed facilitation to CE.

The interhemispheric transcallosal fibres that course between the left and right cerebral hemispheres provide an obvious anatomical substrate for interactions between left and right cortical motor networks. Nonetheless, the mere presence of fibre pathways linking specific regions in the two hemispheres does not itself indicate that they play a functional role in mediating the expression of such phenomena as crossed facilitation or indeed CE. Although its existence is

frequently inferred on the basis of changes in the states of corticospinal projections from the 'quiescent' M1, i.e., based on increases in MEP amplitude, it cannot on this basis alone be concluded that crossed facilitation arises from direct interactions between the primary motor cortices (Ruddy & Carson, 2013). Changes in the excitability of corticospinal projections from M1 may simply represent the 'downstream' effects of interhemispheric interactions occurring elsewhere within the cortical motor network.

Mirror movements – involuntary contractions that arise during intended unilateral activation of the homologous muscles of the opposite limb, are an overt manifestation of motor irradiation. They are observed in a number of neurological conditions and are often present in normally developing children below 8 or 9 years of age (Mayston et al., 1999). Following intracortical injection of muscimol (a $GABA_A$ agonist) to ipsilateral M1, monkeys exhibit mirror movements during the generation of grasping movements (i.e., the focal movements being made by the limb contralateral to the site of injection). These mirror movements are abolished by the subsequent injection of muscimol to the M1 contralateral to the limb in which they were originally expressed (Tsuboi et al., 2010). This pattern of outcomes suggests that cross activation giving rise to the expression of mirror movements arises from common drive to both primary motor cortices from other brain centres. Converging evidence is provided by the observation that in non-human primates, there is a strong correlation between the directional tuning of cells in PMd during reaching movements made by the ipsilateral and contralateral limb, while for cells in M1 the degree of association is markedly lower (Cisek et al., 2003).

It is also possible to make the inference that interactions between at least some subdivisions of M1 are unlikely to constitute the origin of interactions between left and right cortical motor networks, by considering their interhemispheric structural connectivity. The current view is that in some higher primates including humans, the caudal sector of M1 encompassing the bank of the central sulcus (the so-called "new-M1"), is the origin of fast-conducting corticospinal axons that project monosynaptically onto spinal motoneurons (Rathelot & Strick, 2009; Witham et al., 2016). It has been surmised that in comparison to the rostral sector of M1 (the so-called "old-M1") – located on the convexity of the precentral gyrus, the caudal sector exerts direct control over motor output (Rathelot & Strick, 2009). The firing patterns of cells in this region (i.e., the caudal sector) are correlated with the temporal pattern of force production and the dynamics of motor output (Sergio et al., 2005), whereas a role in the selection or "shaping" of movements has been ascribed to the rostral sector (Vigano et al., 2019).

In the Juelich histological atlas of the human brain (Eickhoff et al., 2006; Eickhoff et al., 2007; Eickhoff et al., 2005), the area labeled posterior M1 (M1p) aligns most closely with the location of the caudal sector, while the area labelled anterior M1 (M1a) approximates the location of the rostral sector (Geyer et al., 1996). It is notable therefore that the number of transcallosal streamlines that pass through M1p is smaller than for all other regions of the cortical motor network (Ruddy et al., 2017a). This corresponds to data obtained using intracortical microstimulation mapping and neuronal tracing techniques in non-human primates (Dancause et al., 2015). Furthermore, the apparent fibre density (a

measure of microstructural organisation) of the streamlines passing through both left M1p and right M1p is lower than that which characterizes all other projections between homologous regions in the cortical motor network (Ruddy et al., 2017a). This set of structural constraints is consistent with the conjecture that the scope for direct interhemispheric interactions via transcallosal projections decreases along a functional gradient that reaches a nadir in those regions most prominently engaged in generating motor output (Carson, 2005). It was proposed previously that this pattern of organisation serves to minimise intermanual interference at the level of motor execution, while facilitating the interhemispheric communication that is likely to be an essential aspect of movement planning (Liu et al., 2002). Thus, while it remains likely that interhemispheric transcallosal fibres provide an anatomical substrate for interactions between left and right cortical motor networks, the balance of evidence suggests that the scope for such is lowest for those regions of the cortical motor network (i.e., M1p) that contribute the bulk of direct monosynaptic projections to the spinal cord.

While crossed facilitation has on occasion been operationalised as an 'index' of cross activation (e.g., Cabibel et al., 2020; Lee et al., 2010), it is unsafe to assume that the MEP – the principal means by which crossed facilitation is inferred, provides a faithful representation (e.g., Bestmann & Krakauer, 2015) of the broadly distributed bilateral changes in brain activity that occur during the generation of unilateral movements. These limitations apply also to measures of motor irradiation (e.g., EMG and kinetic recordings of the untrained limb), as well as to blood-oxygen-level-dependent (BOLD) estimates of cerebral activity obtained with functional MRI (fMRI). It should be noted therefore, that since these

measures can each provide only a narrow index of cross activation, the absence of statistical associations between variations in their magnitude and levels of CE is not in itself a sufficient basis upon which to reject the cross activation hypothesis.

Notwithstanding the fact that the modulation of CSE can provide only a restricted and highly partial representation of changes in brain state, it remains possible to examine empirically whether it is related to expressions of CE. There are however caveats. As training-related alterations in CSE are bound intimately to the dimensions of motor training (Berghuis et al., 2017; Colomer-Poveda et al., 2019b; Leung et al., 2018), the extent to which CE is related to variations in CSE is likely to be both task- and protocol-dependent. In seeking to examine whether such relationships exist therefore, we adopt an "intervention themed" approach. A second issue concerns a subtle yet important shift in focus: from changes in brain state that arise *during* unimanual movements to changes in state that *follow* consequently. It is worth emphasising that it is the latter approach (i.e., whereby measures are obtained pre- and post-intervention) that is almost universally assessed in studies of CE. There exists also a tendency to examine CSE in the untrained limb with participants at rest rather than during performance of the training or transfer task. It remains to be established whether the subsets of circuits sampled by TMS at rest following an intervention should be considered representative of those in which the relevant training-related adaptations are instantiated during the course of training.

In considering unilateral resistance training regimens, it is convenient to distinguish 'acute' from 'chronic' training protocols on the basis of their duration, with the latter defined as a minimum of two training sessions per week for two

weeks or more (Colomer-Poveda et al., 2019b). In a recent systematic review, it was established that net elevations in the excitability of corticospinal projections to the agonist muscles of the untrained limb ($CSE_{untrained}$) are observed mainly in the context of chronic resistance training protocols (8/12 studies) and far less reliably in acute training regimens (2/11 studies) (Colomer-Poveda et al., 2019b). If, however, the minimum training duration (i.e., for 'chronic' training protocols) is extended to three weeks, only a non-significant increase in $CSE_{untrained}$ is observed (for a meta-analysis, see Manca et al., 2018). In circumstances in which the degree of change in $CSE_{untrained}$ registered in chronic training protocols (i.e., ≥ 2 wks) has been correlated with the percentage change in maximum voluntary contraction attained by the untrained limb, no statistical associations (i.e., in individual studies) have been reported (Colomer-Poveda et al., 2019b). In other words, those participants for whom the largest increases in $CSE_{untrained}$ are obtained do not tend to exhibit the greatest gains in strength. This applies both to circumstances in which CSE has been assessed at rest, as well as during weak contractions of the trained or untrained agonist (Colomer-Poveda et al., 2019b).

In the case of ballistic training protocols in which short-term unilateral practice engenders bilateral increases in movement acceleration, net elevations in the excitability of corticospinal projections to the untrained agonist have been reported in some instances (e.g., Carroll et al., 2008; Dickins et al., 2015a; Hinder et al., 2011; Lee et al., 2010; Poh et al., 2013; Reissig et al., 2015) but not others (Ruddy et al., 2016). As we have noted previously (Carson et al., 2016), there is not however any evidence of a statistical association (i.e., in a ballistic movement training context) between training-related alterations in $CSE_{untrained}$ and the level

of absolute/relative improvement attained by the untrained limb (Carroll et al., 2008) or interlimb transfer (Dickins et al., 2015a; Ruddy et al., 2016). Furthermore, while the benefits of CE training are typically confined to movements that engage the homologues of task-agonist muscles, elevations in the excitability of corticospinal projections to homologous and heterologous muscles of the untrained limb – including those that do not make a direct mechanical contribution to the movement, have been reported (Carroll et al., 2008). These findings are consistent with the supposition that unilateral ballistic movement training engenders generalized increases in CSE that are independent of changes in movement performance (Berghuis et al., 2017; Carroll et al., 2008).

As with ballistic skill and chronic resistance training protocols, unilateral visuomotor tracking tasks have also been shown to engender training-related increases in $CSE_{untrained}$ (Christiansen et al., 2017; Leung et al., 2015; Leung et al., 2018). Notably, and consistent with other training paradigms, these changes are not however associated with interindividual variations in interlimb transfer (Christiansen et al., 2017) or relative improvement (Leung et al., 2018). It is worth noting also that there exist many training tasks in which training-related alterations in $CSE_{untrained}$ have not been observed following unimanual training, e.g., repetitive finger tapping (Avanzino et al., 2014), two-ball rotation (Nojima et al., 2012), and finger-to-thumb opposition (Dickins et al., 2015a). Altogether therefore, it would seem that irrespective of the method by which CE is expressed (e.g., in terms of absolute improvement, relative improvement, or interlimb transfer), its magnitude is ostensibly independent of alterations in the level of CSE registered in the untrained limb (for systematic reviews, see Colomer-Poveda et

al., 2019a; Colomer-Poveda et al., 2019b; for a meta-analysis, see Manca et al., 2018). These same conclusions, at least in young adults, apply also to the phenomenon of motor irradiation (Hinder et al., 2011; Reissig et al., 2015).

1.4.3 INTERHEMISPHERIC PRIMARY MOTOR FUNCTION

In seeking to appraise the functional contributions of M1 to CE, it is necessary to consider whether there occur changes in the states of circuits that cannot be assessed using single-pulse TMS, yet which may play an instrumental role in mediating the expression of the interlimb effect. It has been proposed that as a consequence of unilateral training, there may occur a decrease in inhibitory drive from the motor cortex contralateral to the training limb, to the motor cortex from which corticospinal projections descend to the untrained limb (e.g., Hortobagyi et al., 2011). It is through modulation of these inhibitory interhemispheric interactions that the functional adaptations that engender CE are postulated to arise (Lee & Carroll, 2007). A fundamental consideration in this regard however, is that the role of inter-hemispheric inhibition may be to support contrast enhancing and integrative functions, rather than to suppress or impede processing in contralateral brain regions (Carson, 2020). It is therefore unclear why an increase in functional capability should follow – even in principle, from a decrease in interhemispheric inhibition. There is a further challenge in that interhemispheric inhibition (hereinafter '$IHI_{physiological}$') encapsulates a widely differentiated set of physiological processes (Carson, 2020) that cannot currently be gauged directly in humans.

The term ‘interhemispheric inhibition’ has also been applied to a specific electrophysiological phenomenon (hereinafter ‘$IHI_{electrophysiological}$’) that is obtained when two magnetic stimuli – a ‘conditioning’ (CS) and ‘test’ stimulus (TS) – are delivered in close succession over one region of cortex followed by another contralaterally. The intensity of both stimuli is usually above that necessary to elicit a MEP in the muscles of the contralateral limb. In the prototypical variant, a decrease in the amplitude of the MEP that is obtained in response to the TS, is observed when the CS has been applied 6-15 ms previously, i.e., to the opposite M1 (Ferbert et al., 1992). There is also a long-latency variant that uses interstimulus intervals (ISIs) in the order of 50 ms. The short- and long-latency variants have in common that the magnitude of the effect (i.e., the notional depth of inhibition) increases (at rest) with the CS intensity (Calvert et al., 2020; Ibey et al., 2015; Ni et al., 2009b). Yet they appear to differ in that the magnitude of the short-latency effect (at fixed CS intensities) can be increased by simultaneous contractions of muscles in the contralateral (i.e., to the CS) limb (Ferbert et al., 1992; Perez & Cohen, 2008; Talelli et al., 2008; Uehara et al., 2014; Vercauteren et al., 2008). It has been surmised on the basis of pharmacological studies that the two $IHI_{electrophysiological}$ variants are also mediated by at least partially distinct GABAergic circuits (e.g., Irlbacher et al., 2007). In seeking to determine whether there exists a relationship between manifestations of CE and variations in interhemispheric inhibition (or indeed facilitation), it is critical to emphasise that, in spite of shared nomenclature, $IHI_{electrophysiological}$ (i.e., obtained by means of dual-coil TMS) does not provide a faithful assay of the functions assumed by interhemispheric inhibition in a normal physiological context (for a detailed

discussion of this issue, see Carson, 2020). Of course, it remains legitimate to enquire whether there are reliable changes in $IHI_{electrophysiological}$ in circumstances in which CE has occurred, and if so, whether there are age-related variations in the expression of these changes. The physiological significance of any such changes will however remain extremely challenging to determine.

Viewed in this light, consideration can be given to CE studies in which this electrophysiological method has been employed. In this regard, it has generally been the case that a measure of $IHI_{electrophysiological}$ has been derived by delivering the CS over the M1 contralateral (and the TS over the M1 ipsilateral) to the training limb. In such circumstances, the magnitude of $IHI_{electrophysiological}$ is frequently considered an index of inhibition of the 'untrained' M1 by the 'trained' M1. In a recent systematic review that distinguished 'acute' from 'chronic' resistance training protocols on the basis of their duration, it was noted that training-related alterations in the expression of $IHI_{electrophysiological}$ are remarkably inconsistent (Colomer-Poveda et al., 2019b). When assessed acutely (i.e., in a single training session), short-latency $IHI_{electrophysiological}$ may be diminished markedly from pre- to post-training (Hortobagyi et al., 2011). This is commensurate with evidence derived from studies in which a sequential pinch force task (Camus et al., 2009) or serial reaction time task (SRTT) (Perez et al., 2007b) were employed. No evidence has however been presented of a statistical association between changes in $IHI_{electrophysiological}$ and measures of performance (i.e., obtained in the non-trained limb) in any acute training study with which we are familiar.

In the case of chronic resistance training protocols (i.e., those defined as a minimum of two training sessions per week for two weeks or more), the direction of training-related change in $IHI_{electrophysiological}$ is much more variable. Indeed, relative to pre-training levels, short-latency $IHI_{electrophysiological}$ may be elevated (Zult et al., 2016), reduced (Hortobagyi et al., 2011), or even unchanged in magnitude (as with long-latency IHI, see Manca et al., 2016). In the only study to date to provide evidence of a statistical association between training-related alterations in $IHI_{electrophysiological}$ and CE, Hortobagyi and colleagues reported increasingly positive correlations (r = 0.61-0.72) between the percentage change in short-latency $IHI_{electrophysiological}$ and the level of relative improvement attained by the untrained limb – each expressed relative to baseline (i.e., pre-intervention) levels, following 10, 15, and 20 sessions of unilateral isometric finger abduction training (Hortobagyi et al., 2011). Over the course of the 8 wk intervention, the authors reported that short-latency $IHI_{electrophysiological}$ decreased by an average of 30.9%, while the mean level of relative improvement attained by participants was 21.8%. Although acute alterations in $IHI_{electrophysiological}$ were not associated with the expression of CE, these findings suggest that long-term variations in $IHI_{electrophysiological}$ may reflect processes that facilitate the consolidation and retention of gains attained by the untrained limb. There are no other studies (of which we are aware) in which an association between the magnitude of CE and training-related alterations in $IHI_{electrophysiological}$ (or indeed the ipsilateral silent period (iSP)) has been reported.

Based on the limited number of studies in which measures of $IHI_{electrophysiological}$ have been obtained in the context of chronic unimanual

resistance training regimes, or single-session studies using a variety of tasks, it can be concluded that while changes in short-latency $IHI_{electrophysiological}$ sometimes accompany improvements in the performance of the untrained limb, there is very little evidence of a statistical association (*cf.*, Hortobagyi et al., 2011). Introductory textbooks in statistics stress that the presence of a correlation does not imply causation. Nonetheless, should causal relationships be present, correlations are to be expected. Two possibilities are thus presented. Firstly, it may be the case that the measures that have been employed to date (i.e., MEPs in general and $IHI_{electrophysiological}$ in particular) are not sufficiently sensitive or discriminating to capture the physiological changes that mediate the observed modifications in behaviour (Carson, 2020). Alternatively, the circuits that have been engaged by TMS (whether delivered to one hemisphere or to both) are simply not those that play an instrumental role in mediating the neural adaptations that underpin the interlimb effect (Carson et al., 2016).

1.4.4 INTRACORTICAL PRIMARY MOTOR FUNCTION

On anatomical grounds alone, it appears unlikely that there is significant direct interhemispheric modulation of neurons in the caudal portion of M1 (otherwise known as new M1 or M1p). The findings summarised above also make clear that there is very little empirical evidence to support the conjecture that direct interhemispheric interactions between neurons in rostral M1 (at the precentral convexity of the central sulcus) – which along with the caudal portion of PMd (Aberra et al., 2020; Dubbioso et al., 2021) are more likely to be activated by TMS

(Dancause et al., 2015; Dubbioso et al., 2021), constitute the mechanistic basis of CE. Such considerations do not however preclude the possibility that other interhemispheric projections (e.g., from one or more non-primary motor regions) may play an instrumental role. It is conceivable, for example, that the M1 ipsilateral to the training limb is subject to alterations in afferent input from centres in the same or opposite hemisphere (e.g., PMd, SMA) which may receive or relay transcallosal input. Although it is not possible using "paired-pulse" TMS delivered to M1 alone, to determine the origin of any such modulating changes in afferent input, these techniques can, in principle, provide an initial indication as to whether M1 circuits that mediate electrophysiological phenomena such as "intracortical inhibition" and "intracortical facilitation" are subject to training-related changes in reactivity.

The essence of paired-pulse TMS is that two magnetic stimuli (a CS and TS) are applied in close temporal contiguity over the same region of brain – in practice, the border between the rostral M1 and caudal PMd (Dubbioso et al., 2021) – at circumscribed intensities. By this means, such measures as short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), intracortical facilitation (ICF), and short-interval intracortical facilitation (sICF), may be obtained. SICI is generated when a subthreshold CS is paired with a suprathreshold TS, in circumstances in which the two stimuli are separated by an ISI of 1-6 ms (Kujirai et al., 1993). As the extent of the depression in the amplitude of the MEP evoked by the TS is potentiated by $GABA_A$ agonists (Di Lazzaro et al., 2005; Ilic et al., 2002; Teo et al., 2009; Ziemann et al., 1996) and its duration similar to $GABA_A$ receptor-mediated inhibitory postsynaptic

potentials evoked in animal preparations (Krnjevic & Schwartz, 1967), the consensus view is that SICI reflects short-lasting postsynaptic inhibition engendered by $GABA_A$-ergic circuits (Reis et al., 2008; Ziemann, 2003, 2008; Ziemann et al., 2015). By contrast, LICI – which is elicited by a dyad of suprathreshold stimuli separated by an ISI of 50-200 ms (Valls-Sole et al., 1992; Wassermann et al., 1996), is held to reflect long-lasting cortical inhibition engendered by $GABA_B$ receptors (Kukaswadia et al., 2005; Paulus et al., 2008). The cortical silent period (cSP), which refers to a period of attenuated (i.e., 'silent') EMG activity that is evoked when a suprathreshold TS is applied to the opposite M1 during voluntary contractions of the target muscle (Fuhr et al., 1991), represents a further measure of cortical inhibition. Like LICI, the cSP is held to reflect $GABA_B$ receptor-mediated inhibition (Premoli et al., 2014; Siebner et al., 1998; Werhahn et al., 1999). Somewhat counterintuitively, the duration of the cSP (and notably not LICI) has also been shown to scale with spectroscopically-derived measures of glutamate concentration (Tremblay et al., 2013). This constitutes only one of several examples in which these two measures of "$GABA_B$ transmission" are known to diverge. Intracortical facilitation (ICF) is obtained in a similar fashion as SICI (i.e., subthreshold CS, suprathreshold TS) with the exception that a longer ISI of 6-25 ms is employed instead (Kujirai et al., 1993). Its mechanistic basis remains perplexing. It is believed that ICF may reflect activity in NMDA receptor-dependent glutamatergic circuits (Paulus et al., 2008; Ziemann, 2003, 2008). Nonetheless, there is a strong possibility that the effect is mediated instead by a cortico-reticular pathway, that can also be activated by the sound click generated by the discharging TMS coil (Fisher et al., 2012). Its short

interval counterpart – unimaginatively known as short-interval intracortical facilitation (sICF), is elicited most commonly by a suprathreshold TS that *precedes* a subthreshold CS separated by three discrete ISIs (~1.3-4.5 ms) whose periodicity corresponds closely to the frequency (~670 Hz) of I-wave generation (Avanzino et al., 2007; Tokimura et al., 1996; Ziemann et al., 1998). The prevailing view is that sICF arises as a result of i) the elicitation of I-waves (i.e., by the CS and TS) in which the peaks are in-phase, and 2) the arrival of the CS during an interval in which the firing probability has been increased significantly by the preceding TS (Di Lazzaro et al., 2018).

The extent to which each of these measures is modulated by unimanual training, when assessed in the ipsilateral M1, has been addressed in several meta-analyses and systematic reviews concerned exclusively with unimanual resistance training paradigms (Colomer-Poveda et al., 2019b; Manca et al., 2018). Based on these analyses, there does not appear to be any evidence that ICF, LICI, or sICF are modulated reliably by either acute or chronic resistance training protocols. By contrast, the cSP and SICI are diminished markedly. At first glance, the former finding (i.e., a decrease in the duration of the cSP) may seem inconsistent with the lack of LICI modulation, since both measures are held to reflect $GABA_B$ receptor-mediated inhibition. This dissociation is however common (Benwell et al., 2007; Inghilleri et al., 1996; McDonnell et al., 2006; Poston et al., 2012; Tremblay et al., 2013) and the two measures should not be viewed as equivalent. In the first instance, the cSP is held to reflect the states of elements at various levels of the neuraxis (Reis et al., 2008; Škarabot et al., 2019) including spinal mechanisms that contribute to the early (i.e., initial ~50-80 ms) portion of the signal (Fuhr et

al., 1991; Ziemann et al., 1993). By contrast, LICI is considered an index of cortical inhibition only (Werhahn et al., 1999). There are also qualitative differences in interpretation. Specifically, while the cSP is held to reflect the *duration* of $GABA_B$ receptor-mediated inhibition, LICI has been conceptualised as a measure of its *magnitude* (McDonnell et al., 2006). The two measures thus provide complementary yet divergent information (i.e., 'how much' vs. 'how long') concerning the level of $GABA_B$ activity registered within the target hemisphere.

To what extent are training-related alterations in the magnitudes of these measures related to CE? The balance of evidence is consistent with the view that while training-related decreases in cSP duration and SICI magnitude are observed consistently in the untrained M1 following unimanual resistance training, they are not associated reliably with variations in CE – at least in circumstances in which the effect is expressed in terms of relative improvement (Colomer-Poveda et al., 2019b; Manca et al., 2018). Similar findings (in respect of SICI) have been reported in the context of a unimanual ballistic finger abduction protocol (e.g., Hinder et al., 2013). It remains to be established whether these same conclusions apply to other measures of CE (e.g., interlimb transfer), and whether they are generalisable to other domains of training (i.e., beyond those mentioned). While the functional contributions of adaptations within the rostral M1 (and caudal PMd) ipsilateral to the training limb cannot be excluded, there is as yet no substantiating empirical evidence that they are instrumentally related to CE.

1.4.5 POTENTIAL AGE-RELATED VARIATIONS IN THE MEDIATING ROLE OF M1

On the basis of the preceding analyses, there would appear to be little evidence that CE is mediated by interhemispheric interactions between the primary motor cortices, nor by adaptations within M1, or alterations in the excitability of corticospinal projections to the muscles of the untrained limb. Accordingly, a detailed consideration of age-related variations may appear moot. This would however neglect an important consideration: the possibility that the neural mechanisms which mediate CE may change with age.

It is received wisdom that across a range of cognitive and motor tasks, older adults exhibit greater and more diffuse intra- and inter-hemispheric activation than their younger counterparts. This understanding is based primarily on the study of regional elevations in the fMRI-derived BOLD response (Bernard & Seidler, 2012; Cabeza, 2002; Reuter-Lorenz et al., 2000; Ward, 2006). The reduction in lateralisation of cerebral activity inferred through these methods is held in some quarters to arise from age-related atrophy of rostral callosal segments (Müller-Oehring et al., 2007). From a functional perspective, there exists intense debate as to whether such additional activation should be considered adaptive, i.e., to compensate for age-related declines in brain structure or biochemical composition (Mattay et al., 2002; Naccarato et al., 2006; Seidler et al., 2010; Wu & Hallett, 2005), or maladaptive – to the extent that the "dedifferentiation" of brain function may engage regions that impede task performance (Cassady et al., 2020; Logan et al., 2002; Riecker et al., 2006). It has been surmised that unimanual movement execution engenders a greater degree of bilateral motor cortical activity in the brains of older adults, based on regional elevations in BOLD signal intensity

(Heuninckx et al., 2008; Mattay et al., 2002; Michely et al., 2018; Ward et al., 2008). Taken at face value, a strict interpretation of the cross activation model of CE would lead to the prediction that older adults should exhibit higher levels of CE than their younger counterparts (Dickins et al., 2015a; Graziadio et al., 2015a; Hinder et al., 2011). Notwithstanding a lack of empirical support (§2.3, *cf.* Graziadio et al., 2015a), it is now clear that the fundamental basis of this supposition (i.e., regional elevations in the fMRI-derived BOLD response) requires renewed critical evaluation. In recent years, the effect of age on the cerebral vasculature and its potential to confound BOLD-based estimates of cerebral activity has gained increasing recognition (for a review, see Tsvetanov et al., 2021b). In both voxel-based and independent component analyses of regions with high vascular reactivity, it has been demonstrated that when controlling for variability in estimates of cardio- and neuro-vascular function (e.g., diastolic or systolic blood pressure, cerebral blood flow), the variance in resting state (BOLD) fluctuation amplitude is no longer associated significantly with age (Tsvetanov et al., 2021a). The spatial extent of cardiac-modulated voxels in the cerebral white matter is also increased markedly in later life, with similar trends evident in the cerebral grey matter (Viessmann et al., 2019).

In mice, it is known that oscillations in the contractile tone of the arteriole endothelium (so-called 'vasomotion') are synchronised transhemispherically (Mateo et al., 2017). A key question to consider therefore is whether elevations in ipsilateral BOLD activation, which are characteristically observed during unimanual movements and amplified significantly in older age, may arise as a consequence of correlated vasomotion, rather than activity in local neuronal

circuits. A second question is whether a greater degree of vasomotion (and a stronger correlation with BOLD activity) may be present in the brains of older adults. It has been demonstrated previously that in hypercapnic conditions (i.e., increased partial pressures of arterial CO_2), older adults exhibit a greater degree of vasodilation compared to younger subjects, as well as lower levels of vasoconstriction in response to hypocapnia (Tarumi & Zhang, 2018; Tomoto et al., 2020; Zhu et al., 2013). As increases in the partial pressure of oxygen in the parenchymal microvessels are phase-locked to arteriole dilation (Mateo et al., 2017), it is conceivable that elevations in the level of BOLD activity registered in the brains of older adults may arise, at least in part, from age-related elevations in the degree of vasodilation in the cerebral microvessels. The extent to which increases in the magnitude of the BOLD response registered in the opposite hemisphere (i.e., during unilateral movement) arise as an artefact of correlated vasomotion, and the degree to which this may vary with age, remains to be investigated further.

Notwithstanding the possibility that age-related elevations in (neuroimaging-based measures of) 'cross activation' may be driven by vascular confounds, it remains feasible to use electrophysiological techniques based on TMS to assess whether there occur lifespan variations in the extent of interhemispheric interaction. It is generally accepted that young and older adults exhibit comparable levels of short- and long-latency $IHI_{electrophysiological}$ when assessed at rest by TMS applied over the hand motor areas (short $IHI_{electrophysiological}$: Hermans et al., 2018; Hinder et al., 2012; Mooney et al., 2018; Talelli et al., 2008; long $IHI_{electrophysiological}$: Hermans et al., 2018; Hinder et al.,

2012; Talelli et al., 2008). During contemporaneous contractions of muscles contralateral to the conditioned MEP (i.e., ipsilateral to the TS), age-related variation does however emerge. Although short-latency $IHI_{electrophysiological}$ is elevated similarly by contraction in both young and older adults (Hinder et al., 2010; Mooney et al., 2018; Talelli et al., 2008), increases in the magnitude of the long-latency variant otherwise observed in young adults are attenuated markedly in older individuals (Talelli et al., 2008). In some instances, the extent of attenuation is such that a net facilitation is obtained, i.e., relative to levels assessed at rest (Talelli et al., 2008). In respect of the iSP, age-related increases in its latency to onset and offset, as well as its duration – each thought to be indicative of increasing levels of inhibition, have been reported (Davidson & Tremblay, 2013; Petitjean & Ko, 2013; Strauss et al., 2019). Although a transcallosal route is considered most likely (Hupfeld et al., 2020), the precise origins of iSP-expressed inhibition have however yet to be delineated. Taken together, it would seem that both short- and long-latency $IHI_{electrophysiological}$ are virtually unchanged in older individuals (i.e., relative to levels observed in young adults) when assessed at rest, while only the long-latency variant is diminished during 'active' conditions (Talelli et al., 2008). The iSP, which is necessarily elicited during contraction, appears to be elevated reliably in older individuals.

With respect to the range of paired-pulse TMS measures described previously (§4.3), there is little evidence of systematic age-related variation. In a recent meta-analysis, it was established that no reliable differences between young and older adults are evident in respect of the cSP (4 studies), ICF (3 studies), or SICI (11 studies), when these measures are obtained at rest (Bhandari et al., 2016;

see also Corp et al., 2021). In the case of LICI, reports of age-related variation are remarkably inconsistent ($LICI_{young}$ > $LICI_{old}$: Hermans et al., 2018; Hermans et al., 2019; Opie et al., 2015; Opie & Semmler, 2014a; $LICI_{old}$ > $LICI_{young}$: McGinley et al., 2010; no age differences: Mooney et al., 2017; Opie et al., 2018b). Lifespan variations in sICF are similarly unreliable ($sICF_{young}$ > $sICF_{old}$: Opie et al., 2018a; Opie et al., 2020; $sICF_{old}$ > $sICF_{young}$: Clark et al., 2011; no age differences: Shibuya et al., 2016; Van den Bos et al., 2018), although the direction of age-related discrepancies (where these arise) may be ISI-dependent (Clark et al., 2011).

It is also pertinent to consider whether there are lifespan variations in the extent to which these measures may be modulated by training that leads to demonstrable motor learning. In the present context, the information desired is that concerning the states of circuits ipsilateral to the limb engaged in training. Unfortunately, this information is not readily available. Studies in which TMS-derived measures of intracortical function have been obtained for different age cohorts have focused almost exclusively upon responses evoked in muscles of the training limb. On this basis, it is evidently not possible to draw any inferences in relation to the processes which mediate CE. In addition, and as highlighted previously, the minimum requirement for causal mediation to be inferred is a change in behaviour that is indicative of learning, for which there is correlated variation in the expression of the electrophysiological measure. The mere presence of a change in the electrophysiological measure that accompanies an alteration in performance is simply not sufficient. Similarly, for age-related variation to be

inferred, the magnitude of the relevant association must necessarily change with age.

1.4.6 SUMMARY: ON THE ROLE OF PRIMARY MOTOR CORTEX

In seeking to provide a mechanistic account of CE, the pervasive (contemporary) emphasis upon M1 is evidently misplaced. Quite simply, there is very little evidence to support the supposition that adaptations in the states of circuits in this brain region play an instrumental role in the expression of CE – at least when it is assessed acutely. There are however caveats. Firstly, the potential contribution of M1 has been examined almost exclusively in terms of the relative improvement realised by the untrained limb. It remains unclear if similar conclusions apply also to other indices of CE (e.g., interlimb transfer). Secondly, it may be the case that the TMS-based assays that have been employed to date are not sufficiently sensitive to capture the neural adaptations that underpin the observed changes in behaviour. While the possibility that CE is mediated, at least in part, by adaptations in circuits that lie within, or which project onto, circuits in M1 ipsilateral to the training limb cannot be excluded, it is not supported obviously by empirical findings. Moreover, while age-related changes in the involvement of circuits in M1 cannot be discounted, there are no direct indications that this is the case.

1.5 OTHER NODES WITHIN THE CORTICAL MOTOR NETWORK

1.5.1 THEORETICAL CONTEXT

While corticospinal projections from M1 provide the primary means by which the expression of CE is given effect, the neural adaptations that underlie its mediation may be instantiated in other brain centres (Ruddy & Carson, 2013; Ruddy et al., 2017b). In this respect, the potential role of non-primary 'motor' regions including PMd and SMA, and in particular the rich interhemispheric connectivity they afford, has garnered particular attention (Gabitov et al., 2016; Perez et al., 2007a; Perez et al., 2008; Ruddy et al., 2017b).

It has long been supposed that the neural adaptations which underpin CE may be instantiated at one or more loci that are accessible to motor networks that control effectors on both sides of the body. This is the principal tenet of the "bilateral access" hypothesis (Imamizu & Shimojo, 1995; Laszlo et al., 1970; Taylor & Heilman, 1980). The essence of this model is that unilateral experience gives rise to the elaboration of "engrams" which can be accessed by circuits within both cerebral hemispheres (Nadel & Buresova, 1968) (Figure 1.6). A hypothetical extension of the Nadel-Buresova scheme has been described (Ruddy & Carson, 2013), which entails that a motor engram encoded contralateral to the training limb – when accessed during post-training movements undertaken with the untrained limb (the "read-out" phase), is duplicated in the opposite hemisphere (the "write-in" phase) (see Figure 1.7). This model is based in turn on a phenomenon to which the term "cross-callosal tutoring" has been applied (Hilgard & Bower, 1966; Russell & Ochs, 1961; Travis, 1964).

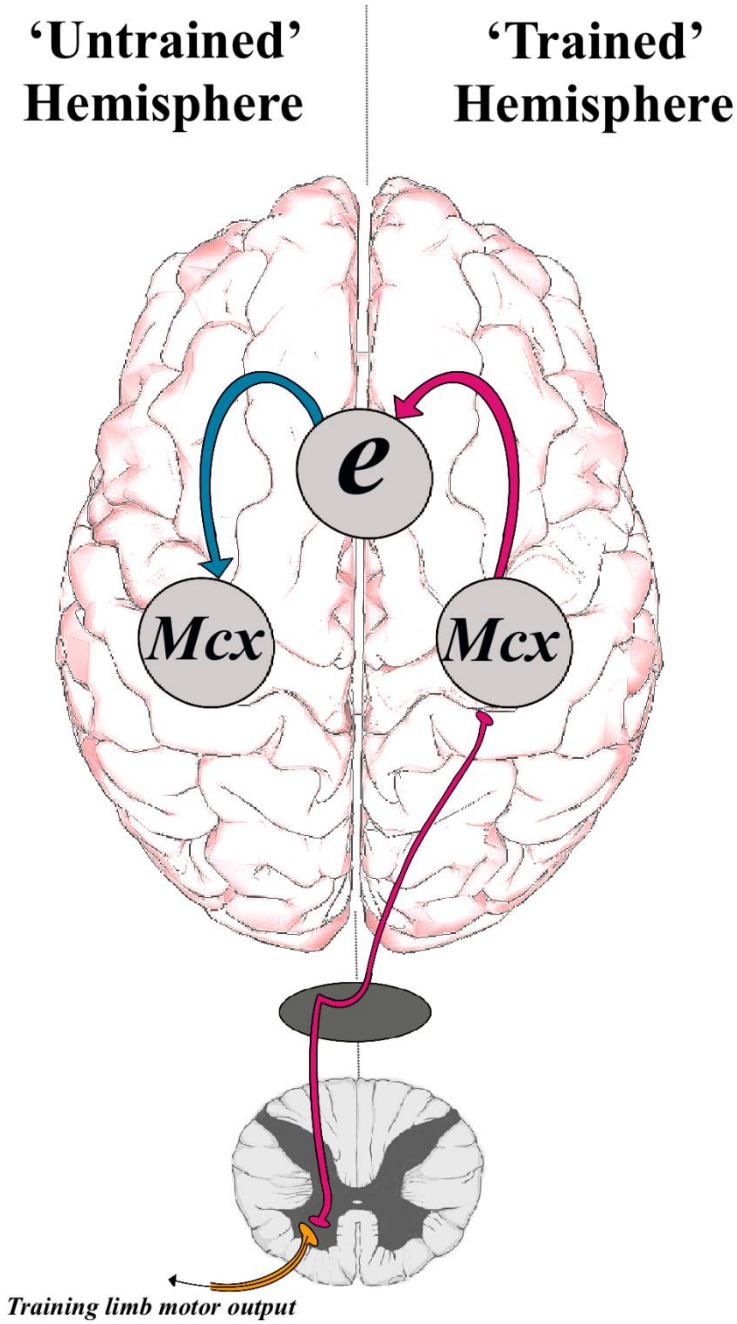


Figure 1.6: Bilateral access model of cross education. Repeated execution of the unimanual motor command by the motor cortex ('*Mcx*') of the 'trained' hemisphere (right of image) results in the elaboration (red solid arrow) of a motor engram ('*e*'). The motor engram is expressed at a locus (middle of image) that is accessible to motor networks that control effectors on both

sides of the body. The blue solid arrow denotes the capacity of motor circuits within the 'untrained' hemisphere (left image) to access the motor engram during the execution of training movements with the untrained limb.

In the sections which follow, we consider the potential role of specific brain regions that constitute elements of the cortical motor network (i.e., other than M1), in mediating the adaptations upon which the expression of CE may be based. By and large, the emphasis is upon estimates of intracortical and interhemispheric connectivity derived using electrophysiological and neuroimaging methods. We exclude consideration of "interference" studies based on repetitive TMS (rTMS) which have focused almost exclusively upon the role of the SMA (e.g., Perez et al., 2007a; Perez et al., 2008). It is estimated that TMS delivered using standard coils at 120% of resting motor threshold may activate a region of cortex that spans several cm^2 and one to two gyri (Opitz et al., 2014). As SMA is separated from its homologue only by the narrow embankment of the longitudinal fissure, it seems unlikely that in interference studies, unilateral stimulation of SMA can be assured.

As non-primary motor regions have seldom been examined directly in studies of CE, we must attempt to draw upon evidence derived from paradigms that have been devised to study other facets of motor learning. In this regard, the available evidence is much more limited than one might imagine. This is due to the fact that assessments of the degree to which learning has occurred, as opposed to changes in the level of performance, are seldom utilised in conjunction with brain imaging, or in many studies in which electrophysiological methods are

employed. Of all the relevant variables that have a determining influence on performance, only a subset will define the state of learning (Adams, 1967). Tests of transfer and retention must therefore be employed as a basis upon which to advance the explanation that changes in capability are relatively permanent *and* a function of training/practice (Christina, 1997). Tests of retention refer to circumstances in which capability is assessed – after some period of time has elapsed, under conditions that are equivalent to those that were present during training/practice. The term 'transfer' is usually employed when capability is gauged in conditions that differ from those that characterised its initial acquisition. In such terms, retention is a special case of transfer. Retention and transfer are related in that the post-acquisition context can vary from the acquisition context not only with respect to the dimension of task similarity, but also with respect to the dimension of time (Christina, 1997). In principle therefore, evidence derived from studies in which neural activity registered during training/practice is analysed with respect to capability expressed during a retention test, may provide information that is relevant to our understanding of mechanisms that mediate transfer. Even when the requirement for tests of transfer or retention is satisfied however, it is seldom demonstrated that an instrumental relationship, or at the very least an association, exists between the degree of change in some measure of neural processing, and the learning that accrues to an individual (Carson et al., 2016). As a consequence, and perhaps remarkably, there are presently few sources of information relevant to determining the degree to which specific nodes within the cortical motor network mediate many forms of motor learning.

1.5.2 DORSOLATERAL PREFRONTAL CORTEX

In humans, the dorsolateral prefrontal cortex (dlPFC) encompasses the lateral portion of Brodmann areas 9/46 within the middle frontal gyrus of the frontal lobe (Hoshi, 2006; Passingham & Wise, 2012; Petrides, 2005; Yamagishi et al., 2016). Its role in cognition (D'Esposito et al., 1995; Mansouri et al., 2009) and psychiatric disorders (Manoach et al., 2000; Rajkowska et al., 2001) is acknowledged widely. Yet much less is known of its involvement in motor control and learning, particularly in older adults. The dlPFC is broadly connected to multiple brain regions, including premotor and primary motor areas, as well as subcortical and cerebellar centres (for a review, see Miller & Cohen, 2001). A superordinate role in movement selection has been ascribed to dlPFC (Hasan et al., 2013). It has also been implicated in the early phases of motor skill acquisition (for a review, see Dayan & Cohen, 2011). It is received wisdom that in later life, there occurs a 'shift' in functional brain activity – from posterior to anterior regions – that is associated with age-related variations in cognitive and motor performance (Davis et al., 2008; Michely et al., 2018). The manifestation of this phenomenon via alterations in the functional contributions of prefrontal cortex (PFC) in general, and dlPFC in particular, has been emphasised (Cabeza & Dennis, 2012; Reuter-Lorenz & Cappell, 2008). Consideration might therefore be given to the possibility that changes in the structural/functional integrity of dlPFC may contribute to age-related variations in the processes that mediate CE.

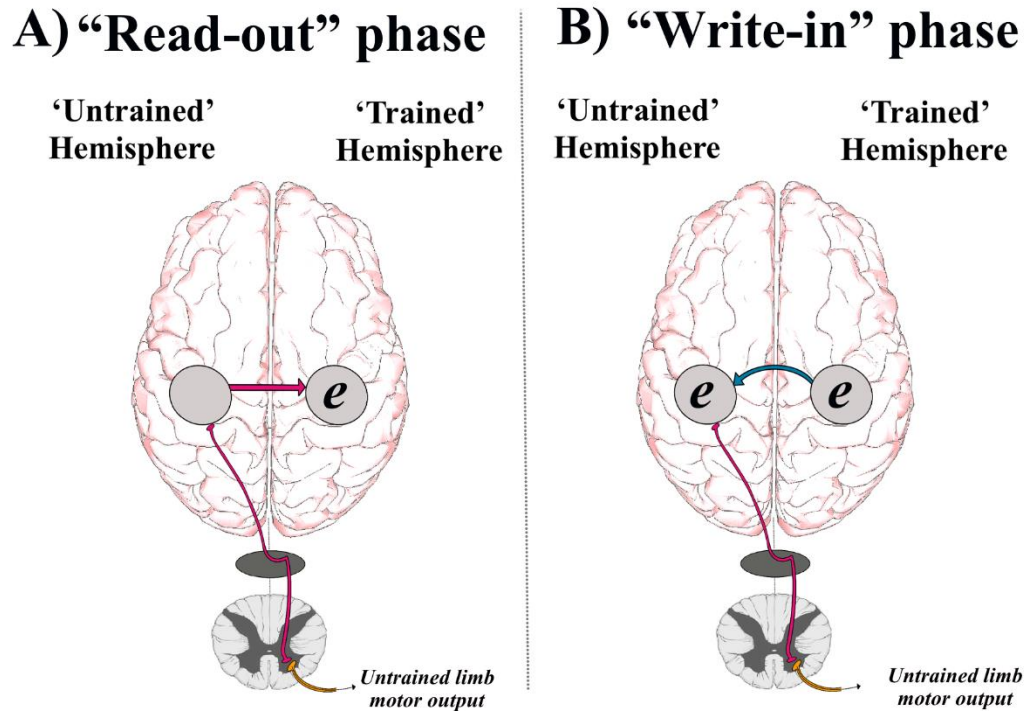


Figure 1.7: Biphasic bilateral access model of cross education. Panel (A) illustrates the 'read-out' phase where the motor engram ('*e*') elaborated within the 'trained' hemisphere (right of panel) following repeated execution of unimanual movements with the training limb, may be accessed by the motor circuits of the 'untrained' hemisphere – via transcallosal pathways (red solid arrow) – during post-training movements undertaken with the untrained limb. The absence of the motor engram in the 'untrained' hemisphere (i.e., of Panel A) indicates that an engram duplicate has not yet been formed. Panel (B) illustrates the subsequent 'write-in' phase during which a duplicate engram (*e*) is expressed within the 'untrained' hemisphere (blue solid arrow) following repeated execution of training movements undertaken with the untrained limb. Adapted from Ruddy and Carson (2013).

Although in several studies attempts have been made to relate changes in performance exhibited by individual participants during a practice phase, to concurrent alterations in PET- or fMRI-based estimates of frontal brain activity (e.g., Anguera et al., 2011; Grafton et al., 1994), we are aware of very few instances in which transfer or retention tests have been employed to gauge accurately the extent of motor learning. Retention tests have on occasion been employed to examine interindividual (including age-related) variations in the BOLD response registered in dlPFC during (Lin et al., 2013; Lin et al., 2011) or following (Lin et al., 2012) the acquisition of response sequences presented in either a repetitive or an interleaved order. In such instances however, the emphasis has been upon differences attributable to the mode of sequence presentation (i.e., the role of contextual interference), rather than upon individual differences in the extent of motor learning per se. In this regard, it is known that prefrontal lesions give rise to deficits in the acquisition of tasks that require the learning of an explicit sequence, and of those in which the sequence is primarily implicit (Gomez Beldarrain et al., 2002). Nonetheless, it remains frequently the case that performance curves, rather than tests of transfer or retention, are employed in assessing (in both young and older adults) the degree to which some characterisation of the dorsal frontal cortices, such as functional connectivity (e.g., Mary et al., 2017), is associated with the acquisition of a response sequence. We emphasise again the point which was broadly recognised in previous eras: performance during acquisition is at best ambiguous with respect to the amount learned (Schmidt & Bjork, 1992).

In circumstances in which elevations in structural MRI estimates of the thickness of the right dlPFC (Sale et al., 2017), as well as increases in the levels of fractional anisotropy (FA) registered in streamlines projecting from dlPFC (Reid et al., 2017), have been observed in conjunction with four weeks of unimanual training (a finger-to-thumb opposition sequence task) in healthy young adults, there are no obvious associations between changes in sequence execution speed and MRI-derived indices of brain structure. It is also notable that in these circumstances, no reliable changes in grey or white matter structure in cortex ipsilateral to the training limb are registered (Reid et al., 2017; Sale et al., 2017). Performance curves alone have also been used to document an association between age-related variations in the volume of lateral prefrontal cortex and practice-related changes in a composite measure of the speed and accuracy of mirror tracing, with larger volumes associated with better performance (Kennedy & Raz, 2005).

While it is conceivable that changes in the structural/functional integrity or connectivity of dlPFC contribute, at least in part, to age-related variations in the mediation of CE, there is no substantiating empirical evidence of which we are aware. Indeed, while it is evidently the case that the dlPFC is activated consistently in a range of tasks that have been used with the aim of studying motor learning (Hardwick et al., 2013), in most instances only measures of performance – rather than tests of retention and transfer, have been obtained. When paradigms such as sequence acquisition tasks, that provide other means of supporting an inference that learning has occurred, have been employed, it is most frequently the case that variations in dlPFC activity or connectivity have been associated with differences

in performance engendered by alternative training regimes (e.g., blocked versus interleaved practice). Necessarily however, causal factors involved in producing condition-specific differences in the degree of motor learning, are not the same as those responsible for individual variations in the extent of motor learning per se (see Keller, 2010). The conclusion to be drawn therefore is that very little is known of any potential functional role that might be played by the dlPFC in mediating any aspect of motor learning.

1.5.3 DORSAL PREMOTOR CORTEX

In primates, the convexity of premotor cortex encompasses the lateral portion of BA6 and constitutes the most abundant source of frontal afferent input to the digit representation of M1 (Dum & Strick, 2002, 2005; Muakkassa & Strick, 1979; Strick, 1985). The region may be differentiated into rostral and caudal sectors on the basis of its cytoarchitecture (Barbas & Pandya, 1987). It may alternatively be parcellated into dorsal and ventral sectors at the spur of the arcuate sulcus (Rizzolatti et al., 1998; Schubotz et al., 2010; Tomassini et al., 2007). The rostral sector of premotor cortex is known to exhibit dense connectivity with prefrontal regions, while its caudal counterpart – often conceptualised as a "true motor area" (Schubotz & von Cramon, 2003, pp. 121), projects primarily to the ipsilateral M1 and spinal cord (Dum & Strick, 1991; Ghosh & Gattera, 1995; Marconi et al., 2001; Schubotz & von Cramon, 2003). In respect of the dorsal and ventral sectors, it is well established that the former constitutes a rich source of interhemispheric connectivity with homologous and heterologous motor regions

in the opposite hemisphere (Fling et al., 2013; Ruddy et al., 2017a), while the latter is known to project to a plethora of prefrontal, subcortical, mesencephalic, and spinal structures (Borra et al., 2010; Kantak et al., 2012).

In restricting one's focus to those sectors most prominently engaged in motor control and learning, it is undoubtedly dorsal premotor cortex (PMd) that has received the most attention (Abe & Hanakawa, 2009; Genon et al., 2017; Hardwick et al., 2013). It has been established that in non-human primates, the firing rates of neurons in this region are related to several kinematic parameters of movements executed by the ipsilateral limb, including acceleration and velocity, as well as direction and amplitude (Fu et al., 1993; Kubota & Hamada, 1978; Kurata, 1993). Recent advances achieved by computational analysis of neuroimaging data have revealed that PMd is composed of a distinct and highly complex functional architecture. For example, by combining connectivity-based parcellations with meta-analytic modelling, it is possible to partition PMd into no fewer than five subdivisions (Genon et al., 2017; Genon et al., 2018). The first subdivision is the rostral or "pre-" PMd, which, by virtue of its coupling with prefrontal regions, is held to support higher order cognitive processes in a manner analogous to area F7 in non-human primates. The second is the central PMd, which is conceptualised as a "relay centre" through which other, more functionally specialised, subdivisions are linked. The third and fourth subdivisions are those of the dorsal and ventral PMd. Whilst closely coupled, the former is held to mediate the generation of rhythmic and/or sequential hand and finger movements, while the latter is thought to subserve "eye-related" functions. The final subdivision is that of the caudal PMd (or "PMd proper"), which is known for its rich bilateral

connectivity with M1 and SMA, as well as for its presumed role in motor learning and movement execution (Genon et al., 2017). While this topographical arrangement is remarkably similar across both cerebral hemispheres, there is nonetheless evidence of functional lateralisation, at least during many forms of motor training. In particular, it has been demonstrated that across as many as 70 motor learning paradigms, left PMd is activated consistently during the acquisition phase, irrespective of which limb is being trained (for a meta-analysis, see Hardwick et al., 2013). Its rostroventral sector has also been shown to contain a module not present in its homologue that may be linked to several abstract cognitive functions (e.g., explicit long-term memory) (Genon et al., 2018).

Despite its complex functional topography, the role of PMd in motor learning and its connectivity with other elements of the cortical motor network are typically examined without reference to its subdivisions. Hitherto, the role of PMd in mediating neural adaptations which engender CE has seldom been examined. In circumstances in which training-related variations in the degree of PMd activation, or in its functional connectivity, have been appraised, the relationship between these changes and individual differences in CE has invariably been disregarded. Consequently, even in circumstances in which a change has occurred, it is not possible to gauge whether that change should be considered instrumental or *incidental* to the processes which underlie the expression of CE. With these caveats in mind, we describe briefly those studies in which the role of (dorsal) premotor cortex has been examined in a CE context.

Following three weeks of unimanual isometric handgrip dynamometry training performed 5d wk^{-1}, Farthing and colleagues reported increased levels of

BOLD activity in ipsilateral premotor cortex during post-training contractions executed with the untrained limb (Farthing et al., 2011). These effects were not however obtained in a separate experiment in which a six-week (4d wk^{-1}) unimanual isometric ulnar deviation program was employed instead. In this latter study, Farthing and colleagues reported no evidence of increased ipsilateral (or indeed contralateral) BOLD activity in PMd during post-training movements undertaken with the untrained limb, although they did observe an increase in left PMd activation during post-training movements undertaken by the trained right limb (Farthing et al., 2007). As noted previously, no measures of association (i.e., between changes in functional brain activity and behavioural performance) were reported by either study. In a study that required participants to perform a unimanual finger-to-thumb opposition task (trained intensively a day earlier) with an untrained effector, Gabitov et al. (2016) reported bilateral elevations in M1 BOLD activation which exceeded that registered when a similar but novel sequence was performed instead. Notably, the increase in BOLD activity that was registered in the 'trained' M1 when the trained sequence was performed with the untrained limb (when expressed relative to that associated with performance of the novel sequence), was correlated positively with changes in resting state connectivity between the 'trained' and 'untrained' M1, as well as between the 'trained' M1 and 'untrained' PMd. As these increases in functional connectivity failed to correlate with one another, it was concluded that the transfer of "sequence-specific" information must be mediated by "excitatory" mechanisms driven by the trained M1 via two independent pathways (Gabitov et al., 2016). As no measures of CE were reported in the aforementioned study, it is not however

possible to discern whether the training-related changes in functional connectivity discussed above, were instrumentally related to the interlimb effect.

Although alterations (i.e., relative to baseline/rest) in premotor connectivity frequently accompany the preparation and execution of unimanual actions, e.g., ↓PMd-M1 $IHI_{electrophysiological}$ (Hinder et al., 2012; Koch et al., 2006; Kroeger et al., 2010; Liuzzi et al., 2010; Uehara et al., 2013), few studies have examined the relationship between the magnitude of these changes and the level of motor learning/performance attained/demonstrated subsequently. In circumstances in which these measures have been obtained and correlated, it is generally the case that changes in PMd connectivity (e.g., $IHI_{electrophysiological}$) that have been obtained during motor preparation, have been analysed with respect to some parameter of the movement they preceded, rather than characteristics of movements undertaken following a period of training (i.e., transfer/retention). In one such example (i.e., a unimanual ballistic finger abduction protocol), Hinder and colleagues reported decreased levels of $IHI_{electrophysiological}$ between left PMd and right M1 (i.e., relative to baseline) in the interval between "warning" signal onset (i.e., an illuminated light-emitting diode that pre-empted the "go" signal) and left limb movement (Hinder et al., 2012). Notably, this effect was obtained in older adults only, in whom earlier releases of inhibition were predictive of faster responses to the movement cue. An increased manifestation of interactions between ipsilateral premotor areas and the contralateral M1 during unimanual actions undertaken by older adults has likewise been inferred from studies of effective connectivity (Lariviere et al., 2019; Wang et al., 2019b), a measure

which reflects the extent to which one neural system exerts an "influence" on another (Friston, 2011).

As well as contributing to age-related variations in motor *performance*, there exists an emerging recognition that PMd, and in particular the microstructural integrity of its connections with other elements of the cortical motor network, may also account for age-related diminutions in motor *learning* (Schulz et al., 2014). It is recognised widely that DWI-based estimates of structural connectivity are associated with interindividual variations in cognitive (Cox et al., 2019; Fan et al., 2019) and motor function (Adab et al., 2020; Carson, 2018; Hirsiger et al., 2016). These measures may therefore be considered preferable to traditional indices of functional connectivity such as those based on resting state approaches, which correlate only weakly with task-based (fMRI) measures (Rehme et al., 2013), vary remarkably both between and within scanning sessions (Honey et al., 2009), and which may arise between regions in the absence of direct anatomical projections (Damoiseaux & Greicius, 2009; Honey et al., 2009).

In a unimanual sequential finger tapping paradigm, Schulz and colleagues devised an index of motor skill acquisition that was based upon the number of times a trained sequence was executed correctly within a fixed period of time (90 s blocks, 6 blocks daily, 5 days duration). These values were expressed as a proportion of the average number of non-trained/random sequences performed correctly over the course of training. According to the authors, a key advantage of this approach is that it enables assessment of the degree of improvement that is specific to the training sequence with respect to the stable level of performance

associated with the task (Schulz et al., 2014; see also Krakauer & Shadmehr, 2006). Using this approach, Schulz and colleagues reported that the total amount of learning (i.e., the absolute difference between the first and final training blocks) was correlated positively with the microstructural integrity of fibres projecting from the contralateral M1 to ipsilateral PMd, the contralateral M1 to bilateral SMA, and the ipsilateral PMd to ipsilateral SMA (Schulz et al., 2014). Notably, these effects were obtained in older adults only; no such relationships were evident in the younger subject group, nor in respect of motor performance.

While it seems plausible that PMd, by virtue of its extensive functional and structural connectivity, may contribute to the processes which mediate the expression of CE, very little is known of its effective contributions. Even in circumstances in which training-related alterations in its connectivity/activity have been appraised, no corresponding measures of association have yet been reported. Although preservation of the microstructural integrity of PMd projections is associated with better acquisition of fine motor skills in older individuals (e.g., in sequential finger tapping tasks), the capacity for such indices to account for lifespan variations in the mechanisms which mediate CE remains to be determined.

1.5.4 Supplementary motor area

In primates, the supplementary motor area (SMA) occupies the medial portion of BA6 and may be partitioned into rostral and caudal sectors on the basis of its cytoarchitecture (Behrens et al., 2006; Matelli et al., 1991; Vorobiev et al.,

1998). The posterior portion of the 'classical' SMA which lies immediately rostral to M1 is known as "SMA-proper", while the agranular region which lies further rostral on the mesial cortical surface is known as "pre-SMA" (Luppino et al., 1991; Matsuzaka et al., 1992; Picard & Strick, 1996). It is widely held that pre-SMA – by virtue of its extensive connectivity with prefrontal regions (for a review, see Nachev et al., 2008), constitutes a functional node of a prefrontal network that is most prominently engaged in cognitive rather than motor function (Hardwick et al., 2013; Nachev et al., 2008; Ruddy & Carson, 2013). By contrast, its caudal counterpart – SMA-proper, has long been implicated in movement preparation and interlimb coordination (Aramaki et al., 2006; Duque et al., 2010; Grefkes et al., 2008; Nachev et al., 2008; Swinnen, 2002). It projects extensively to the ipsilateral M1 via intergyral U-fibres (Goldberg, 1985; Vergani et al., 2014), and transcallosally to homologous and heterologous motor regions in the opposite hemisphere (Fling et al., 2013; Ruddy et al., 2017a). In the discussion which follows therefore, we largely restrict our analysis to the role of SMA-proper – a region for which the term "SMA" is henceforth applied.

On the basis of connectivity analyses, it is generally held that SMA functions as a source of top-down modulation that regulates interhemispheric interactions between the primary motor cortices (Grefkes et al., 2008; Sarfeld et al., 2012; Serrien et al., 2002; Siebner et al., 2001; Welniarz et al., 2019). During unimanual movements, the degree of coupling registered between SMA and M1 (i.e., intra-hemispherically) is enhanced significantly in the hemisphere contralateral to the active limb. In contrast, the degree of coupling registered between the SMA contralateral and the M1 ipsilateral to the moving limb (i.e.,

inter-hemispherically) is markedly reduced (Grefkes et al., 2008; Volz et al., 2015a). These findings, along with those derived from ablation studies (e.g., Chan & Ross, 1988), have been cited frequently to support the conjecture that SMA suppresses motor overflow to the opposite hemisphere (i.e., during unimanual movements) by effecting "non-mirror transformations" of the selected motor program (Beaule et al., 2012; Cincotta & Ziemann, 2008).

Using constrained spherical deconvolution-based tractography, Ruddy et al. (2017) obtained DWI-based estimates of transcallosal microstructure with the view of relating interindividual variations in left-right SMA structural connectivity to interlimb transfer. In the context of a unimanual ballistic wrist flexion protocol, the authors reported that interindividual variations in apparent fibre density (a measure of microstructural organisation) and fractional anisotropy (FA) (a general index of microstructural status) were negatively correlated with and predictive of transfer acutely (i.e., at the end of the training session), and remained correlated with, though not predictive of, the level of transfer registered one-week later (*cf*., FA). That is, those individuals in whom SMA-SMA microstructural integrity was *greatest* exhibited the *lowest* levels of interlimb transfer. The functional contribution of SMA to CE has likewise been inferred from functional imaging studies. In a variant of the serial reaction time task (SRTT), Perez and colleagues reported that the degree of absolute improvement realised by the untrained limb following unimanual training (i.e., the decrease in response time from pre- to post-training) was correlated positively with the level of post-training BOLD activity registered in the SMA ipsilateral to the training limb (Perez et al., 2007a).

In older adults, it has been proposed that the microstructural integrity of projections that arise from SMA, and which terminate upon M1, may account for interindividual variations in the extent of motor learning. In a unimanual sequential finger tapping task, Schulz and colleagues reported that estimates of FA obtained for streamlines passing between the M1 contralateral to movement and both SMAs, was correlated positively with an index of motor skill acquisition (Schulz et al., 2014; for a description of the behavioural measure, see §5.3). There was no evidence of similar such relationships in a sample of young adults. It has been suggested that decreased levels of functional connectivity within the SMA network (which is comprised of such nodes as the cingulate, parietal, and prefrontal cortices, as well as the pre- and post-central gyri), may constitute an early correlate of (age-related) motor decline (Lammers et al., 2020). It has, for example, been demonstrated that age-related decreases in maximum grip strength – for which lifespan variations are indicative of incipient changes in brain health (for a review, see Carson, 2018), are associated with lower levels of resting state connectivity between SMA and a motor cortex seed (Seidler et al., 2015).

1.5.5 Summary: Other nodes within the cortical motor network

The interhemispheric structural connectivity of frontal motor regions far exceeds that associated with the subdivision of M1 (i.e., M1p) from which the majority of direct corticospinal projections are known to arise (Fling et al., 2013; Ruddy et al., 2017a). Nonetheless, in only a few instances have investigators sought to examine the functional contributions of these regions to CE. Where this

has been the case, an association between the magnitude of the observed behavioural change, and a derived index of brain structure/function, has seldom been observed (*cf.* Ruddy et al., 2017b). As a consequence, very little is known presently of the potential functional contributions of non-primary motor regions to the neural adaptations which mediate CE. Among older adults, it is known that those individuals who show superior performance of already well learned movement skills, tend to exhibit a higher degree of coupling (defined using dynamic causal modelling of regional BOLD activity) along a prefrontal-premotor-M1 axis (e.g., Michely et al., 2018). As an avenue for future research therefore, the possibility that the functional integrity of this axis influences the quality of motor learning in general, and the extent of CE in particular, is worthy of further exploration.

1.6. THALAMOCORTICAL PATHWAYS

1.6.1 THEORETICAL CONTEXT

Of all the white matter tracts that descend from or course within the human brain, the thalamocortical tract is the most susceptible to age-related microstructural decline (Cox et al., 2016). In a lifespan sample of more than 3,500 participants in whom age-related variations in white matter structure were examined across a total of 27 fibre tracts, the level of mean diffusivity (MD) registered in the thalamic radiation was most strongly and negatively associated with age (Cox et al., 2016). Within the motor network, the thalamocortical tract

mediates interactions between such regions as the basal ganglia and M1 via the motor thalamus (McFarland & Haber, 2002; Sommer, 2003), a collection of nuclei that project to all layers of cortex including layer V corticospinal neurons (Hooks et al., 2013). Until recently, the capacity for thalamic afferents in M1 to undergo adaptation in response to motor training (beyond the developmental period) was largely unknown. It has however been demonstrated in rat that following motor skill acquisition, there occurs a marked increase in thalamocortical input to corticospinal neurons projecting to spinal motoneurons that innervate task agonist muscles (e.g., at the level of C8), but not to corticospinal neurons that project to rostral spinal segments (e.g., at the level of C4) which innervate muscles that are ostensibly uninvolved in the learned movement task (Biane et al., 2016). The quantal amplitudes (i.e., the postsynaptic response to release of a single presynaptic vesicle) measured at thalamo-corticospinal synapses (i.e., in layer V of M1) are also elevated selectively, with the largest increases observed in task-relevant subpopulations (Biane et al., 2016). It is recognised increasingly that training-related adaptations in thalamocortical structure (Hasegawa et al., 2020) and function (Biane et al., 2016; Tanaka et al., 2018) may contribute, at least in part, to the processes which underlie motor learning. A similar case has been made in respect of the striatal nuclei with which many motor cortical regions interact via these projections (Cataldi et al., 2021). Conceivably, these same mechanisms may share much in common with those which underpin the expression of CE, and may therefore constitute a basis for age-related variations in its mediation.

1.6.2 STRIATAL AND THALAMIC CONTRIBUTIONS TO MOTOR LEARNING

In the crab-eating macaque, it has been demonstrated that lesions of the ventrolateral thalamic nucleus (*pars oralis*) – which is functionally homologous with the human ventrolateral anterior thalamic nucleus (VLa) (Macchi & Jones, 1997), engender marked deficits in the capacity to relearn a visuomotor handle-pulling exercise (Canavan et al., 1989). These findings are suggestive of a thalamic contribution to motor (re)learning. Although in humans training-related increases in thalamic activation are a remarkably consistent feature of motor practice (for a meta-analysis, see Hardwick et al., 2013), we are aware of only one study in which this region has been examined directly in a CE context. In a variant of the SRTT undertaken with the left limb only, Perez and colleagues reported post-training increases in the level of BOLD activity registered in the right VLa (Perez et al., 2007a). Notably, the magnitude of this activity was correlated positively with the level of absolute improvement attained by the untrained limb (i.e., the decrease in response time from pre- to post-training). A similar relationship was evident in respect of the level of pre-training BOLD activity registered in the ventrolateral posterior thalamic nucleus (VLp), which was also correlated positively with interindividual variations in absolute improvement (Perez et al., 2007a).

While training-related alterations in the states of various motor cortical regions have been studied extensively (see preceding sections), relatively little is known of the di- and mes-encephalic structures with which the thalamic radiations allow them to communicate. One such structure is that of the corpus striatum, which is comprised of a tetrad of nuclei within the basal ganglia: the caudate

nucleus and putamen dorsally, and the nucleus accumbens and olfactory tubercle ventrally. The corpus striatum is the recipient of a vast array of glutamatergic inputs from cortical, limbic, and thalamic afferents, which are integrated by local ensembles of (predominately) GABAergic medium spiny neurons (for reviews, see Kreitzer & Malenka, 2008; Valjent & Gangarossa, 2021). Its role in motor learning has been described previously (Cataldi et al., 2021). Yet, perhaps predictably, nothing is known of its involvement in CE.

Following four-weeks of unimanual finger-to-thumb opposition sequence training undertaken with the left limb only, bilateral alterations in the microstructural integrity of several striatal nuclei have been reported (Reid et al., 2017). These changes include an increase in the FA of streamlines registered for the right caudate nucleus, as well as a decrease in MD (for which larger values are indicative of diminishing microstructure) in the left nucleus accumbens (i.e., ipsilateral to the training limb). In respect of white matter projections, an increase in FA registered for streamlines passing through the right caudate nucleus and right middle frontal gyrus (containing dlPFC) has also been reported (Reid et al., 2017). The functional significance of these structural adaptations has yet to be resolved, i.e., insofar as they concern the degree of improvement realised by the trained or untrained limb. Nonetheless, the mere potential for pathways which mediate (striato)thalamocortical interactions to undergo neuroplastic adaptation, raises the possibility that they may play a role in motor learning. Whether these adaptations extend to the mediation of CE remains to be established.

1.6.3 SUMMARY: THALAMOCORTICAL PATHWAYS

It has been established that unimanual training engenders bilateral elevations in striatothalamic activity (Perez et al., 2007a). These changes are accompanied by bilateral alterations in the microstructure of several striatal nuclei (Reid et al., 2017). In the case of functional imaging measures, levels of pre- and post-training BOLD activity registered within the VLp and VLa respectively (i.e., contralateral to the training limb), are known to scale with interindividual variations in absolute improvement following unimanual SRTT training (Perez et al., 2007a). This finding alone represents a rare instance in which a (statistical) association between measures of functional brain activity and an index of CE has been reported. Although its functional contribution to CE remains to be investigated further, the observation that the thalamic radiation is the white matter tract most susceptible to age-related decline (Cox et al., 2016) should be sufficient to prompt interest in whether there are age-dependent variations in the degree to which it mediates the processes which engender CE. An association between estimates of white matter microstructure derived for fibres constituting the thalamic radiation and age-related diminutions in cognitive performance has already been established (Cox et al., 2019). As the brain networks engaged in many cognitive tasks overlap with those recruited in the course of motor training (for a review, see Cremen & Carson, 2017), there is thus a further reason to pursue this line of enquiry.

1.7 SUMMARY AND CONCLUSIONS

In this narrative review, we discussed several pathways with the potential to mediate the neural adaptations that underpin the expression of CE. An emphasis upon the degree to which these structures, and the networks in which they are imbedded, are the subject of age-related neurodegeneration was provided throughout. Based on these analyses, the supposition that CE is mediated by ipsilateral corticospinal pathways cannot be sustained. The functional contributions of corticoreticulospinal projections, including those which terminate ipsilateral to their origin, remain however to be determined. With respect to the supposition that unimanual training engenders 'motor overflow' to the ipsilateral hemisphere that can be detected via kinetic, EMG, or MEP recordings obtained from the untrained limb, and which serves ultimately to enhance its functional capability, the conclusions we draw are less equivocal. In particular, there exists no evidence to suggest that CE (whether quantified in terms of absolute/relative improvement or interlimb transfer) is instrumentally related to alterations in the excitability of corticospinal projections to the untrained limb (Colomer-Poveda et al., 2019b; Manca et al., 2018). In respect of the conjecture that the neural mechanisms which mediate CE may change with age, it should be noted that interindividual variations in CST microstructure (Cox et al., 2016), as well as several experimental indices of 'motor overflow' (Dickins et al., 2015a; Reissig et al., 2015), are affected only negligibly by advancing age. Taken together, these findings would suggest that changes in the states of corticospinal projections that

terminate upon motor pools that innervate the untrained limb, are unlikely to account for lifespan variations in CE, or in the mechanisms which mediate it.

It is widely held that CE is mediated by interhemispheric interactions within the cortical motor network. In this respect, a disproportionate focus has been placed upon bilateral interactions between the primary motor cortices. Although the expression of the interlimb effect is contingent upon the output of corticospinal neurons that reside primarily in the caudal sector of M1, it should be emphasised that cells within this region receive only sparse input from homologous and heterologous areas in the opposite hemisphere (Ruddy et al., 2017a). It is perhaps unsurprising therefore that adaptations expressed within the 'untrained' M1 – when assessed with TMS-based approaches, are not instrumentally related to CE (*cf.* Hortobagyi et al., 2011). Indeed, few TMS-based measures are modulated reliably relative to pre-training levels; the cSP and SICI are notable exceptions. As with measures of CSE and motor irradiation, lifespan variations in the magnitudes of such TMS-based measures are also rarely observed. While one cannot exclude the possibility that CE is mediated by circuits within M1 which cannot be assayed using current experimental techniques, there are no direct indications that this is the case.

It is recognised increasingly that while the caudal sector of M1 may represent the principal conduit through which CE is expressed, the relevant adaptations are most likely instantiated in other brain centres (Ruddy & Carson, 2013; Ruddy et al., 2017b). It has been reported that the microstructural integrity of transcallosal projections that course between non-primary motor regions (e.g., PMd, SMA) exceeds that of all other nodes within the cortical motor network

(Ruddy et al., 2017a). In relation to projections that arise directly from SMA, interindividual variations in tissue microstructure appear to be associated with measures of interlimb transfer (Ruddy et al., 2017b). Training-related elevations in SMA BOLD activity have also been shown to scale with other measures of CE (Perez et al., 2007a). It has been suggested that in older adults, the successful acquisition and optimal execution of unimanual skills is associated with an increased influence of prefrontal and premotor regions (e.g., Michely et al., 2018). The possibility that there are similar age-related changes in the mediation of CE awaits experimental scrutiny. Thalamocortical projections exhibit steeper age-related declines in microstructural organisation than transcallosal fibres (Cox et al., 2016). It is likewise the case however, that the functional implications of these changes for motor learning in general, and with respect to CE in particular, have yet to be investigated thoroughly.

In order to advance the therapeutic potential of CE training in older persons, it is perhaps obvious that further research is warranted to examine the effects of age on the magnitude (and indeed expression) of the behavioural effect. This is a point that cannot be understated. Although the clinical applications of CE-based interventions have been promoted for some time, relatively few studies have engaged those participants (i.e., older adults) for whom these interventions are likely to confer the greatest therapeutic benefits. A further matter is that of mechanism. While a focus upon adaptations mediated by changes in the state of circuits in M1 was once sufficiently motivated (and indeed these could be studied conveniently in TMS equipped laboratories), this is arguably no longer the case. Consideration must be given to the role of non-primary motor regions (e.g., PMd,

SMA) and indeed to motor networks considered as functional entities that are subject to coherent patterns of neural degeneration (Seeley et al., 2009).

Chapter 2

Induction of Interhemispheric Facilitation by Short Bursts of Transcranial Alternating Current Stimulation

2.1 INTRODUCTION

In their seminal work published 60 years ago, Asanuma and Okuda (1962) demonstrated that the application of electrical stimuli to cat pericruciate cortex (encompassing the feline analogue of human primary motor cortex (M1)) engendered excitatory responses to stimuli applied homotopically to the opposite hemisphere. These effects were abolished, and in some cases, inhibition was observed, as the intensity of the initial stimulus was increased. In humans, excitatory interactions between the two cerebral hemispheres may be probed, at least in principle, by dual-coil transcranial magnetic stimulation (TMS). The essence of the technique is that a subthreshold conditioning stimulus (CS) (i.e., below the intensity required to evoke a volley that descends to the spinal cord) is delivered over one M1, followed shortly by a suprathreshold test stimulus (TS) applied over the opposite M1. In the prototypical variant, an increase in the

amplitude of the motor-evoked potential (MEP) obtained in response to the TS, is observed when the CS has been applied 3-6 ms previously (Bäumer et al., 2006; Ferbert et al., 1992; Hanajima et al., 2001). This interval accords with the latencies of transcallosal volleys (Ni et al., 2020). This effect – for which the term "interhemispheric facilitation" (IHF) was coined, is however impossible to elicit in many individuals. Even in those in whom it can be obtained, the expression of the effect is remarkably inconsistent (Ferbert et al., 1992). Although its reliability may be enhanced by titrating carefully the CS intensity (Baumer et al., 2006; Hanajima et al., 2001) or inter-stimulus interval (ISI) (Ni et al., 2020), the elicitation of IHF remains nonetheless challenging.

It has been suggested that the difficulty in obtaining IHF may be due to the distributed effects of the transcallosal volley evoked by the CS. Although callosal fibres are generally glutamatergic (Innocenti, 1986; Werhahn et al., 1999) and exert an excitatory effect on their immediate synaptic targets, a significant proportion of these fibres terminate upon inhibitory interneurons and pyramidal cells with axon collaterals that synapse on GABAergic neurons (Carr & Sesack, 1998; Conti & Manzoni, 1994; Karayannis et al., 2007). When low intensity conditioning stimulation is used, and the effects of the transcallosal volley are sufficiently focal, IHF may be obtained. As the intensity of the CS is increased however, additional activation of inhibitory circuits may be sufficient to mask any facilitation that has also been invoked (Bäumer et al., 2006; Ferbert et al., 1992).

Unlike TMS, which engenders a voltage gradient well in excess of the 100-200 V m^{-1} required to elicit MEPs (Alekseichuk et al., 2019), the application of transcranial alternating current stimulation (tACS) (i.e., 1-2 mA peak-to-peak) –

based on evidence derived from intracranial recordings (Krause et al., 2019; Lafon et al., 2017; Opitz et al., 2016), gives rise to maximal field strengths in the order of 0.2-0.8 V m^{-1}. While these values fall below the thresholds necessary to activate voltage-gated ion channels within the neuronal membrane (Jackson et al., 2016), they may be nonetheless sufficient to alter the probability that action potentials will be invoked by physiological inputs (Schwab et al., 2019). Consistent with this supposition, we have demonstrated that a short burst of 140 Hz tACS (~0.5 s; 1 mA peak-to-peak) can act as either the first or second element of paired associative stimulation protocols which induce changes in corticospinal tract (CST) excitability (Carson et al., 2021; McNickle & Carson, 2015). Although this form of tACS alters the state of neural circuits in the opposite hemisphere (Carson et al., 2021), it is not known whether the magnitude and focality of the effect lies within the "narrow window" (Bäumer et al., 2006) necessary for the invocation of IHF.

In the present study, we examined whether tACS delivered via electrodes placed over M1, increased the amplitudes of MEPs elicited 6 ms later (i.e., at an ISI shown previously to engender IHF) by suprathreshold TMS applied to the opposite M1. In separate conditions, the duration of the conditioning stimulation was varied between 6-500 ms. In addition to 140 Hz tACS (Carson et al., 2021; McNickle & Carson, 2015), we included conditions in which 670 Hz tACS was applied. The intent was to mimic the discharge frequencies of corticospinal neurons (Di Lazzaro et al., 2012) which arise from magnetic (conditioning) stimuli. As the effects of tACS may be mediated by stochastic resonance, rather

than entrainment (Fertonani & Miniussi, 2017), we also employed high-frequency (i.e., 100-640 Hz) transcranial random-noise stimulation (tRNS).

In all instances, the coil used to generate the magnetic TS was oriented to induce current flow in the anterior-to-posterior (AP) direction. In a study that examined the relationship between the latencies of MEPs obtained with various coil orientations and fMRI-derived measures of functional connectivity seeded on the M1 hotspot, Volz et al. (2015b) concluded that MEPs elicited by AP TMS are more likely to reflect the contributions of short-latency cortico-cortical inputs from premotor regions (including those relayed by interhemispheric projections) compared to those obtained with other coil orientations. We hypothesised that tACS applied to right M1 would elevate (relative to a "TS only" control condition) the amplitudes of MEPs elicited by suprathreshold TMS TS applied 6 ms later to the opposite (left) M1.

2.2 METHODS

2.2.1 PARTICIPANTS

Thirty neurologically healthy volunteers (17 females, aged 18-34 years, mean age = 21.9 years, SD = 4.88 years) each participated in a single experiment. None reported a history of neurological/psychiatric disease, or any medication use for which TMS or tACS/tRNS were contraindicated (Antal et al., 2017; Rossi et al., 2011; Rossi et al., 2009). All participants were right-handed as per the Edinburgh Handedness Inventory (Oldfield, 1971) and provided written informed consent to procedures approved by the Trinity College Dublin School of Psychology Research Ethics Committee. Apart from study pre-registration, all testing was conducted in accordance with the Declaration of Helsinki.

2.2.2 APPARATUS AND PROCEDURES

2.2.2.1 Electromyography

Electromyographic (EMG) signals were recorded bilaterally from flexor carpi radialis (FCR) and extensor carpi radialis longus (ECR), using pairs of Ag/AgCl electrodes (Cleartrace 1700, ConMed, Haverhill, MA, USA). A reference electrode was placed on the lateral epicondyle of the right humerus. The skin overlaying the electrode sites was prepared with a topical abrasive (Nuprep, Weaver & Co., Aurora, CO, USA) and sanitised with a topical antiseptic (70% isopropanol). EMG signals were amplified (gain = 1000), band-pass filtered (30-1000 Hz), and notch filtered (50 Hz) using a Biopac system (NL844 & NL131,

Biopac Systems Inc., Santa Barbara, CA, USA), digitized at a sampling rate of 10 kHz (Power1401, CED, Cambridge, UK), and recorded with Signal software (Signal 7.01, CED, Cambridge, UK).

2.2.2.2 Transcranial Magnetic Stimulation

Monophasic magnetic stimuli were delivered via a Magstim 200 stimulator (Magstim Company Ltd., Whitland, UK) equipped with a 55 mm mid-diameter figure-of-eight coil. The optimal position ("hotspot") to elicit a MEP in the left and right FCR muscles was first determined. The procedure commenced by moving the coil in ~0.5 cm increments about a craniometrically defined location (2 x 6 cm anterolateral to the vertex). Thereafter, the hotspot was defined as the position over the scalp from which MEPs were elicited most reliably in the target muscle (FCR) of the contralateral limb. The axis of intersection between the two loops was oriented at 45° to the sagittal plane to induce AP current flow across the motor strips. To demarcate the optimal position, an outline of the anterior bifurcation of the coil was sketched upon the participant's head using a felt-tip marker. The FCR hotspot of left M1 (i.e., the area of scalp over which the test coil was positioned) was registered in three-dimensional space using a TMS coil navigation system (NDI TMS Manager, Northern Digital, Waterloo, Canada). The FCR hotspot of right M1 was delineated for the purposes of positioning the tACS/tRNS electrodes (§2.2.2.3). The resting motor threshold (rMT) was obtained using a maximum likelihood protocol – namely parameter estimation by sequential testing (Awiszus & Borckardt, 2011), to determine the minimum

stimulation intensity required to elicit a MEP with a peak-to-peak amplitude of 50 μV in the right FCR muscle (Rossi et al., 2009), i.e., in left M1 only.

2.2.2.3 Transcranial Alternating Current and Random Noise Stimulation

tACS and tRNS was delivered by a battery-driven stimulator (A-M Systems Model 2200, Carlsborg, WA, USA) via a concentric-ring electrode montage (Figure 2.1) (NeuroConn, Ilmenau, Germany). A disc-shaped 'target' electrode (radius = 1.25 cm, area = 4.91 cm^2) was placed radially over the FCR hotspot of right M1 and encircled equidistantly by a ring-shaped (annular) 'return' electrode (inner radius = 3.50 cm, outer radius = 4.25 cm, area = 18.26 cm^2). Each electrode was fixed tangentially to the scalp using an electroconductive paste (Ten20, Weaver & Co., Aurora, CO, USA). The electrode connectors were positioned posteriorly to maximize focal stimulation of M1 (Saturnino et al., 2015). Electrode impedance was monitored and maintained below 5 kΩ.

In the tACS conditions, the alternating waveforms were bipolar sinusoids with fixed amperage (1 mA peak-to-peak, i.e., ± 0.5 mA). The frequency (140 Hz or 670 Hz) was varied across conditions (see below). In the tRNS conditions, a random level of current – drawn from a Gaussian distribution with zero mean and a variance for which ~99.7% of values were between ± 0.5 mA, was generated for each sample. The random waveforms were composed of band-limited (100-640 Hz) white Gaussian noise with a constant power spectral density (Terney et al., 2008). The maximum current densities were 0.20 mA cm^{-2} and 0.05 mA cm^{-2} for the target and return electrodes respectively.

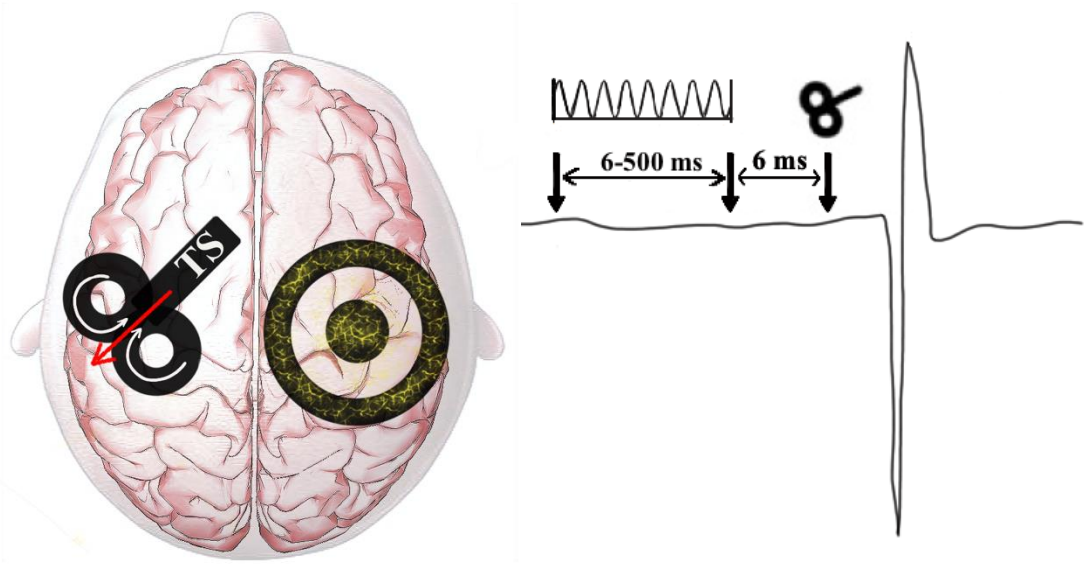


Figure 2.1: tACS/tRNS-TMS montage and time course of a single trial. *Left*: Superior view of the head illustrating the tACS/tRNS-TMS montage. The white arrows on the TMS coil (left of head) illustrate the direction of current flow through the coil, while the red arrow denotes the direction of the induced cortical eddy current (i.e., in the anterior-to-posterior direction). The tACS/tRNS montage (right of head) consists of a central disc-shaped electrode encircled by a peripheral annular electrode. Neither the tACS/tRNS electrodes nor TMS coil are drawn to scale. *Right*: Time course of a single tACS/tRNS-TMS trial and corresponding MEP trace. The tACS/tRNS waveform, which had a duration in the range 6-500 ms, was succeeded by a suprathreshold TMS pulse (120% rMT) delivered 6 ms following the termination of tACS/tRNS. The time intervals are not drawn to scale.

2.2.3 GENERAL PROCEDURES

Participants were seated in a comfortable chair with their upper limbs supported and stabilized by vacuum cushions (Olympic Vac-Pac, Olympic Medical, Seattle, WA, USA), the forearms in mid-pronation, and the elbows semi-flexed (100-120°). To ensure that participants could not anticipate the onset of stimulation, the interval between successive trials was jittered by 50% (8 ± 4 s). In each trial, tACS/tRNS was delivered to the FCR hotspot of right M1 and succeeded 6 ms later by suprathreshold TMS delivered at 120% rMT to the FCR hotspot of left M1. This ISI (i.e., 6 ms) has been shown previously to elicit IHF (Baumer et al., 2006; Hanajima et al., 2001).

For each of the three types of stimulation (140 Hz tACS, 670 Hz tACS, 100-640 Hz tRNS), the duration was altered across conditions in the following manner: 140 Hz tACS: 30 ms, 100 ms, 500 ms; 670 Hz tACS and 100-640 Hz tRNS: 6 ms, 12 ms, 100 ms, 500 ms. The study thus comprised 11 experimental (i.e., tACS/tRNS + TMS) conditions and a control condition in which TMS (always at 120% rMT) was delivered in the absence of preceding tACS/tRNS. There were three blocks, each separated by 5 min rest intervals, in which 8 trials from each experimental condition and 16 trials of the control condition were delivered in pseudorandom order, i.e., 104 trials per block. The order in which the conditions were presented within a block differed across blocks and participants.

2.2.4 DATA ANALYSIS

The root mean square (rms) of the background EMG recorded in right FCR and right ECR was calculated for a window 506-6 ms prior to tACS/tRNS onset. In seeking to eliminate instances in which elevated excitability of the spinal motoneuron pool may have augmented MEP amplitudes, we implemented a multi-step procedure to exclude trials characterised by inflated levels of background EMG. In the first instance, we excluded all trials for which any corresponding rms value (i.e., in right FCR or right ECR) exceeded 2.5 μV. Thereafter, we calculated, for each participant, the quartiles of the remaining rms values separately for each muscle. In circumstances in which an individual rms value was above the upper whisker of the distribution (in this instance set to the third quartile plus 1.5 times the interquartile range), the corresponding MEP was disregarded. Overall, 86.4% of responses were retained. The trimmed means and winsorized standard deviations (trimming intervals = 0.2) of the remaining rms values were 1.34 ± 0.11 μV in right FCR and 1.36 ± 0.21 μV in right ECR.

We also sought to exclude participants for whom the level of background EMG in the retained recordings was correlated to an unacceptable extent with the corresponding MEP amplitude. To this end, we first determined that for each participant, the MEP amplitudes (in right FCR only) and rms values (in right FCR and right ECR) were equivalent between blocks. This was demonstrated by means of a robust two one-sided t-test (rTOST) procedure (all *p*s < 0.05) with an epsilon value of 0.72 (Robinson, 2016). Thereafter, we performed rank-based correlations (based on Kendall's tau) between all MEP amplitudes and the corresponding rms values in right FCR and right ECR (i.e., after collapsing across blocks). Those

participants in whom correlation coefficients of $\tau > 0.12$ were observed in either muscle, i.e., where the magnitude of the correlation coefficient was considered "small" or larger (Lovakov & Agadullina, 2021), were excluded from analysis. Overall, 26/30 datasets were retained.

In the remaining participants, the geometric mean (i.e., the antilog of the lognormal mean) of the retained peak-to-peak MEP amplitudes was calculated separately for each analysis cell (e.g., block 1, 140 Hz tACS). This step was only performed in circumstances in which a minimum of five responses in a given analysis cell survived the initial screening procedures, to ensure sufficient within-session reliability of MEP amplitudes (Cavaleri et al., 2017). In circumstances in which it was not possible to assign a value to a cell (e.g., due to an inadequate number of MEPs), its value was approximated using a missForest imputation procedure (Stekhoven & Buhlmann, 2012). Overall, imputation was applied to 5.7% (53/936) of cells.

It is recognised widely (e.g., Abelson, 2012) that in repeated measures designs, inferential tests which rely upon standard normal theory often fail to satisfy several key assumptions, including normality of the sample distribution. When assessed using the Shapiro-Wilk test, 73% (24/33) of cells failed to satisfy the conventional criterion of asymptotic normality ($p < 0.05$). Accordingly, we employed robust non-parametric methods, which are known to minimise both the potential influence of outliers and deviations from normality, as the basis of our inferential analyses. In the first instance, a robust two-factor repeated measures model based on the Welch-James Statistic was computed, in which block (levels = 1, 2, 3) and condition (11 tACS/tRNS-TMS conditions, 1 TMS only) were fixed

effects, using the welchADF package in R (Villacorta, 2017). Based on this model, planned contrasts were undertaken between the trimmed mean (trimming interval = 0.2) MEP amplitudes associated with each tACS/tRNS-TMS condition and that of control (i.e., TMS only). To assist in interpretation, the robust variant of Cohen's *d* (d_R) and the corresponding bootstrapped 95% confidence intervals (2,000 replicates) are also presented for each contrast (Table 2.3.1) (Algina et al., 2005).

In seeking to control for the multiplicity (n = 11) of contrasts, Benjamini-Hochberg false discovery rates (FDR) (Benjamini & Hochberg, 1995) were calculated (Table 2.1). This approach entails ordering a set of p-values in ascending magnitude (*p(min)*… *p(max)*) and adjusting them based on the formula p_{FDR} (which is also known as the "q-value") = $Q\left(\frac{i}{m}\right)$ where i = the rank of the *mth* p-value, m = the total number of p-values, and Q = 0.05 (the acceptable false discovery rate). It is a uniformly more powerful approach than conventional methods that seek to control the family-wise error rate (e.g., Bonferroni corrections). A key advantage of the FDR approach is that the adjusted estimate can also be given a Bayesian interpretation. Specifically, it can be viewed as the propensity for a claim that an effect (i.e., a "non-null" finding) is present, to be wrong (Murray & Blume, 2020). More specifically, whereas by convention the frequentist p-value is interpreted as P(data | H_0), the Bayesian "q-value" is simply the opposite, i.e., P(H_0 | data). It is regarded as both a strength and weakness of the Bayesian approach that each person can have their own sense of how such propensities should be interpreted, i.e., there is no universally accepted threshold

beyond which a propensity is considered “significant”. Ultimately therefore it is for the reader to decide how to view the evidence that is reported.

2.3 RESULTS

2.3.1 INTERHEMISPHERIC FACILITATION INDUCED BY SHORT BURSTS OF 140 HZ TRANSCRANIAL ALTERNATING CURRENT STIMULATION

The trimmed means of the peak-to-peak amplitudes obtained for MEPs elicited 6 ms following the termination of 30 ms of 140 Hz tACS delivered over the opposite M1 were greater (WelchT (1, 15) = 9.03, p = 0.009, d_R = 0.56) than those recorded in the control (TMS only) condition (Table 2.1, Figure 2.2). The FDR propensity that this effect is mistaken was estimated to be 10.7% (Table 2.1). In Figure 2.3, the magnitudes of the differences between the MEP amplitudes exhibited in the 30 ms 140 Hz tACS condition, and in the control condition, are shown for the 26 participants included in the analyses. The two other 140 Hz tACS contrasts (control vs. 100 ms 140 Hz tACS, and control vs. 140 Hz tACS 500 ms) failed to attain conventional levels of statistical significance (Table 2.1).

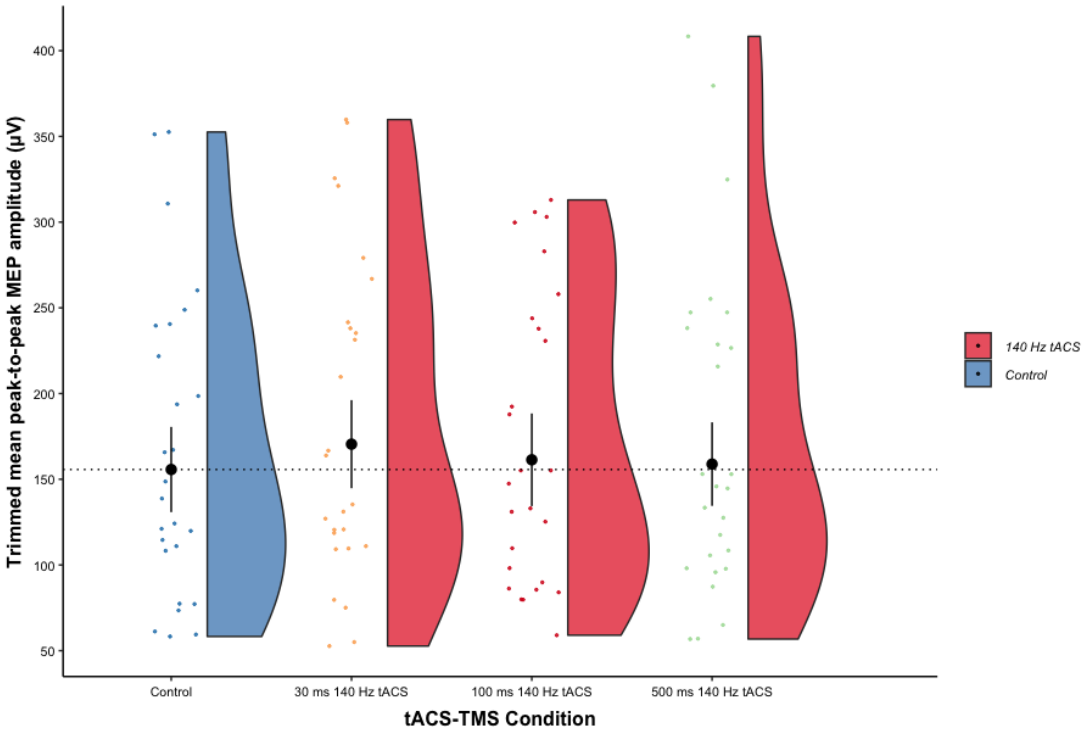


Figure 2.2: Raincloud plot illustrating trimmed mean peak-to-peak MEP amplitudes in the 140 Hz tACS conditions. The filled black circles denote trimmed mean MEP amplitudes (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals (calculated across participants within each condition). Individual data points are also plotted. The half violin plots illustrate the distributions of data points in each condition. The dashed horizontal line denotes the trimmed mean MEP amplitude of the control (i.e., TMS only) condition.

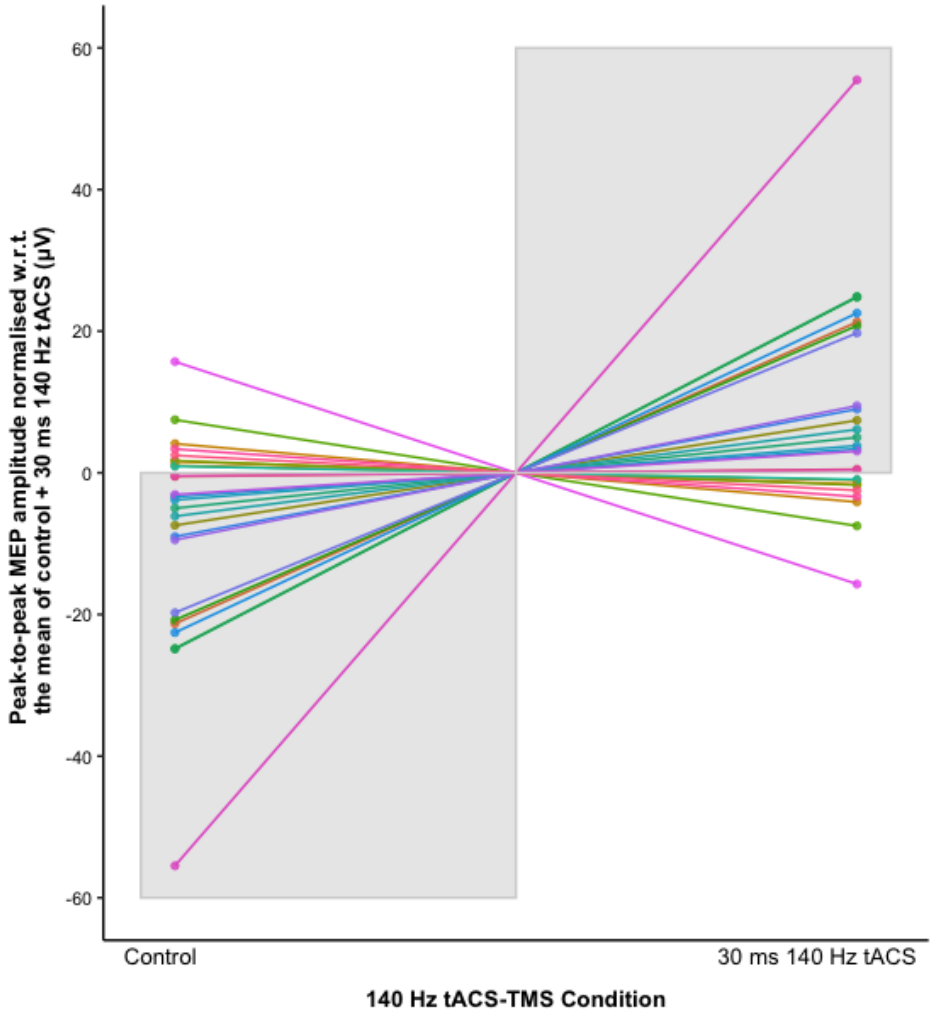


Figure 2.3: Line plots illustrating the difference in MEP amplitude between the control and 30 ms 140 Hz tACS conditions in individual participants. Each data point denotes the geometric mean peak-to-peak MEP amplitude in each condition normalised with respect to the mean of the control and 30 ms 140 Hz tACS conditions. Individuals whose lines pass through the grey quadrants are those who exhibited a larger MEP amplitude in the 30 ms 140 Hz tACS condition relative to control. By contrast, those participants whose lines pass through the white quadrants exhibited a smaller MEP amplitude in the 30 ms 140 Hz tACS condition relative to control.

2.3.2 NO EVIDENCE OF INTERHEMISPHERIC FACILITATION INDUCED BY SHORT BURSTS OF 670 HZ TRANSCRANIAL ALTERNATING CURRENT STIMULATION

The trimmed means of the peak-to-peak MEP amplitudes elicited by TMS 6 ms following the termination of 6 ms, 12 ms, 100 ms, and 500 ms of 670 Hz tACS delivered over the opposite M1, did not differ from those elicited in the control (TMS only) condition (Figure 2.4, Table 2.1).

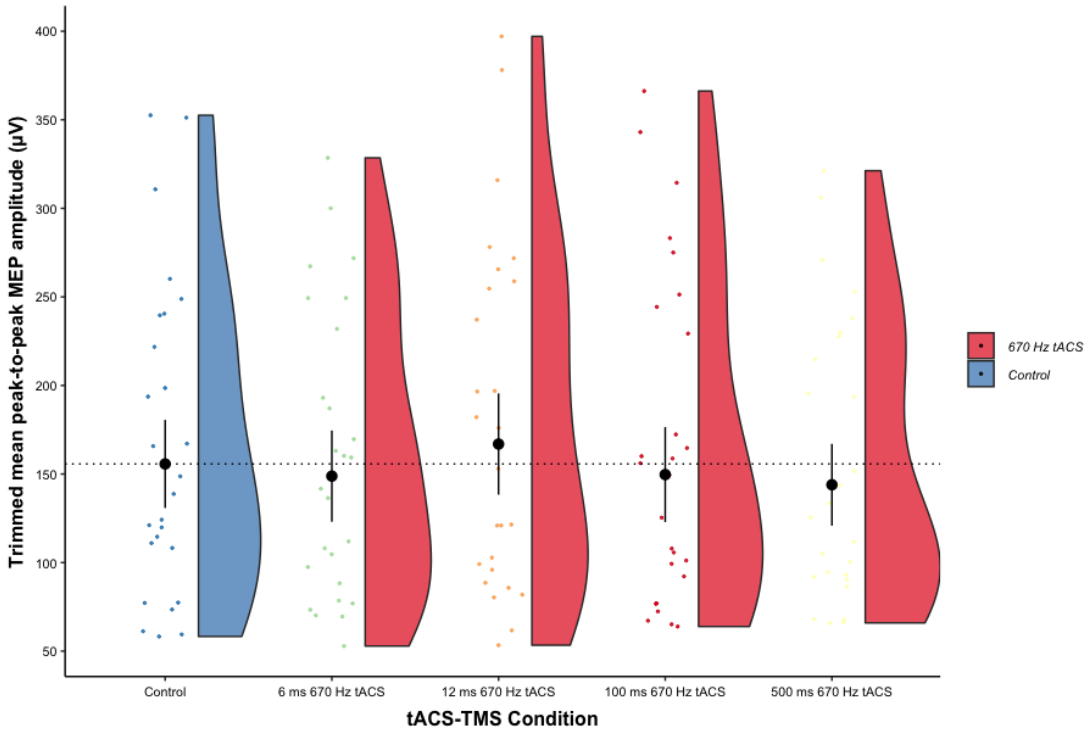


Figure 2.4: Raincloud plot illustrating trimmed mean peak-to-peak MEP amplitudes in the 670 Hz tACS conditions. The filled black circles denote trimmed mean MEP amplitudes (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals (calculated across participants within each condition). Individual data points are also plotted. The half violin plots illustrate the distributions of data points in each

condition. The dashed horizontal line denotes the trimmed mean MEP amplitude of the control (i.e., TMS only) condition.

2.3.3 No evidence of interhemispheric facilitation induced by short bursts of 100-640 Hz transcranial random-noise stimulation

The trimmed means of the peak-to-peak MEP amplitudes elicited by TMS 6 ms following the termination of 6 ms, 12 ms, 100 ms, and 500 ms of 100-640 Hz tRNS delivered over the opposite M1, did not differ from those elicited in the control (TMS only) condition (Figure 2.5, Table 2.1).

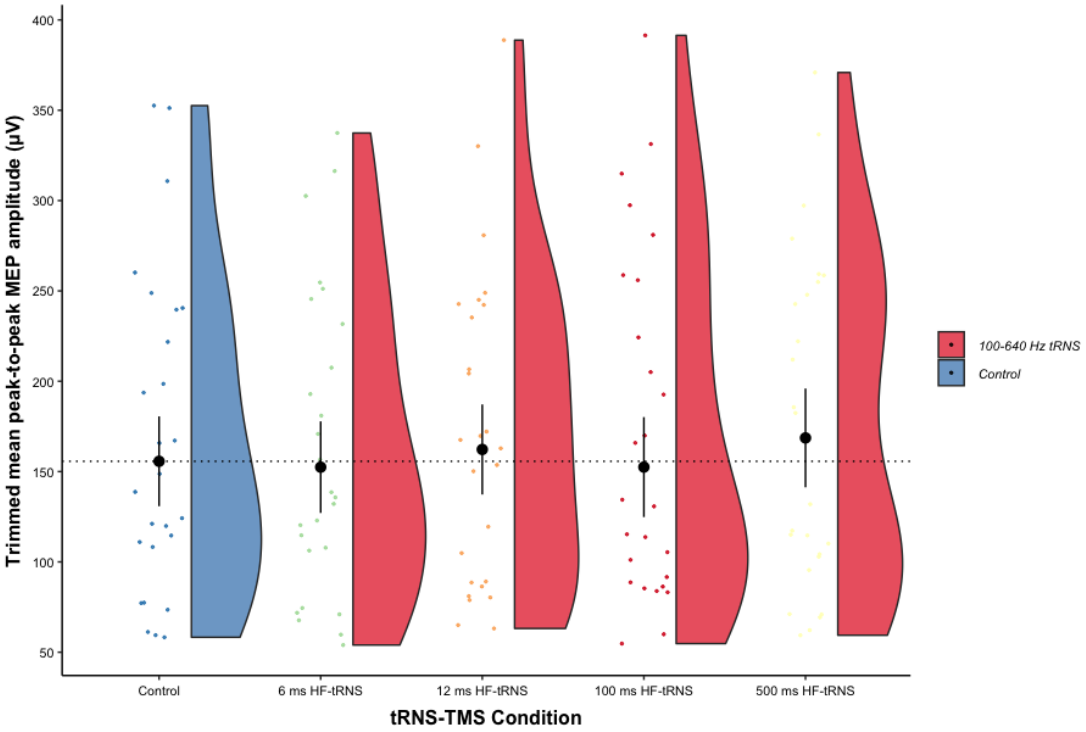


Figure 2.5: Raincloud plot illustrating trimmed mean peak-to-peak MEP amplitudes in the 100-640 Hz tRNS conditions. The filled black circles denote trimmed mean MEP amplitudes (trimming interval = 0.2). The error bars

represent the corresponding 95% confidence intervals (calculated across participants within each condition). Individual data points are also plotted. The half violin plots illustrate the distributions of data points in each condition. The dashed horizontal line denotes the trimmed mean MEP amplitude of the control (i.e., TMS only) condition. Note that HF-tRNS = high-frequency (100-640 Hz) transcranial random-noise stimulation.

Table 2.1.

Summary of pairwise comparisons between the trimmed mean MEP amplitudes recorded in each experimental condition (i.e., tACS/tRNS preceding TMS) and those of the control condition (i.e., TMS only).

Frequency	Duration	ppMEP	WelchT	SD_w	FDR	d_R (95% CI)
140 Hz	30 ms	167.64	9.03	65.44	0.107	0.56 (0.21, 0.98)
(tACS)	100 ms	156.29	3.88	68.89	0.406	0.20 (-0.09, 0.43)
	500 ms	151.81	0.08	67.21	0.932	0.06 (-0.31, 0.62)
670 Hz	6 ms	145.32	1.05	62.67	0.552	0.15 (-0.12, 0.47)
(tACS)	12 ms	158.05	2.28	72.70	0.455	0.23 (-0.02, 0.57)
	100 ms	144.67	0.71	63.36	0.619	0.15 (-0.19, 0.55)
	500 ms	142.82	1.07	67.44	0.636	0.19 (-0.15, 0.64)
100-640 Hz	6 ms	151.23	0.14	64.13	0.953	0.05 (-0.22, 0.36)
(tRNS)	12 ms	160.10	2.92	67.98	0.432	0.30 (-0.05, 0.70)
	100 ms	149.82	0.01	74.29	0.960	0.01 (-0.37, 0.21)
	500 ms	158.00	1.71	69.26	0.506	0.27 (-0.14, 0.74)
Control	-	150.30		64.56	-	-

ppMEP = trimmed mean peak-to-peak MEP amplitude (μV); SD_w = Winsorized standard deviation (μV); FDR = estimate derived using the Benjamini-Hochberg false discovery rate procedure; d_R = robust Cohen's *d;* the degrees of freedom were 1 (numerator) and 15 (denominator) for each contrast.

2.4 DISCUSSION

Conditioning 30 ms duration bursts of 140 Hz tACS applied unilaterally to M1, may potentiate the amplitudes of MEPs elicited 6 ms later by "test" TMS delivered over the opposite M1. The extent of this IHF (~12% increase relative to TMS only) was substantially lower than the 50% reported by Ni et al. (2020) for a traditional protocol in which (~60% rMT) conditioning TMS was delivered (5 ms) prior to a (posterior-to-anterior (PA) current flow-inducing) TS. It was also lower than values in the range 20-24% obtained by Baumer et al. (2006), using a CS intensity of 80% active motor threshold (aMT) and a TS (ISI = 6 or 8 ms) that induced AP current flow. Notably however, the potentiating effect of 30 ms 140 Hz tACS was larger than that seen by Bäumer et al. (< 10%) when they used a (weaker) CS intensity of 60% aMT. In these previous investigations, no steps were taken to compensate for the positive skewness that can be a characteristic of unconditioned MEP amplitudes, and of the ratios used to express conditioned MEP response amplitudes. In the present study, MEP amplitudes were log transformed when generating measures of central tendency (i.e., the geometric mean) for each analysis cell. This may account, in part, for the lower IHF estimates that were obtained. Alternatively, it may simply be the case that the physiological effects of 1 mA 140 Hz tACS are weaker than those induced by ~60% rMT or 80% aMT TMS.

It is recognised increasingly that the effects of tACS on the states of motor cortical circuits may be frequency dependent. With respect to a range (≤ 75 Hz) that encompasses both the β and γ bands (i.e., those that have been studied most

extensively), there is little evidence that motor potentials evoked by TMS are altered reliably either during or following the termination of (≤ 75 Hz) tACS (Antal et al., 2008; Bologna et al., 2019; Guerra et al., 2019; Nowak et al., 2017). If, however, tACS is delivered at frequencies of 140 Hz (Inukai et al., 2016; Moliadze et al., 2010), 250 Hz (Moliadze et al., 2010), or 333 Hz (Guerra et al., 2020), but not at 80 Hz (Moliadze et al., 2010) or 667 Hz (Guerra et al., 2020), the amplitudes of MEPs elicited by TMS applied over M1 are potentiated while alternating current passes through this brain region.

The precise means by which a restricted range of tACS frequencies (i.e., 140 Hz, 250 Hz and 333 Hz) modulates motor cortical output, whereas lower and higher frequencies do not, remains to be resolved. One possibility raised with respect to 140 Hz tACS in particular (Moliadze et al., 2010), is that the exogenous current interacts with sharp wave ripple complexes of similar frequency that are observed characteristically in (para)hippocampal regions (Buzsaki et al., 1992; O'Keefe & Nadel, 1978). These complexes, which have durations (~50-150 ms) similar to those of the tACS applied in the present study (Buzsaki et al., 1983; Takagi, 2021), are held to engender selective activation of neocortical areas with presumed roles in memory formation (Logothetis et al., 2012; Todorova & Zugaro, 2020). Although tACS is most frequently directed towards superficial regions of cortex, its effects are not necessarily so confined. Indeed, it has been demonstrated that 1 mA tACS may engender voltage gradients as high as 0.20 V m^{-1} in the parahippocampi and amygdalae of human volunteers (Louviot et al., 2022). There is not however any evidence of a temporal association between the occurrence of ripple range discharges in mediotemporal areas (registered by

means of intracranial recordings in humans) and corresponding changes in ripple band power detected in M1 (Vaz et al., 2019).

An alternative proposal is that (> 100 Hz) tACS may potentiate thalamocortical output to M1 by downregulating the firing rates of neurons in the subthalamic nucleus (STN). In patients with Parkinson's disease, it is known that deep brain stimulation (DBS) applied at frequencies > 100 Hz reduces the firing rates of STN neurons (Meissner et al., 2005). As decreases in STN activity should engender decreased facilitation of pallido- and nigro-thalamic afferents, the inhibitory influence that these afferents exert on thalamocortical output should consequently fall. Although the evidence base is rather scant, it has been demonstrated that the electric field induced in STN by 1 mA tACS (~0.08 V m^{-1}) may exceed the background activity recorded in this region by several orders of magnitude (Ruhnau et al., 2018). It is also notable that the inhibitory effects observed in the pars reticularis of the substantia nigra following high-frequency (130 Hz) STN DBS, are markedly greater when low-intensity (0.02-0.08 mA) rather than high-intensity (0.10-0.24 mA) DBS is applied (Maurice et al., 2003). In principle therefore, short bursts of 140 Hz tACS may increase the amplitudes of MEPs elicited from the contralateral M1 by decreasing the probability of STN firing, thereby facilitating thalamocortical drive to M1.

With respect to high-frequency tACS, Guerra and colleagues reported that 667 Hz tACS with the "target" electrode placed over M1, did not increase the amplitudes of MEPs elicited by TMS when it was delivered above the same brain region (Guerra et al., 2020). In the present study, 670 Hz tACS applied unilaterally over M1 (for 6, 12, 100 or 500 ms) had no discernible effect on MEPs elicited 6

ms later by TMS delivered over the opposite M1. Although various explanations have been offered to account for the absence of an effect of ~670 Hz tACS on MEP amplitudes (e.g., Guerra et al., 2020), a more general consideration is that the high-frequency (> 600 Hz) repetitive discharge in pyramidal neurons that is invoked by magnetic stimulation of M1, differs markedly from physiological discharge frequencies which are approximately 100 impulses/s (Lemon & Kraskov, 2019). The typical firing rate of callosal cells during motor activity is lower again (Beloozerova et al., 2003; Soteropoulos & Baker, 2007). It is not apparent therefore that ~670 Hz tACS exhibits the potential for entrainment of these types of cells, other than at subharmonic frequencies. The assumption underpinning the interpretation of the findings obtained in the present study was that any observed effect of tACS on the state of circuits in the opposite hemisphere, was mediated indirectly through callosal projections that terminate upon cells within the cortical regions to which the TMS was applied. The paucity of effect attributable to 670 Hz tACS accords with the low probability that such stimulation can entrain networks of neurons which, via transcallosal projections, alter the states of circuits in the opposite hemisphere.

It was also the case that tRNS comprising band-limited (100-640 Hz) white Gaussian noise applied for 6, 12, 100 or 500 ms, had no reliable impact on the amplitudes of MEPs elicited 6 ms following the termination of current flow by TMS applied over the opposite M1. Potok et al. (2021) demonstrated that tRNS (100–500 Hz) with a peak-to-baseline amplitude of 2 mA, and the "target" electrode placed either over or adjacent to M1, increased the probability that subthreshold (< rMT) TMS would elicit MEPs when it was delivered above the

same brain region. The size of this unilateral effect (d = 1.28) was roughly twice the contralateral effect obtained for the 30 ms 140 Hz tACS condition in the present study (d = 0.56). When however, the tRNS current used by Potok et al. (2021) was 0.5 mA peak-to-baseline (equivalent to the 1 mA peak-to-peak amplitude used in the present study), there was no reliable effect. It is possible therefore, that the intensity of tRNS we applied was simply insufficient to modify the discharge characteristics of neurons with the potential to influence (via callosal projections) the states of circuits in the opposite hemisphere.

The effects of 140 Hz tACS on the amplitudes of MEPs elicited by TMS applied to the contralateral M1, were present only when tACS was applied for 30 ms but not when it was delivered for 100 or 500 ms. One explanation for this finding is that longer bouts of stimulation (≥ 100 ms) may increase the firing probabilities of inhibitory interneurons, which, when active, mask the focal facilitation expressed by the test MEP. This may be analogous to increasing the CS intensity in a dual-coil TMS paradigm. The rank ordering of effects in the 140 Hz tACS conditions (i.e., 30 ms > 100 ms > 500 ms, see Figure 2.2 and Table 2.1) is consistent with this conjecture.

It has been highlighted previously that the expression of tACS-mediated facilitation may depend upon the phase of the exogenous current and/or that of the rhythm it entrains/augments (Bergmann et al., 2019; Guerra et al., 2016; Liu et al., 2018a). When TMS is applied to M1 during different phases of tACS (1 mA peak-to-peak; 20 Hz) administered to the same brain region, potentiation of the motor potential evoked by TMS may be obtained at phase angles of ~270º (Guerra et al., 2016). If, however, the delivery of TMS is timed to coincide with a phase angle

of 90º, the amplitude of the response may be conversely diminished (Guerra et al., 2016). As the onset of tACS in the present study was timed such that its offset always occurred 6 ms prior to TMS, the phase angle at stimulation offset following 30 ms of 140 Hz tACS (~72º, based on completion of 4.2 cycles) differed from that of both the 100 and 500 ms bursts (0º, based on completion of 14 and 70 cycles respectively). Although it seems unlikely that variations in the phase of the offset alone would be sufficient to account for the variations in effect seen in the present study, in future studies this factor might be more strictly controlled (or manipulated systematically).

There are several limitations associated with the present study. In the first instance, although IHF is elicited most commonly when the test coil is oriented to induce AP current flow across the motor strip (Hanajima et al., 2001), at lower CS intensities the effect may be obtained more readily with PA test stimuli (Bäumer et al., 2006). In recognising that the direct physiological effects of tACS/tRNS are several orders of magnitude weaker than those induced by TMS, there exists a possibility that the tACS-induced IHF-like effect observed in the present study, may be less pronounced when the MEPs are elicited by AP rather than PA stimuli. A second limitation is that we did not examine the effects of 30 ms duration bursts of 670 Hz tACS or 100-640 Hz tRNS. It is therefore unclear if the IHF effect induced by 30 ms 140 Hz tACS was frequency- (140 Hz) or duration- (30 ms) dependent. A further issue concerns the interval used to separate the conditioning and test stimuli. In a recent study, Ni and colleagues demonstrated that by varying the ISI in increments of 0.1 ms (i.e., in a dual-coil experiment), IHF was maximally elicited by ISIs ≈ 4.5 ms (Ni et al., 2020). Notably, the time course of

facilitation was characterised by a monotonic increase in IHF that commenced 1.5 ms prior to attainment of peak IHF levels (i.e., when determined separately in each individual), following which a decrease was observed (Ni et al., 2020). It is therefore conceivable that the ISIs (~6 ms) that we and others have employed may lie beyond the inflection point of the IHF/ISI curve, such that only submaximal IHF (or none at all) is obtained. A final issue concerns the magnitude of the FDR estimate associated with the 30 ms 140 Hz tACS condition (FDR = 0.107). Although the value of a Bayesian interpretation is that it enables a subjective assessment of the effect's veracity (e.g., that there is a 10.7% propensity that the effect is mistaken), a strictly frequentist approach would regard the effect as simply "non-significant" (i.e., $p > 0.05$). Viewed in this light, it is conceivable that the conditioning effects of 30 ms 140 Hz tACS may be viewed by some parties as negligible or even non-existent.

In this proof-of-principle study, our findings suggest that a short (30 ms duration) burst of 140 Hz (1 mA) tACS applied unilaterally to M1, may increase the amplitudes of MEP elicited (6 ms) subsequently by magnetic stimulation delivered over the opposite M1. There remains scope to determine whether there are specific combinations of stimulation parameters (e.g., tACS current, duration, frequency, ISI) that permit this form of IHF to be generated more reliably than that obtained with conventional dual-coil TMS methods. In addition, it should be noted that the findings discussed above were derived exclusively from a sample of young adults. It cannot be assumed that these methods are necessarily valid or reliable in older volunteers, in whom age-related alterations in primary motor

cortical function have been extensively documented (for a review, see Calvert & Carson, 2022).

Chapter 3

Probing Interhemispheric Dorsal Premotor-Primary Motor Cortex Interactions with Threshold Hunting Transcranial Magnetic Stimulation

3.1 INTRODUCTION

Callosal pathology has been implicated in a number of neurodegenerative conditions including amyotrophic lateral sclerosis (Bede & Hardiman, 2017; Dukic et al., 2019), classical progressive supranuclear palsy (Lenka et al., 2017), and Huntington's disease (Phillips et al., 2013). In order to improve clinical trial sensitivity and to equip clinicians with early diagnostic tools, there exists an urgent need to develop quantitative, affordable biomarkers for each of these conditions. In this regard, the establishment of a reliable methodology with which to quantify the functional integrity of callosal projections, which does not depend upon costly neural imaging, is likely to be of practical utility in both clinical and basic scientific contexts.

Dual-site transcranial magnetic stimulation has been applied widely with the aim of assaying interactions between the two primary motor cortices (M1).

Interhemispheric inhibition (IHI) refers to a decrease in the amplitude of a "test" motor evoked potential (MEP) that is obtained in response to stimulation delivered over M1, in circumstances in which an initial "conditioning" stimulus (CS) has been applied 6-15 ms previously to the opposite M1 (Ferbert et al., 1992). Direct callosal projections between the caudal sectors of left and right M1, i.e., the cortical zones from which the majority of fast-conducting corticospinal axons that innervate spinal motoneurons arise (Rathelot & Strick, 2009; Witham et al., 2016), are however relatively sparse (Ruddy et al., 2017a). An argument can therefore be made that in applying electrophysiological techniques for diagnostic/prognostic purposes, the focus should instead be upon interhemispheric projections which, on anatomical grounds at least, are more likely to be implicated in integrative functions.

In this respect, interhemispheric projections arising from dorsal premotor cortex (PMd) are of particular interest. PMd exhibits rich connectivity with both the caudal and rostral M1 of the opposite hemisphere, via callosal projections that are characterised by high fibre density (Ruddy et al., 2017a). The region also has well documented involvement in motor pathology (Bestmann et al., 2010; Liao et al., 2019). In principle, the functional contributions of interhemispheric projections from PMd may be probed non-invasively using TMS to obtain electrophysiological measures such as IHI (Fiori et al., 2017; Mochizuki et al., 2004). With respect to PMd TMS conditioning however, only a limited range of "peri-threshold" intensities (90-110% rMT) and inter-stimulus intervals (ISIs) have thus far been investigated. A central objective of the present study was to

define a range of stimulation parameters that can be used reliably to elicit PMd-M1 IHI.

When TMS is applied to M1, the magnetic stimulating coil is most frequently oriented such that the induced cortical eddy current travels in a posterolateral to anteromedial (otherwise termed the "posteroanterior" or "PA") direction. At least partially distinct populations of fibers are excited when the test coil is oriented to induce anteroposterior (AP) currents across the motor strip (Di Lazzaro et al., 2001). It is widely held that the magnitudes of late indirect (e.g., I_3) waves generated by TMS, which are preferentially elicited by AP stimuli (Sakai et al., 1997), may reflect the states of excitation of pyramidal neurons with cells bodies in premotor cortex on the crown of the precentral gyrus, or somatosensory cortex on the crown of the postcentral gyrus, which project onto layer V cells in M1 via long-range corticocortical fibers (Laakso et al., 2014; Triesch et al., 2015). These afferent fibres, which constitute the main cortical input to M1 (DeFelipe et al., 1986; Jones, 1983), may be especially sensitive to AP currents (Esser et al., 2005; Laakso et al., 2014). Although callosal fibres are the epitome of long-range corticocortical projections, they are known to ramify in multiple layers (Cissé et al., 2003). It is thus challenging to predict on theoretical grounds alone whether the effects of input to M1 invoked by CS applied to the opposite PMd, will be revealed most clearly by test stimuli that induce PA or AP currents. A second objective of the present study therefore was to assess the impact of test coil orientation (i.e., inducing PA or AP current) on the magnitude of PMd-M1 IHI.

Adaptive threshold hunting (ATH), which is sometimes referred to as threshold tracking TMS (Cirillo & Byblow, 2016; Vucic et al., 2018), is a method

that incorporates maximum likelihood estimation to maintain constant the amplitude of the test MEP (the "threshold hunting target" or "THT") by adjusting the TS intensity *online* during the stimulation protocol (Awiszus et al., 1999). Consequently, IHI is defined as the percentage change in stimulator output that is necessary to evoke a response of THT amplitude (e.g., 200 μV) in the presence of conditioning, rather than the percentage change in MEP amplitude at some fixed TS intensity (see Figures 1C & 1D). The advantages of ATH are that: 1) by maintaining fixed the amplitude of the test response, the spinal, peripheral, and central mechanisms that mediate the expression of MEPs are held to exert a relatively consistent influence (Fisher et al., 2002; Opie & Semmler, 2014b); and 2), if the THT lies on the appropriate portion of the nonlinear TMS stimulus-MEP response curve, the method is thought to reduce the influence of the trial-to-trial variability that is an inherent characteristic of magnetically evoked motor responses (Vucic et al., 2006). In the present study, we employed a fully automated dual-coil ATH protocol to examine PMd-M1 IHI across a range of CS intensities (90, 110, 130% rMT), interstimulus intervals (8, 10, 40 ms) and test coil orientations (AP, PA).

3.2 METHODS

3.2.1 PARTICIPANTS

Thirty-two neurologically healthy volunteers (15 females, aged 18-35 years, mean age = 24.6 years, SD = 5.63 years) each participated in a single experiment. None reported a history of neurological or psychiatric disease, or any medication use for which TMS was contraindicated (Rossi et al., 2011; Rossi et al., 2009). All participants were right-handed as per the Edinburgh Handedness Inventory (Oldfield, 1971) and provided written informed consent to procedures approved by the Faculty of Engineering and Physical Sciences Research Ethics Committee at Queen's University Belfast. Apart from study preregistration, all procedures were conducted in accordance with the Declaration of Helsinki.

3.2.2 APPARATUS AND PROCEDURES

3.2.2.1 Electromyography

Electromyographic (EMG) signals were recorded from left and right extensor carpi radialis longus (ECR) using pairs of Ag/AgCl electrodes (Cleartrace 1700, ConMed, Haverhill, MA, USA). A reference electrode was placed on the lateral epicondyle of the right humerus. The skin overlaying the electrode sites was prepared with a topical abrasive (Nuprep, Weaver & Co., Aurora, CO, USA) and sanitised with a topical antiseptic (70% isopropanol). As part of the procedures for determining the position of the right PMd hotspot, we also recorded EMG activity from the left first dorsal interosseous (FDI) muscle

using a pair of 10 mm Ag/AgCl cup electrodes (Viasys Healthcare, Old Woking, UK) impregnated with an electroconductive paste (EC2, Grass Technologies, West Warwick, RI, USA). EMG signals were amplified (gain = 1000), band-pass filtered (30-1000 Hz), and notch filtered (50 Hz) using a Digitimer system (NL824 & NL820, Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK), digitized at a sampling rate of 10 kHz (Power1401, CED, Cambridge, UK), and recorded with Signal software (Signal 7.01, CED, Cambridge, UK).

3.2.2.2 Transcranial Magnetic Stimulation

Monophasic magnetic stimuli were delivered via a pair of Magstim 200 stimulators (Magstim Company Ltd., Whitland, UK), each equipped with a 55 mm mid-diameter figure-of-eight coil. The optimal position ("hotspot") to elicit a MEP in the left and right ECR and left FDI muscles was first determined. The procedure commenced by moving the coil in ~0.5 cm increments about a craniometrically defined location (2 x 6 cm anterolateral to the vertex). Thereafter, the hotspot was defined as the position over the scalp from which MEPs were elicited most reliably in the target muscle (left/right ECR, left FDI) of the contralateral limb. In left M1, the axis of intersection between the two loops was oriented at 45º to the sagittal plane to induce PA current flow across the motor strip. In right M1, the TMS coil was oriented parallel to the coronal plane to induce lateromedial (LM) current flow across the motor strip (see Figure 3.1). The M1 hotspots were registered in three-dimensional space using a neuro-navigation system (Brainsight, Rogue Resolutions Ltd., Cardiff, UK). Right PMd was defined craniometrically as the region of scalp situated 2.5 x 1.0 cm anteromedial to the

FDI hotspot of right M1, which was determined previously with LM-directed currents (Mochizuki et al., 2004). This location has been shown previously to lie within the meta-analytically defined boundaries of PMd, based on neuroimaging data (Fiori et al., 2017). Once defined, the PMd hotspot was also registered using the Brainsight system.

rMTs were obtained using a maximum likelihood protocol – namely parameter estimation by sequential testing (PEST) (Awiszus & Borckardt, 2011), to determine the minimum stimulation intensity required to elicit a MEP with a peak-to-peak amplitude of 50 µV in the contralateral ECR muscle (Rossi et al., 2009). The PEST procedure, which is identical to that incorporated in the ATH protocol, utilises a sigmoid-shaped logistic function to determine the stimulation intensity at which there exists a 0.5 probability of eliciting a MEP with a pre-defined peak-to-peak amplitude (i.e., 50 µV). This function and its implementation in the commonly used MTAT 2.0 programme are described elsewhere by its author (Awiszus, 2003). In left M1, the rMT was determined twice – once with the test coil oriented to induce AP current flow, and once with the test coil oriented to induce current flow in the PA direction. In right M1, the rMT was determined with the test coil oriented to induce LM current flow. The minimum stimulation intensity required to elicit the THT – in this case defined as a MEP with a peak-to-peak amplitude of 200 µV in right ECR, was determined separately with AP and PA currents (see Figures 1A and 1B).

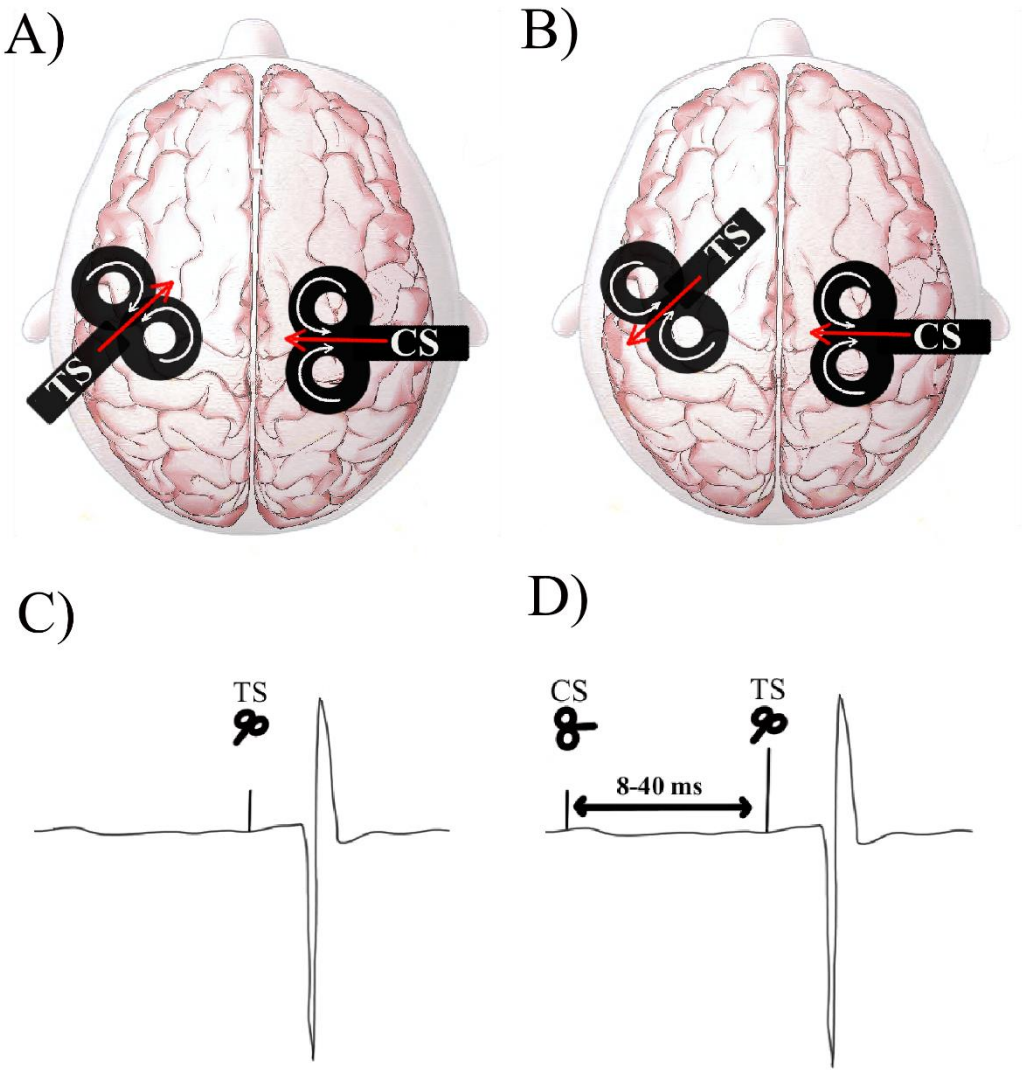


Figure 3.1: TMS coil arrangements and illustration of adaptive threshold hunting-derived interhemispheric inhibition trial. (A, B) Superior view of the head illustrating the dual-site transcranial magnetic stimulation (TMS) coil arrangements. The white arrows on the TMS coils illustrate the direction of current through the coil, while the red arrows denote the direction of the induced cortical eddy current. The conditioning stimulus (CS) coil always induced current flow in the lateromedial direction. In this schematic, the CS is applied to primary motor cortex. The test stimulus (TS) coil induced current flow in either the posteroanterior (A) or anteroposterior (B)

directions. (C, D) Example of an adaptive threshold hunting interhemispheric inhibition trial. The height of the magnetic artefact is proportional to the TS intensity. In the absence of a CS (C), a lower TS intensity is required to elicit the threshold hunting target (THT). In the presence of a CS (D), a higher TS intensity is necessary (i.e., "larger artefact") to evoke the THT.

The use of the PEST algorithm for the purposes of threshold hunting has been reported previously. To facilitate ease of use, and to reduce the potential for human error that is an inherent risk of manual implementations, we established a fully automated procedure in which an interface between Signal (CED Ltd., Cambridge UK) and MATLAB (MathWorks Inc., MA, USA) scripts was used to track EMG output, update stimulator output, and calculate threshold intensities *online* during data collection. In brief, peak-to-peak MEP amplitudes were calculated immediately after each MEP was sampled. Thereafter, MEP amplitudes were passed to a PEST algorithm to determine the next stimulation intensity, to which the stimulator was set automatically using the Magstim 200 digital control protocol. The experimenters were required only to hold the coil in position (using Brainsight guidance) as 20 pulses were delivered every 5 s (jittered ± 500 ms), following which a threshold stimulus intensity was determined (e.g., rMT, THT).

3.2.2.3 Interhemispheric Inhibition

The CS was applied to right M1 or right PMd. The conditioning coil was oriented parallel to the coronal plane to induce LM current flow. The test coil orientation was varied by block to induce current flow in either the AP or PA

directions (see Figures 1A and 1B). The TS intensity was adjusted online to determine the stimulation intensity required to elicit the THT (i.e., a MEP with a peak-to-peak amplitude of 200 μV in right ECR) in the presence of conditioning. Throughout each block, a TS with an intensity equivalent to that necessary to elicit the THT in the absence of conditioning, was delivered following every fifth trial. This was performed to monitor the consistency of the nonconditioned THT response over the course of the experiment, i.e., relative to the expected amplitude of 200 μV.

In assessing IHI between right and left M1 ($IHI_{M1\text{-}M1}$), the CS intensity was applied at 110%, 120%, or 130% rMT. The interstimulus interval (ISI) was 10 or 40 ms. Altogether, the combination of three CS intensities (110%, 120%, 130% rMT), two ISIs (10, 40 ms), and two TS orientations (AP, PA) yielded 12 $IHI_{M1\text{-}M1}$ conditions. In seeking to assess IHI between right PMd and left M1 ($IHI_{PMd\text{-}M1}$), the CS intensity was applied at 90%, 110%, or 130% rMT. It should be emphasised that the CS intensity applied to right PMd was expressed as a percentage of the rMT obtained from right M1, based on the amplitudes of MEPs elicited in left ECR. The ISI was 8, 10, or 40 ms. Altogether, the combination of three CS intensities (90%, 110%, 130% rMT), three ISIs (8, 10, 40 ms), and two TS orientations (AP, PA) yielded 18 $IHI_{PMd\text{-}M1}$ conditions.

3.2.3 General procedures

Participants were seated in a comfortable chair with their upper limbs supported, the forearms in mid-pronation, and the elbows semi-flexed (100-120°).

There were four blocks of stimulation (M1-$M1_{AP}$, M1-$M1_{PA}$, PMd-$M1_{AP}$, PMd-$M1_{PA}$), each separated by 5 min rest intervals. Only a single TS orientation (AP, PA) was employed in each block. The block orders were counterbalanced and pseudo-randomised across participants. The order in which each condition (i.e., a combination of CS intensity and ISI) was presented within each block was pseudo-randomised. The interval between the completion of trials in one condition, and the commencement of trials in the following condition, was approximately 2 minutes. The duration of each block was ~43 and ~28 min for the IHI_{PMd-M1} and IHI_{M1-M1} blocks respectively. Due to the extended duration of the testing session (>3 hours), some participants were unable to complete all conditions (i.e., the time allocated for testing was in some cases reached prior to completing the four blocks). The number of participants that completed each condition is provided in Tables 3.1-3.4.

3.2.4 DATA ANALYSIS

The root mean square (rms) of the background EMG recorded in right ECR (i.e., the "target" muscle of the IHI protocol) was calculated *online* for a window 0-90 ms prior to CS onset. In seeking to eliminate instances in which elevated excitability of the spinal motoneuron pool may have augmented MEP amplitudes, we disregarded from the PEST procedure all trials in which the corresponding rms value exceeded 5 μV.

Interhemispheric inhibition was defined as the change in test stimulator output necessary to evoke a MEP of THT amplitude (200 μV) in the presence of conditioning, expressed as a percentage of the nonconditioned THT intensity:

$$\text{IHI (\%)} = \left(\frac{(THT_{cond.} - THT_{non-cond.})}{THT_{non-cond.}}\right) \cdot 100$$

where larger positive values are indicative of greater inhibition.

It is widely recognised (e.g., Abelson, 2012) that in repeated measures designs, inferential tests which rely upon standard normal theory often fail to satisfy several key assumptions, including normality of the sample distribution. When assessed using the Shapiro-Wilk test, 43.3% (13/30) of cells failed to satisfy the conventional criterion of asymptotic normality ($p < 0.05$). Accordingly, we employed robust non-parametric alternatives to multifactor repeated-measures ANOVAs, which are known to minimise the potential influence of outliers and deviations from normality, as the basis of our inferential analyses using the nparLD package in R (Noguchi et al., 2012). These models, in which CS intensity and ISI were included as fixed effects, were computed separately for each block (i.e., PMd-$M1_{AP}$, M1-$M1_{PA}$, etc.). In the event of a significant main effect and/or interaction arising, post-hoc analyses based on Yuen's t-tests (trimming interval = 0.2) were computed. In order to verify that IHI was present in each condition, a series of one-sample 95% percentile bootstraps (10,000 samples) – in which Huber's one-step M-estimator (Ψ) was used as a robust measure of location, were computed using the WRS2 package in R (Mair & Wilcox, 2016). In seeking to

control for multiplicity, adjusted *p*-values were obtained using the Hochberg step-up procedure (Hochberg, 1988). To assist in the interpretation of the tests of significance, the robust variant of Cohen's *d* (d_R) and the corresponding bias-corrected-and-accelerated (BCa) bootstrapped 95% confidence interval (10,000 samples) were obtained (Algina et al., 2005; Kirby & Gerlanc, 2013). To ensure that the nonconditioned THT response (i.e., the MEP elicited every fifth trial during each IHI assessment) varied about the expected THT amplitude (i.e., 200 μV), robust tests of equivalence (based on 20% trimmed means) were also undertaken (Robinson, 2016).

3.3 RESULTS

3.3.1 DORSAL PREMOTOR-PRIMARY MOTOR CORTEX INTERHEMISPHERIC INHIBITION ELICITED BY POSTEROANTERIOR TEST STIMULI

PMd-M1 IHI with the test coil oriented to induce PA current flow was reliably expressed across most conditions, with the exception of the "8 ms ISI, 90% rMT CS" and "10 ms ISI, 110% rMT CS" conditions (Table 3.1 and Figure 3.1A). A robust rank-based non-parametric model with CS intensity (levels = 90%, 110%, 130% rMT) and ISI (levels = 8 ms, 10 ms, 40 ms) as fixed effects revealed a main effect of CS intensity (F (1.83, ∞) = 5.49, p = 0.005). There was no effect of ISI (p = 0.710) or a CS intensity x ISI interaction (p = 0.535). Post-hoc Hochberg-corrected Yuen's t-tests revealed that the magnitude of PMd-M1 IHI (elicited with PA test stimuli) tended to increase as a function of CS intensity. Specifically, we found that the magnitude of PMd-$M1_{PA}$ IHI elicited with a CS intensity of 130% rMT was significantly greater than that obtained by a CS intensity of 90% rMT [t (13) = 3.00, $p_{corrected}$ = 0.031, d_R = 0.84 (0.40, 1.64)]. All other contrasts in which PMd-M1 IHI was compared across CS intensities (i.e., 130% rMT vs. 110% rMT, and 110% rMT vs. 90% rMT) failed to achieve conventional levels of statistical significance (all $ps_{corrected} > 0.05$).

3.3.2 DORSAL PREMOTOR-PRIMARY MOTOR CORTEX INTERHEMISPHERIC INHIBITION ELICITED BY ANTEROPOSTERIOR TEST STIMULI

PMd-M1 IHI was not expressed reliably (all $ps_{corrected} > 0.05$) in any condition in which the test coil was oriented to induce current flow in the AP direction (Table 3.2 and Figure 3.1B). The results of the two-factor analysis are not therefore reported.

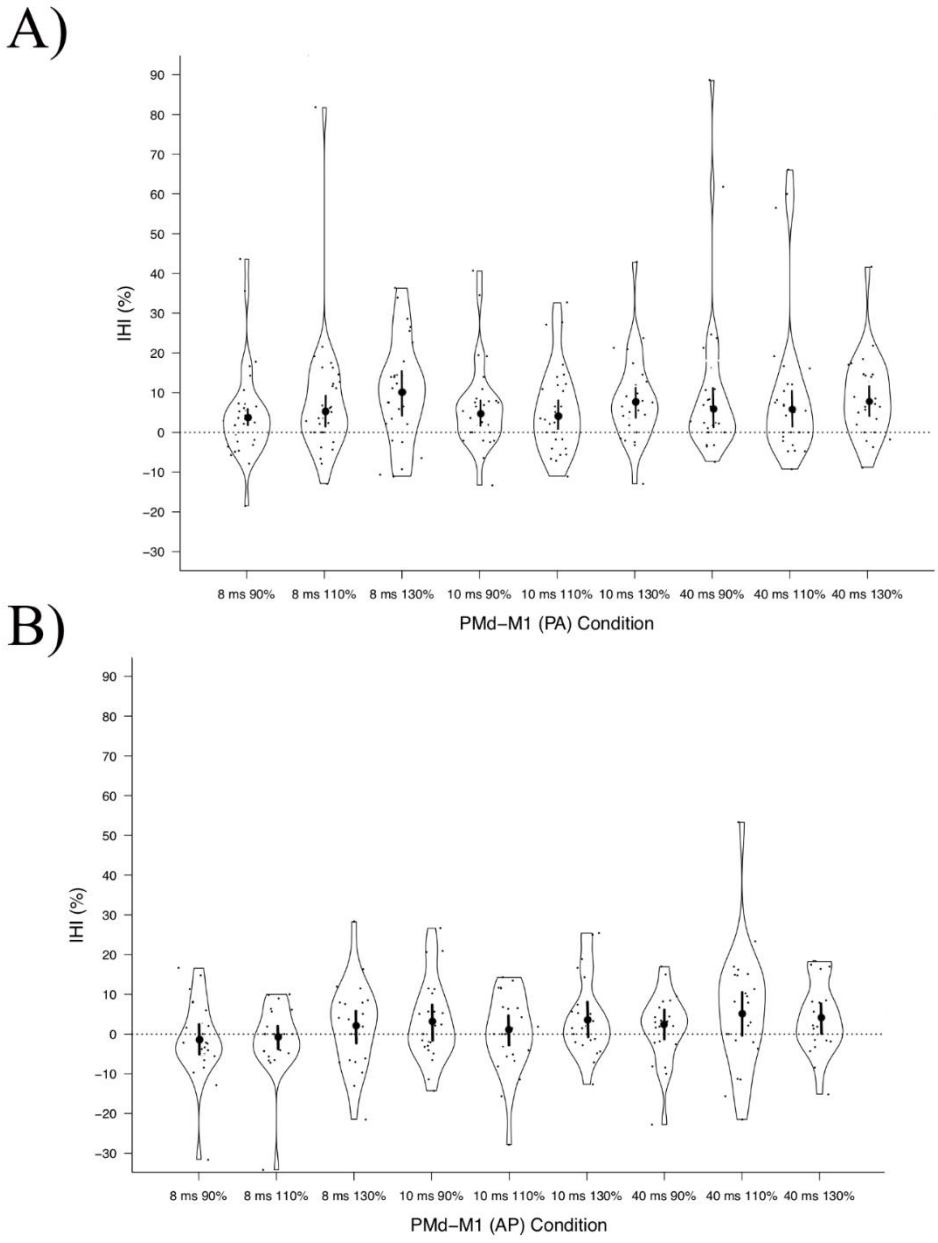


Figure 3.2: Pirate plots illustrating the magnitude of right dorsal premotor cortex-left primary motor cortex interhemispheric inhibition obtained with posteroanterior (A) and anteroposterior (B) test stimuli as a function of condition. Individual data points are also plotted. The error bars represent bootstrapped 95% confidence intervals (10,000 samples). The large, filled circles situated along the error bar represent Huber's psi (i.e., Huber's one-step M-estimator). In each plot, the dashed horizontal line corresponds to zero change in stimulator output (i.e., no interhemispheric inhibition). PMd-M1 IHI = dorsal premotor-primary motor cortex interhemispheric inhibition; PA = posteroanterior; AP = anteroposterior.

Table 3.1.

Dorsal premotor-primary motor cortex interhemispheric inhibition elicited with posteroanterior test stimuli as a function of condition.

ISI	CS	*n*	IHI Ψ (95% CI) / %	$p_{corrected}$	d_R (95% BCa CI)
8 ms	90%	31	2.77 (0.25, 6.30)	0.297	0.43 (0.12, 0.94)
	110%	28	5.89 (2.12, 9.49)	0.028*	0.62 (0.27, 1.07)
	130%	29	10.00 (5.09, 15.02)	0.004*	0.71 (0.27, 1.27)
10 ms	90%	30	4.92 (2.12, 8.54)	0.016*	0.64 (0.32, 1.26)
	110%	30	4.68 (1.03, 8.51)	0.143	0.47 (0.11, 0.93)
	130%	28	7.22 (3.97, 11.27)	0.028*	0.84 (0.47, 1.60)
40 ms	90%	28	5.75 (2.09, 11.29)	0.007*	0.52 (0.20, 0.83)
	110%	26	5.67 (1.83, 10.18)	0.029*	0.52 (0.18, 0.90)
	130%	25	8.29 (4.66, 11.98)	0.004*	0.89 (0.49, 1.66)

Note: these outcomes are based on one-sample 95% percentile bootstraps (10,000 samples). ISI = interstimulus interval; CS = conditioning stimulus intensity as a percentage of resting motor threshold; *n* = number of participants who completed the corresponding condition; IHI Ψ = interhemispheric inhibition based on Huber's one-step M-estimator (Ψ); $p_{corrected}$ = Hochberg-corrected p-values; d_R (95% BCa) = the robust variant of Cohen's *d* with 95% bias-corrected-and-accelerated confidence intervals; * $p_{corrected} < 0.05$

Table 3.2.

Dorsal premotor-primary motor cortex interhemispheric inhibition elicited with anteroposterior test stimuli as a function of condition.

ISI	CS	*n*	IHI Ψ (95% CI) / %	$p_{corrected}$	d_R (95% BCa CI)
8 ms	90%	24	-1.23 (-4.35, 2.54)	0.726	0.14 (-0.30, 0.70)
	110%	23	-0.33 (-3.41, 2.24)	0.726	0.05 (-0.36, 0.66)
	130%	21	2.13 (-1.89, 6.26)	0.726	0.21 (-0.20, 0.88)
10 ms	90%	22	2.34 (-1.50, 7.11)	0.726	0.25 (-0.21, 0.62)
	110%	24	0.88 (-3.24, 4.41)	0.726	0.08 (-0.33, 0.48)
	130%	23	2.60 (-0.58, 8.41)	0.686	0.25 (-0.25, 0.59)
40 ms	90%	23	2.02 (-1.49, 5.53)	0.726	0.31 (-0.23, 1.06)
	110%	22	5.46 (-0.19, 10.82)	0.368	0.45 (-0.02, 1.02)
	130%	23	4.09 (0.37, 8.06)	0.368	0.37 (-0.08, 0.69)

Note: these outcomes are based on one-sample 95% percentile bootstraps (10,000 samples). ISI = interstimulus interval; CS = conditioning stimulus intensity as a percentage of resting motor threshold; *n* = number of participants who completed the corresponding condition; IHI Ψ = interhemispheric inhibition based on Huber's one-step M-estimator (Ψ); $p_{corrected}$ = Hochberg-corrected p-values; d_R (95% BCa) = the robust variant of Cohen's *d* with 95% bias-corrected-and-accelerated confidence intervals; * $p_{corrected} < 0.05$

3.3.3 PRIMARY MOTOR CORTEX-PRIMARY MOTOR CORTEX INTERHEMISPHERIC INHIBITION ELICITED BY POSTEROANTERIOR TEST STIMULI

M1-M1 IHI with the test coil oriented to induce PA current flow was reliably expressed across all conditions (Table 3.3 and Figure 3.2A). A robust rank-based non-parametric model with CS intensity (levels = 110%, 120%, 130% rMT) and ISI (levels = 10 ms, 40 ms) as fixed effects revealed a main effect of CS intensity (F (1.89, ∞) = 4.55, p = 0.012). There was no effect of ISI (p = 0.26) or a CS intensity x ISI interaction (p = 0.638). Post-hoc Hochberg-corrected Yuen's t-tests indicated that the magnitude of M1-M1 IHI increased as a function of CS intensity. In particular, we found that the magnitude of M1-M1 IHI_{PA} elicited with a CS intensity of 130% rMT was significantly greater than that evoked with CS intensities of 120% rMT [t (17) = 3.26, $p_{corrected}$ = 0.009, d_R = 0.72 (0.28, 1.60)] and 110% rMT [t (18) = 3.32, $p_{corrected}$ = 0.009, d_R = 0.88 (0.26, 1.49)]. There was no significant difference in M1-M1 IHI_{PA} between the 120% rMT and 110% rMT CS conditions ($p_{corrected} > 0.05$).

3.3.4 PRIMARY MOTOR CORTEX-PRIMARY MOTOR CORTEX INTERHEMISPHERIC INHIBITION ELICITED BY ANTEROPOSTERIOR TEST STIMULI

M1-M1 IHI with the test coil oriented to induce AP current flow was reliably expressed across all conditions (Table 3.4 and Figure 3.2B). A robust rank-based non-parametric model with CS intensity (levels = 110%, 120%, 130% rMT) and ISI (levels = 10 ms, 40 ms) as fixed effects revealed a main effect of CS intensity (F (1.83, ∞) = 3.91, p = 0.023). There was no effect of ISI (p = 0.496) or a CS intensity x ISI interaction (p = 0.959). Post-hoc Hochberg-corrected Yuen's t-tests did not however indicate the presence of reliable pairwise differences in M1-M1 IHI_{AP} between individual CS intensities (all $ps_{corrected} > 0.05$).

Table 3.3.

Primary motor cortex-primary motor cortex interhemispheric inhibition elicited with posteroanterior test stimuli as a function of condition.

ISI	CS	*n*	IHI Ψ (95% CI) / %	$p_{corrected}$	d_R (95% BCa CI)
10 ms	110%	32	9.33 (5.48, 14.07)	< 0.001*	0.88 (0.53, 1.56)
	120%	32	10.01 (6.30, 14.21)	< 0.001*	1.11 (0.61, 2.07)
	130%	32	14.94 (10.47, 19.67)	< 0.001*	1.24 (0.66, 1.94)
40 ms	110%	31	8.34 (5.51, 11.73)	< 0.001*	1.11 (0.57, 1.86)
	120%	30	9.82 (5.86, 15.87)	< 0.001*	0.96 (0.50, 1.67)
	130%	30	12.44 (8.43, 16.71)	< 0.001*	1.04 (0.65, 1.71)

Note: these outcomes are based on one-sample 95% percentile bootstraps (10,000 samples). ISI = interstimulus interval; CS = conditioning stimulus intensity as a percentage of resting motor threshold; *n* = number of participants who completed the corresponding condition; IHI Ψ = interhemispheric inhibition based on Huber's one-step M-estimator (Ψ); $p_{corrected}$ = Hochberg-corrected p-values; d_R (95% BCa) = the robust variant of Cohen's *d* with 95% bias-corrected-and-accelerated confidence intervals; * $p_{corrected} < 0.05$

Table 3.4.

Primary motor cortex-primary motor cortex interhemispheric inhibition elicited with anteroposterior test stimuli as a function of condition.

ISI	CS	*n*	IHI Ψ (95% CI) / %	$p_{corrected}$	d_R (95% BCa CI)
10 ms	110%	25	6.69 (2.83, 10.62)	0.007*	0.75 (0.35, 1.40)
	120%	22	8.58 (5.60, 11.62)	<0.001*	1.05 (0.57, 1.74)
	130%	27	10.26 (5.24, 15.49)	<0.001*	0.79 (0.28, 1.84)
40 ms	110%	26	5.73 (2.04, 9.29)	0.029*	0.59 (0.19, 1.31)
	120%	25	8.37 (3.86, 13.52)	0.010*	0.78 (0.35, 1.53)
	130%	23	9.02 (5.79, 12.79)	<0.001*	1.17 (0.69, 2.17)

Note: these outcomes are based on one-sample 95% percentile bootstraps (10,000 samples). ISI = interstimulus interval; CS = conditioning stimulus intensity as a percentage of resting motor threshold; *n* = number of participants who completed the corresponding condition; IHI Ψ = interhemispheric inhibition based on Huber's one-step M-estimator (Ψ); $p_{corrected}$ = Hochberg-

corrected p-values; d_R (95% BCa) = the robust variant of Cohen's *d* with 95% bias-corrected-and-accelerated confidence intervals; * $p_{corrected} < 0.05$

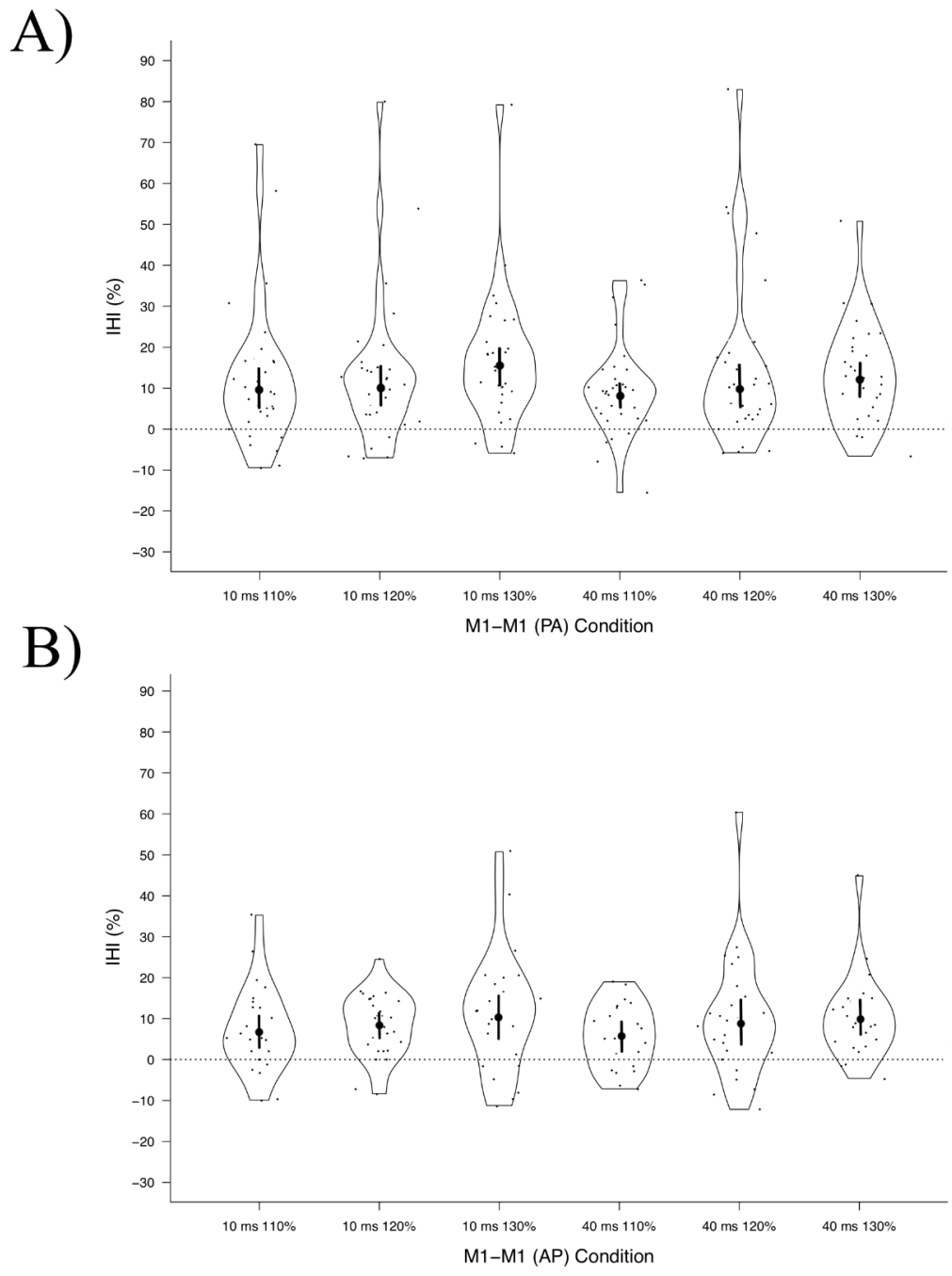


Figure 3.3: Pirate plots illustrating the magnitude of right primary motor cortex-left primary motor cortex interhemispheric inhibition obtained with

posteroanterior (A) and anteroposterior (B) test stimuli as a function of condition. Individual data points are also plotted. The error bars represent bootstrapped 95% confidence intervals (10,000 samples). The large, filled circles situated along the error bar represent Huber's psi (i.e., Huber's one-step M-estimator). In each plot, the dashed horizontal line corresponds to zero change in stimulator output (i.e., no interhemispheric inhibition). M1-M1 IHI = primary motor cortex-primary motor cortex interhemispheric inhibition; PA = posteroanterior; AP = anteroposterior.

3.3.5 THRESHOLD HUNTING TARGETS AND CONTROL MEP AMPLITUDES

The robust tests of equivalence indicated that the amplitudes of the nonconditioned THT response (i.e., the MEP elicited every fifth trial during each IHI assessment) varied about the expected THT amplitude of 200 μV (Table 3.5). This would suggest that the TS intensity required to evoke a response equivalent to the THT amplitude in the absence of conditioning did not vary significantly over the course of the experiment.

On average, the THT was equivalent to 115% rMT in the PA condition (mean rMT_{PA} = 43.3, SD = 9.44; mean THT_{PA} = 49.7, SD = 11.44) and 113% rMT in the AP condition (mean rMT_{AP} = 56.6, SD = 11.19; mean THT_{AP} = 63.7, SD = 13.47). All means and standard deviations are expressed as percentages of maximum stimulator output.

Table 3.5.

Equivalence tests and nonconditioned motor-evoked potential amplitudes as a function of block.

IHI Block	$Mean_{tr}$ MEP / µV	SD_w / µV	Yuen's *t*	*df*	*p*
$PMd\text{-}M1_{PA}$	214.38	67.75	0.70	17	< 0.001*
$PMd\text{-}M1_{AP}$	247.06	94.06	1.44	14	< 0.001*
$M1\text{-}M1_{PA}$	242.14	77.92	1.81	18	< 0.001*
$M1\text{-}M1_{AP}$	232.62	62.17	1.51	14	< 0.001*

Note: $Mean_{tr}$ = 20% trimmed mean; SD_w = Winsorized standard deviation;

* $p < 0.05$

3.4 DISCUSSION

Here, we established the effects of varying such parameters as CS intensity, ISI, and TS orientation on the magnitude of ATH-derived PMd-M1 and M1-M1 IHI, assayed using a fully automated dual-coil TMS methodology. In doing so, we highlight for future application the parameter combinations with which PMd-M1 and M1-M1 IHI may be most effectively assessed.

The specific outcomes of the present study indicate that the expression of PMd-M1 IHI is contingent on the test coil orientation. PMd-M1 IHI was present when the test coil was oriented to induce PA current flow, but not when it was oriented to induce current flow in the AP direction. This suggests that the expression of this phenomenon may rely upon functionally discrete populations of neurons. In the PA condition, the magnitude of PMd-M1 IHI also increased as a function of CS intensity. This finding highlights the importance of carefully selecting the CS intensity should one wish to apply the parameter as a means of assaying interhemispheric motor cortical pathology. For example, in circumstances in which a weak CS intensity is applied, a poor reference measure may be obtained, against which disease-related changes in IHI may be difficult to detect. By contrast, a CS intensity that is too large may engender ceiling effects, as the TS intensity required to maintain the target MEP amplitude may exceed the output capacity of the stimulator. There was no evidence that PMd-M1 IHI_{PA} varied as a function of ISI, which may indicate that the populations of neurons in PMd that are activated at different ISIs may exert a relatively homogeneous influence upon circuits in the contralateral M1 (or conversely that the same sets of

neurons are sampled at each ISI). A detailed discussion of the underlying physiological basis of this latter finding is however beyond the scope of the present analysis.

It has been demonstrated previously that by altering the orientation of the test coil, early (e.g., I_1) or later I-waves (e.g., I_3) may be elicited preferentially by cortical eddy currents that flow respectively in the PA or AP directions (Di Lazzaro et al., 2001; Di Lazzaro et al., 2018; Di Lazzaro & Rothwell, 2014). The implication is that corticospinal volleys generated by different TMS coil orientations may reflect the contributions of at least partially distinct populations of neurons (Hamada et al., 2014; Hannah & Rothwell, 2017; Volz et al., 2014). It has been established that the application of conditioning stimuli unilaterally to M1 preferentially modulates the amplitudes of I_3 waves (and, to a limited extent, I_2 waves) generated by a TS applied subsequently to its counterpart. There is not however any evidence of a corresponding effect on I_1 waves (Di Lazzaro et al., 1999). On this basis it has been inferred that if the test coil is oriented to induce AP current flow, a more sensitive measure of M1-M1 IHI may be obtained (Mooney et al., 2018). In the present study, when the test coil was oriented to induce AP current flow, conditioning stimuli applied to the opposite PMd failed to generate reliable IHI. By contrast, when the TS was oriented to induce PA current flow instead, IHI was present for most ISIs (8, 10 and 40 ms) and CS intensities (90%, 110%, 130% RMT). This pattern of outcomes does not accord with the assumption that the amplitudes of MEPs elicited by test stimuli that induce AP current flow in M1, are reflective of the states of long-range corticocortical afferent fibres to a greater extent than test stimuli that induce PA

currents. As noted above, although callosal fibres fit squarely the definition of long-range corticocortical afferent fibres, they are believed to ramify in multiple layers (Cissé et al., 2003). In future work therefore, consideration might be given to the possibility that in the context of IHI, it is not only the origin of the afferent fibres (i.e., M1 versus PMd) that determines relative sensitivity to AP and PA currents, but also the distribution of the cortical layers to which those fibres project.

When the CS was applied to M1, IHI was expressed when the TS induced current flow in both the PA and AP directions. This is consistent with previous findings (Ghosh et al., 2013; Mooney et al., 2018). The effect size estimates suggest that the depth of inhibition was somewhat larger when the TS induced PA, rather than AP, current flow. As in the PMd-M1 IHI_{PA} condition, and in accordance with extant reports (Ibey et al., 2015; Ni et al., 2009b), the magnitude of M1-M1 IHI_{PA} also increased as a function of CS intensity. This was not however the case when the TS induced AP current flow. Taken together with studies in which differential effects of AP and PA stimulation have been observed with aging (Mooney et al., 2018), our findings suggest that in registering M1-M1 IHI, AP and PA test coil orientations may capture physiologically distinct phenomena, and should therefore both be employed when assessing clinical populations. Irrespective of the test coil orientation, there was no effect of ISI on the magnitude of M1-M1 IHI that was obtained (Uehara et al., 2014).

A key limitation of the present study concerns the craniometric method by which the position of the PMd hotspot was determined and the possibility of current spread to non-PMd areas. It has been suggested that the craniometric

approximation of PMd that we and others (Mochizuki et al., 2004) have employed corresponds to a dorsolateral premotor site that lies at the border of PMd and ventral premotor cortex (PMv) (Fiori et al., 2017). While this position falls within the meta-analytically defined boundaries of PMd (Fiori et al., 2017), the possibility exists that the cortical eddy current induced by the CS at higher stimulation intensities may have spread to, and perhaps activated, cells in PMv. It has been demonstrated previously that conditioning PMv with peri-threshold CS intensities (90-110% rMT) at both short- (8 ms) and long-latency ISIs (40 ms) (all of which were parameters used in the present study) diminishes the amplitude of MEPs elicited from the contralateral M1 (Buch et al., 2010; Fiori et al., 2017). Consequently, the possibility that the PMd-M1 IHI_{PA} effect observed in the present study may be partially mediated by interhemispheric input from PMv cannot be excluded.

Owing to the close proximity of PMd to M1, it is conceivable that current spread to primary motor areas when the CS was applied to PMd may also have contributed to the expression of PMd-M1 IHI_{PA}. Although this risk cannot be excluded fully, we do not consider it likely that any such activation would have impacted meaningfully (or indeed at all) on the measures of IHI obtained. In the first instance, it is well established that the application of subthreshold conditioning stimuli (e.g., 90% rMT) to M1 does not affect the amplitudes of MEPs elicited by test stimuli delivered subsequently to the opposite M1, at least at ISIs that conventionally engender IHI (De Gennaro et al., 2004; Ferbert et al., 1992; Hanajima et al., 2001; Mochizuki et al., 2004). The effects of current spread from PMd to M1 at subthreshold CS intensities (i.e., 90% rMT) are therefore likely

negligible (Mochizuki et al., 2004). Secondly, it is well established that the area of tissue activated by TMS increases as a function of the applied stimulation intensity. One might expect therefore that the effects of current spread to M1, and its theoretical contribution to PMd-M1 IHI_{PA}, should be manifest most prominently at suprathreshold (> rMT) intensities. Moreover, as M1-M1 IHI was observed with *both* AP and PA test coil orientations, it should follow that a similar pattern of outcomes (i.e., an expression of IHI with either test coil orientation) should be evident in respect of PMd-M1 IHI, assuming that such effects were mediated by unintended activation of the ipsilateral M1. This was not however the case. Indeed, while IHI was expressed in the majority of PMd-$M1_{PA}$ conditions, it was conspicuously absent in each PMd-$M1_{AP}$ condition.

In conclusion, we have demonstrated that IHI between PMd and M1 is obtained only with test stimuli that induce current flow in the PA direction and that the magnitude of the effect increases as a function of CS intensity. It should be emphasised however that as the above findings were derived exclusively from a sample of young adults, it cannot be assumed that these methods are necessarily valid or reliable in older volunteers, in whom age-related alterations in both premotor and primary motor function have been previously documented (for a review, see Calvert & Carson, 2022). In investigating PMd-M1 IHI in clinical populations, our findings indicate that a PA test coil orientation, and CS intensities that provide a basis upon which to capture pathological elevations or diminutions of this measure, should be employed. The absence of IHI when the CS was applied to PMd – in circumstances in which the TS induced AP current flow in the opposite M1, emphasises that the anatomical and physiological factors that

determine the impact of test coil orientation on TMS-evoked potentials remain poorly understood.

Chapter 4

On the Relationship Between Dorsal Premotor-Primary Motor Cortex Interhemispheric Inhibition and the Cross Education of Ballistic Motor Skill in Young and Older Adults

4.1 Introduction

Cross education (CE) is the process whereby a regimen of unilateral limb training engenders bilateral improvements in motor function (Carson et al., 2016). It is widely held that the contralateral benefits thus derived may impart therapeutic benefits for patients with unilateral deficits arising from cerebrovascular insult, musculoskeletal injury, or neurologic disease (Farthing & Zehr, 2014; Haggert et al., 2020; Hendy et al., 2012; Sun et al., 2018). It is well established that the brains of humans undergo profound changes in functional and structural connectivity that manifest most prominently in later life (Cox et al., 2016; Seidler et al., 2010). It is also recognised that the adaptations that occur in response to a training impetus

vary substantially across the lifespan (Barry & Carson, 2004). A key question to consider therefore is whether there exist age-related variations in the extent to which the phenomenon of CE is manifested, and relatedly, if the neural mechanisms which meditate its expression also change with age.

We have raised the point previously that the expression of age differences in levels of CE, and the extent of its association with different physiological measures, is likely to depend on its method of derivation (Calvert & Carson, 2022). In most instances, the interlimb effect is expressed in terms of "relative improvement", which refers to the proportional gain in performance realised by the untrained limb (i.e., a change from pre- to post-training). A complementary measure is that of "interlimb transfer", which expresses the relative improvement of the untrained limb as a percentage of that attained by the limb engaged in training. Although these measures are often discussed interchangeably, they are by no means equivalent (e.g., Parikh & Cole, 2013). Unlike measures of relative improvement, interlimb transfer is not correlated with the magnitude of gain that is realised by the limb engaged in training (Ruddy et al., 2016). It is possible that this latter measure reflects a fixed structural constraint, that is related intimately to interindividual variations in structural brain connectivity (Ruddy et al., 2017b). By contrast, the relative improvement realised by the untrained limb may be associated to a greater degree with the dimensions of the specific training regimen, which may account for conspicuous variations in its magnitude across different training tasks. As it is clear that these two measures are likely to capture at least partially distinct phenomena, both measures were obtained in the present investigation.

Although the expression of CE – as a registered change in motor output, is given effect via corticospinal projections from M1 (i.e., ipsilateral to the limb engaged in training), it cannot be assumed that direct interhemispheric interactions between the primary motor cortices constitute the basis of its mediation (Calvert & Carson, 2022; Ruddy & Carson, 2013). While it is evident that ipsilateral elevations in the activity of M1 are manifest during unimanual actions orchestrated by its homologue, such changes are driven mainly by interhemispheric input from non-primary motor regions, most notably dorsal premotor cortex (PMd) (Tak et al., 2021). Notwithstanding its complex (and often underappreciated) functional topography (Genon et al., 2017; Genon et al., 2018), PMd is considered widely to mediate the acquisition of a diverse range of motor skills (Abe & Hanakawa, 2009; Hardwick et al., 2013; Kantak et al., 2012; Tomassini et al., 2011). This view is supported by lesion studies in both humans (Halsband & Freund, 1990) and non-human primates (Petrides, 1986). When recorded directly in primate models, the firing rates of neurons in PMd are related to several kinematic parameters of movements executed by the ipsilateral limb (Fu et al., 1993; Kurata, 1993). This may suggest that during unimanual movements, an "efference copy" of the motor command that is executed by M1 may be instantiated in circuits within the contralateral PMd. When these circuits are engaged subsequently, such as during performance of similar actions undertaken with the untrained limb, a potential basis for improvements in its function may be thus apparent.

In the course of executing unimanual actions, the degree of interhemispheric coupling that is evident between PMd and M1, when expressed

relative to levels observed in young adults, is elevated markedly in older volunteers (Lariviere et al., 2019; Wang et al., 2019b). These changes, which far exceed those registered between bilateral M1, are held to drive age-related elevations in the level of activation that is present in the ipsilateral M1 during unimanual actions (Tak et al., 2021). What purpose, if any, might these changes in functional brain activity ultimately serve? One school of thought is that age-related reductions in hemispheric asymmetries – the effect whereby performance of a (motor) task is accompanied by increased levels of bilaterally symmetric functional brain activity, may compensate for network deficiencies engendered by age-related decline of the cerebral grey and white matter – by recruiting additional brain regions to facilitate task performance (Cabeza, 2002; Cabeza et al., 2002). To the extent that these changes are adaptive and driven mainly by interhemispheric input from PMd to the opposite M1 (Tak et al., 2021), it might be expected that some evidence of functional benefit (e.g., learning) should be associated with connectivity between these regions. This is indeed the case. In the context of a unimanual sequential finger tapping paradigm, Schulz et al. (2014) reported that older individuals in whom the microstructural integrity of transcallosal projections between PMd and M1 was greatest (i.e., based on levels of fractional anisotropy), were those who exhibited the highest levels of unimanual skill acquisition. In light of these observations, an increased reliance upon interhemispheric PMd-M1 interactions, which are likely to be subserved by callosal projections, may provide a basis for age-related variations in the mechanisms which mediate motor learning. Whether this applies to the more

specific case of CE was one of the motivations that underpinned the present investigation.

In seeking to probe interhemispheric interactions between PMd and M1, the use of methods based upon dual-coil transcranial magnetic stimulation (TMS) may offer some utility. The essence of this technique is that a magnetic "conditioning" stimulus (CS) is applied to one region of cortex (in this case, PMd), following which a magnetic "test" stimulus (TS) is applied 6-50 ms later to the opposite M1. In most instances (*cf.* Calvert et al., 2020), the outcome measure is based on a percentage change in the amplitude of the motor-evoked potential (MEP) that is obtained in response to the TS, in circumstances in which prior conditioning stimulation has been applied (i.e., to the contralateral PMd). Although in some instances the amplitude of the "test" MEP is potentiated by prior conditioning of PMd (e.g., Bäumer et al., 2006), in most cases only an inhibitory response is obtained (i.e., where the amplitude of the MEP is decreased). This latter effect has been termed "interhemispheric inhibition" (IHI) (Calvert et al., 2020; Mochizuki et al., 2004; Ni et al., 2009a). A particular advantage of the IHI approach is that by titrating carefully the interstimulus interval (ISI), it is possible to probe interhemispheric interactions that are mediated by at least partially distinct anatomical pathways. If the ISI is sufficiently short (e.g., 8-10 ms), insofar that it accords closely with the latency of the transcallosal volley, the IHI measure may be regarded as an index of *direct* inhibitory interactions between PMd and M1 ("short-latency IHI") (Ni et al., 2009a). If, however, the ISI is extended (e.g., to 40-50 ms), the IHI measure may instead reflect interactions subserved by complex polysynaptic networks whose specific components have yet to be

delineated ("long-latency IHI") (Ni et al., 2009a). As short- and long-latency PMd-M1 IHI may capture at least partially distinct interhemispheric interactions, both measures were therefore obtained in the present investigation.

The aim of the study was twofold. In the first instance, we sought to examine the effect of age on the magnitude of CE (quantified in terms of relative improvement and interlimb transfer) expressed by young and older adults following a single session of unimanual ballistic wrist extension training. In seeking to differentiate improvements in performance that were due to motor practice, from those which reflect the extent of motor learning, measures of CE were calculated both immediately ("post-training") and one-week following the initial training session ("retention"). Although age-related variations in the levels of CE expressed following a regimen of ballistic movement training interventions have been observed somewhat inconsistently, we predicted that in line with outcomes reported by previous investigations (e.g., Dickins et al., 2015b; Hinder et al., 2013; Reissig et al., 2015), young and older adults would exhibit comparable levels of relative improvement and interlimb transfer at both post-training and retention.

The second aim was to examine whether the level of CE expressed by young and older adults was associated with the magnitude of change in short- or long-latency PMd-M1 IHI between the start and end of training. While it cannot be assumed that variations in IHI that occur during the course of motor practice, are necessarily related to the degree of learning that is achieved, these relationships may be approximated if a test of retention (which permits an inference that learning has occurred) is employed (e.g., in a follow-up session

conducted one-week later) (Calvert & Carson, 2022). As higher levels of unimanual skill acquisition are associated with greater levels of microstructural integrity between PMd and M1 in older volunteers (Schulz et al., 2014), we reasoned that training-related variations in short-latency PMd-M1 IHI (i.e., a measure that provides an ostensive index of "direct" PMd-M1 interactions) would be associated with interindividual variations in the levels of CE expressed by older adults in the retention session undertaken one-week later. In recognising that age-related elevations in interhemispheric PMd input are likely to drive movement-related elevations in ipsilateral M1 activity (Tak et al., 2021), we predicted that decreases in the level of short-latency PMd-M1 IHI (which would be expected to potentiate the M1 response) would be associated with higher levels of CE in older volunteers.

4.2 METHOD

4.2.1 PARTICIPANTS

Thirty-nine neurologically healthy young (n = 21, 13 females, aged 18-27 years, mean age = 21.4 years, SD = 2.40 years) and older adults (n = 18, 8 females, aged 65-76 years, mean age = 70.2 years, SD = 3.20 years) each participated in a two-session experiment. Successive sessions were separated by a 7-day interval. The sample size for each group was determined by a power analysis (Faul et al., 2007), which indicated that a sample of n = 18 participants would be sufficient to achieve 80% power (r = 0.49, α = 0.05, β = 0.20), i.e., to undertake within-group correlations between CE and changes in IHI. The effect size estimate used in the power calculation was based on the largest correlation coefficient reported by Hortobagyi et al. (2011) in respect of training-related changes in short-latency M1-M1 IHI and the degree of relative improvement attained by the untrained limb. No participants reported a history of neurological/psychiatric disease, or any medication use for which TMS was contraindicated (Rossi et al., 2011; Rossi et al., 2009). All participants were right-handed as per the Edinburgh Handedness Inventory (Oldfield, 1971) and provided written informed consent to procedures approved by the Faculty of Engineering and Physical Sciences Research Ethics Committee at Queen's University Belfast. Apart from study pre-registration, all procedures were conducted in accordance with the Declaration of Helsinki. Due to the requirement to self-isolate for two-weeks following exposure to a confirmed case of COVID-19, five participants (four young adults, one older adult) were unable to attend the second testing session.

4.2.2 APPARATUS AND PROCEDURES

4.2.2.1 Electromyography

Electromyographic (EMG) signals were recorded bilaterally from extensor carpi radialis longus (ECR) and flexor carpi radialis (FCR), using pairs of Ag/AgCl electrodes (Cleartrace 1700, ConMed, Haverhill, MA, USA). A reference electrode was placed on the lateral epicondyle of the right humerus. As part of the procedures for determining the position of the right PMd hotspot, we also recorded EMG activity from the left first dorsal interosseous (FDI) muscle using a pair of 10 mm Ag/AgCl cup electrodes (Viasys Healthcare, Old Woking, UK) impregnated with an electroconductive paste (EC2, Grass Technologies, West Warwick, RI, USA). The skin overlaying the electrode sites was prepared with a topical abrasive (Nuprep, Weaver & Co., Aurora, CO, USA) and sanitised with a topical antiseptic (70% isopropanol). EMG signals were amplified (gain = 2000) and band-pass filtered (100-1000 Hz) using a Motion Lab system (MA-300, Motion Lab Systems Inc, Baton Rouge, LA, USA), notch filtered (50 Hz) with a Biopac system (NL135, Biopac Systems Inc., Santa Barbara, CA, USA), digitized at 10 kHz (Power1401, CED, Cambridge, UK), and recorded with Signal software (Signal 7.01, CED, Cambridge, UK).

4.2.2.2 Transcranial Magnetic Stimulation

Monophasic magnetic stimuli were delivered via a pair of Magstim 200 stimulators (Magstim Company Ltd., Whitland, UK), each equipped with a 55 mm mid-diameter figure-of-eight coil. The optimal position (“hotspot”) to elicit a MEP

in the left and right ECR and left FDI muscles was first determined. The procedure commenced by moving the coil in ~0.5 cm increments about a craniometrically defined location (2 x 6 cm anterolateral to the vertex). Thereafter, the hotspot was defined as the position over the scalp from which MEPs were elicited most reliably in the target muscle of the contralateral limb. Over left M1, the axis of intersection between the two loops was oriented at 45º to the sagittal plane to induce posteroanterior (PA) current flow across the motor strip. Over right M1, the TMS coil was oriented parallel to the coronal plane to induce lateromedial (LM) current flow across the same brain region. The hotspots were registered in three-dimensional space using a neuro-navigation system (Brainsight, Rogue Resolutions Ltd., Cardiff, UK). The optimal location to stimulate right PMd was defined craniometrically as the region of scalp situated 2.5 x 1.0 cm anteromedial to the FDI hotspot, which was determined with LM currents (Calvert et al., 2020; Mochizuki et al., 2004). This location has been shown previously to lie within the meta-analytically defined boundaries of PMd, based on neuroimaging data (Fiori et al., 2017). Once defined, the PMd hotspot was also registered using the Brainsight system.

The resting motor threshold (rMT) for left ECR was obtained using a maximum likelihood protocol – namely parameter estimation by sequential testing (PEST) (Awiszus & Borckardt, 2011), to determine the minimum stimulation intensity required to elicit a MEP (i.e., with LM-directed currents induced in right M1) with a peak-to-peak amplitude of 50 µV (Rossi et al., 2009). The PEST procedure, which is identical to that incorporated in the threshold hunting protocol used for the purposes of assessing IHI (described below), utilises a sigmoid-

shaped logistic function to determine the stimulation intensity at which there exists a 0.5 probability of eliciting a MEP with a pre-specified peak-to-peak amplitude (e.g., 50 μV).

4.2.2.3 Interhemispheric Inhibition

Measures of short- and long-latency PMd-M1 IHI were obtained by means of a PEST-based adaptive threshold hunting protocol as described in Chapter 3 (see also Calvert et al., 2020). In brief, a fully automated procedure was devised in which an interface between custom-written Signal (CED Ltd., Cambridge, UK) and MATLAB (MathWorks Inc., MA, USA) scripts was used to track EMG output, update stimulator output, and calculate threshold intensities *online* during data collection. Thereafter, the MEP amplitudes were passed to a PEST algorithm to determine the next stimulation intensity, to which the stimulator was set automatically using the Magstim 200 digital control protocol. The experimenters were required only to hold the coil in position (using Brainsight guidance) as 20 pulses were delivered every 5 s (jittered ± 500 ms), following which a threshold stimulus intensity was determined. During each measurement, a TS with an intensity equivalent to that necessary to elicit the THT determined at pre-training, was delivered every fifth trial (i.e., in the absence of conditioning) to enable assessment of any changes in M1 excitability that may have occurred during the course of training.

The procedure commenced by determining the minimum stimulation intensity required to elicit the threshold hunting target (THT) – in this case defined as a MEP with a peak-to-peak amplitude of 200 μV in right ECR (obtained with

PA TMS applied over left M1). In assessing IHI, the CS was applied over right PMd, and the TS applied over left M1 (Figure 4.1A). The CS intensity was set to 110% of the rMT obtained for left ECR. The TS intensity was adjusted online to determine the stimulation intensity required to elicit the THT (i.e., a MEP with a peak-to-peak amplitude of 200 μV in right ECR) in the presence of conditioning. Thus, rather than quantifying IHI as a percentage change in MEP amplitude at some fixed TS intensity (i.e., relative to a control or "non-conditioned" MEP amplitude), IHI was expressed as the percentage change in stimulator output necessary to elicit a fixed MEP amplitude (i.e., the THT) in the presence of conditioning (Figures 4.1B and 4.1C). The benefits of this approach are twofold. Firstly, by maintaining fixed the amplitude of the test response, the spinal, peripheral, and central mechanisms that mediate the expression of MEPs are held to exert a relatively consistent influence (Fisher et al., 2002; Opie & Semmler, 2014b). Secondly, if the THT lies on the appropriate portion of the nonlinear TMS intensity-MEP amplitude curve, the method is thought to reduce the influence of the trial-to-trial variability that is an inherent characteristic of magnetically evoked motor responses (Kiers et al., 1993; Vucic et al., 2006). This is especially beneficial in older volunteers (Mooney et al., 2017), in whom the amplitudes of MEPs are significantly more variable than those of young adults (Pitcher et al., 2003).

There were two PMd-M1 IHI conditions which differed only in terms of interstimulus interval (ISI): i) "short-latency" PMd-M1 IHI, which was defined by an ISI of 8 ms, and ii) "long-latency" PMd-M1 IHI, which was defined by an ISI of 40 ms. For both measures, the CS intensity was applied at 110% rMT (Calvert

et al. (2020). Short- and long-latency PMd-M1 IHI were assessed at three time points: prior to ("pre-training"), midway through ("mid-training"), and following ("post-training") the training session. The order in which the two IHI measures were obtained at each time point was pseudorandomised across participants. No measures of IHI were obtained in the retention session undertaken one-week later.

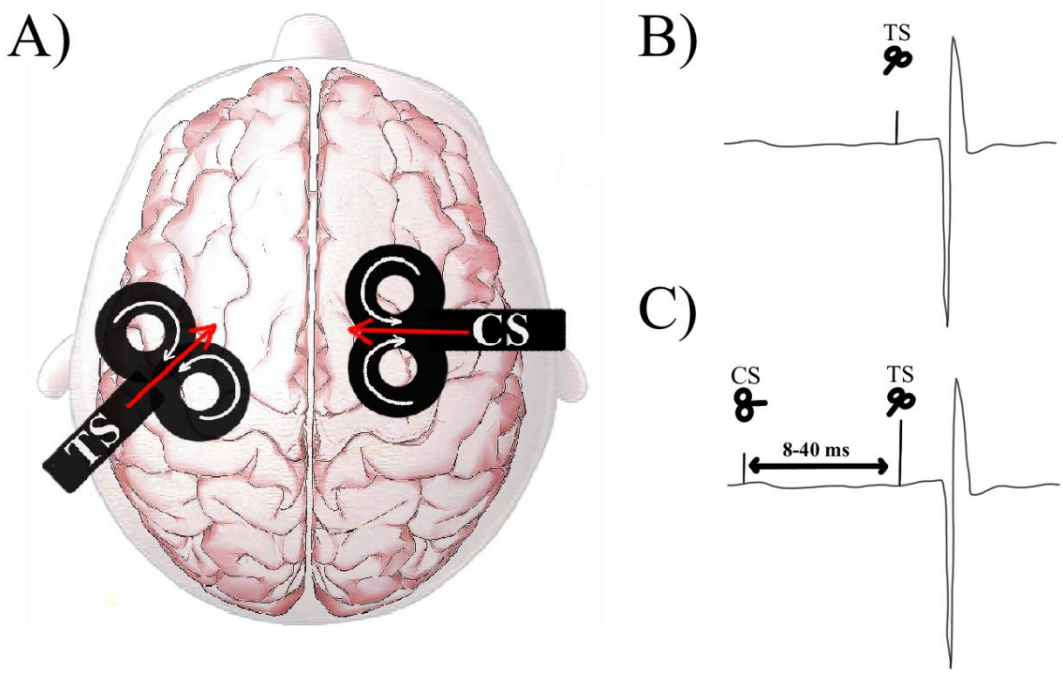


Figure 4.1: TMS coil arrangements and illustration of threshold hunting-derived interhemispheric inhibition. (A) Superior view of the head illustrating the dual-site TMS coil arrangement. The white arrows on the TMS coils illustrate the direction of current flow through the coil, while the red arrows denote the direction of the induced cortical eddy current. The conditioning stimulus (CS) coil induces lateromedial current flow across the right ("trained") dorsal premotor cortex. The test stimulus (TS) coil induces posteroanterior current flow across the left ("untrained") primary motor

cortex. (B, C) Example of an adaptive threshold hunting-derived interhemispheric inhibition (IHI) trial. In each panel (B, C), the height of the magnetic artefact (vertical line below "TS") is proportional to the TS intensity. In the absence of a CS (Panel B), a low TS intensity ("smaller artefact") is required to elicit the threshold hunting target (THT). In the presence of a CS (Panel C), a higher TS intensity (indicated by a larger magnetic artefact) is required to elicit the same THT, i.e., in order to "overcome" the inhibitory influence engendered by the CS.

4.2.2.4 Behavioural task

Participants were seated in a comfortable chair with their upper limbs supported and stabilized by vacuum cushions (Olympic Vac-Pac, Olympic Medical, Seattle, WA, USA), the forearms in mid-pronation, and the elbows semi-flexed (100-120°). The angle between the upper arm and torso was ~15-20º. The hands were secured at mid-palm in manipulanda instrumented to transduce angular displacement of the wrist and mounted coaxially with the extension-flexion axes of the wrists.

The behavioural task was based on a unimanual ballistic wrist extension paradigm. Each movement was cued by the presentation of a tone (400 Hz sine wave, 1 s duration). Throughout training, participants were encouraged to continually increase the peak angular acceleration of the wrist during each extension movement. It was emphasised to participants that the aim of the task was not to respond as fast as possible, but rather to accelerate the limb as fast as possible (i.e., with the greatest force and in their own time) after hearing the tone.

To familiarise participants with the task, five practice movements were undertaken with the left limb only. The final three movements of the sequence were succeeded by auditory feedback which differed depending on the participant's performance. One sound bite indicated that peak acceleration in the most recent trial had exceeded the mean of the two movements which preceded it. The second sound bite indicated that the mean peak acceleration of the two preceding trials had not been surpassed. Prior to commencing the practice movements, participants were provided with the following instructions: "Each movement should be your fastest possible. Listen to the auditory feedback to determine whether you are improving or not. The aim is to hear the "positive" sound bite as often as possible, which indicates that your maximum is improving" (Ruddy et al., 2016).

Upon completing the practice movements, baseline (i.e., "pre-training") measures of behavioural performance were obtained. These required participants to perform 10 discrete unimanual ballistic wrist extension movements (separately with the right and left limbs) in the absence of auditory feedback. Each movement was separated by 7 s intervals, while the assessment of the right and left limbs was separated by a 30 s rest period. The baseline measures were repeated midway through ("mid-training") and following the training regimen ("post-training"). A "retention" session, which consisted of the same measures, was undertaken one-week later. The performance of the right limb was always assessed prior to the left.

The training regimen was divided into two blocks. Each block consisted of 14 sets of 10 training movements (i.e., 140 movements per block). The left limb executed all training movements. In each set, successive movements (more

specifically the 400 Hz tones that cued them) were separated by 7 s intervals. Feedback of performance was provided in the form of two auditory sound bites as described previously. Successive sets were separated by 30 s intervals. Each block was separated by a 15 min interval that comprised an initial 5 min "rest" period, following which IHI measures were obtained. Behavioural performance (i.e., at pre-, mid-, and post-training) was always assessed upon completion of the IHI measurements. The time course of the experiment is illustrated in Figure 4.2.

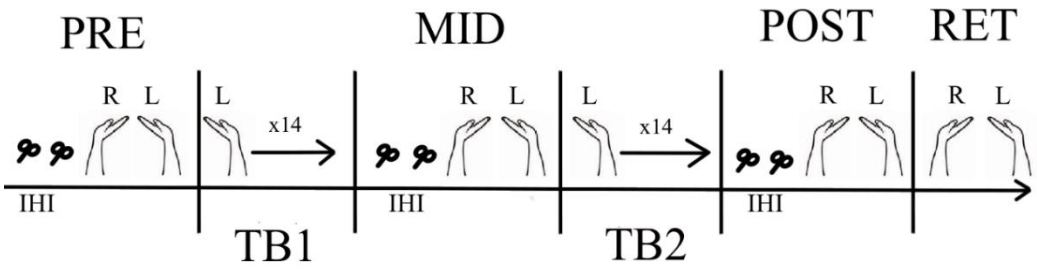


Figure 4.2: Time course of experiment. The first session ("PRE" to "POST") commenced with pre-training measurements of short- and long-latency dorsal premotor-primary motor cortex (PMd-M1) interhemispheric inhibition (IHI), following which pre-training measures of right and left limb performance (10 movements each) were obtained ("PRE"). Thereafter, participants completed training block 1 (TB1), which comprised 14 sets of 10 training movements undertaken with the left limb only. Successive sets were separated by 30 s intervals. The pre-training measures were repeated 5 min following completion of TB1 ("MID"). The second training block (TB2) was identical to the first (i.e., 14 sets of 10 movements). As with the mid-training measures, the post-training measures were obtained 5 min following

completion of the preceding training block ("POST"). In the second (i.e., retention) session ("RET"), which was undertaken one-week following the initial training session, only measures of right and left limb performance (10 movements each) were obtained. Performance of the right limb was always assessed prior to the left. The order in which the short- and long-latency PMd-M1 IHI measures were obtained was pseudorandomised across participants.

4.2.3 DATA ANALYSIS

4.2.3.1 Behavioural data

Following digital filtering (second order, dual-pass Butterworth, 6 Hz low-pass), the transducer-derived displacement signals were differentiated twice to derive acceleration (a). The peak acceleration in wrist extension was obtained for each movement. Thereafter, the median peak acceleration ($\tilde{a}$) was calculated separately for the right and left limbs at each point of measurement (i.e., the median for each set of 10 movements performed at pre-training, mid-training, post-training, and retention) following the application of an outlier rejection method based on the median absolute deviation. Two measures of cross education were computed, namely relative improvement and interlimb transfer. Each measure was calculated at mid-training, post-training, and retention. In the interests of brevity, the relevant equations are provided only for the post-training measures.

Relative improvement was defined as the median peak acceleration of the untrained limb (i.e., at mid-training, post-training, or retention), expressed as a proportion of the median peak acceleration observed at pre-training.

$$\text{Relative}_{\text{untrained}} = \left(\frac{\tilde{a}_{post}}{\tilde{a}_{pre}} \right)$$

Interlimb transfer was defined as the relative improvement attained by the untrained limb, expressed as a proportion of that attained by the limb engaged in training.

$$\text{Interlimb transfer} = \left(\frac{Relative_{\ untrained}}{Relative_{\ trained}} \right)$$

4.2.3.2 Electrophysiological data

The root mean square (rms) of the background EMG recorded in right ECR (i.e., the "target" muscle of the IHI protocol) was calculated *online* for a window 0-90 ms prior to CS onset. In seeking to eliminate instances in which elevated excitability of the spinal motoneuron pool may have augmented MEP amplitudes, we disregarded from the PEST procedure all trials in which the corresponding rms value exceeded 5 μV following Calvert et al. (2020).

IHI was defined as the change in test stimulator output required to elicit the THT in the presence of conditioning (i.e., a MEP of 200 μV in right ECR), expressed as a percentage of the nonconditioned (or "control") THT intensity:

$$\text{IHI (\%)} = \left(\frac{(THT_{cond.} - THT_{non-cond.})}{THT_{non-cond.}}\right) \cdot 100$$

where larger positive values are indicative of greater inhibition.

4.2.3.3 Statistical analyses

Training-related variations in the raw accelerations exhibited by the trained and untrained limbs (expressed in units of degrees per second squared) were examined separately using robust two-factor mixed effects models, in which age was included as a between-subjects factor (levels = young, old) and time as a within-subjects factor (levels = pre-training, mid-training, post-training, retention). Based on these models, planned comparisons were undertaken (both between and within groups) using robust methods, namely one-factor ANOVAs based on trimmed means and Yuen t-tests. To examine age- and training-related variations in the normalised accelerations (i.e., "relative improvement") of the trained and untrained limbs, a robust two-factor mixed effects model was likewise computed (separately for each limb), in which age was included as a between-subjects factor (levels = young, old) and time as a within-subjects factor (levels = mid, post, retention). Planned comparisons were undertaken as above. The same analyses were applied subsequently to the transfer measure.

In seeking to assess training-related changes in short- and long-latency PMd-M1 IHI, the percentage change in each measure was calculated between pre- and mid-training ("mid") and from pre- to post-training ("post"). Thereafter, a robust two-factor mixed effects model was computed (separately by ISI), in which age was included as a between-subjects factor (levels = young, old) and time as a within-subjects factor (levels = mid, post). On the basis of this model, planned

comparisons were undertaken to assess whether training-related changes in short- and long-latency PMd-M1 IHI (i.e., at mid- and post-training) varied as a function of age or time.

To establish whether the amplitudes of the "control" MEPs (i.e., the MEPs obtained during the course of each IHI measurement by a TS delivered at the same intensity as that necessary to evoke the THT) were equivalent throughout the course of training (i.e., from pre to mid to post), a robust two one-sided t-test procedure (rTOST) was employed (Robinson, 2016). This step was necessary to determine the extent to which any changes in the magnitudes of the IHI measures were driven by training-related alterations in the excitability of M1, rather than alterations in the level of inhibitory drive engendered by the contralateral PMd. Although these measures were obtained for each individual, deficiencies in the understanding of some members of the research team regrettably led to a large number of data files being overwritten. In applying listwise deletion to those which remained, the effective sample size for the purposes of the rTOST procedure was limited to 19 participants (10 young adults, 9 older adults).

In order to determine whether interindividual variations in CE were related to the magnitude of change in short- and long-latency PMd-M1 IHI that was expressed at post-training, a series of percentage-bend correlation analyses were performed (separately by age group). Overall, the combination of two IHI measures (short-latency, long-latency), two assessments of performance (post-training, retention), two age groups (young, old), and two measures of CE (relative improvement, interlimb transfer) yielded a total of 16 correlations. In seeking to account for the multiplicity of contrasts, adjusted *p*-values were obtained using the

Benjamini-Hochberg false discovery rate (FDR) procedure (Benjamini & Hochberg, 1995). To assist in the interpretation of the tests of significance, i.e., with regards to age and pairwise differences in performance and changes in IHI, the robust variant of Cohen's *d* (d_R) was computed (Algina et al., 2005), using the bootES package in R (Kirby & Gerlanc, 2013). All multi-factor models were derived from the WRS2 package in R (Mair & Wilcox, 2016).

4.3 RESULTS

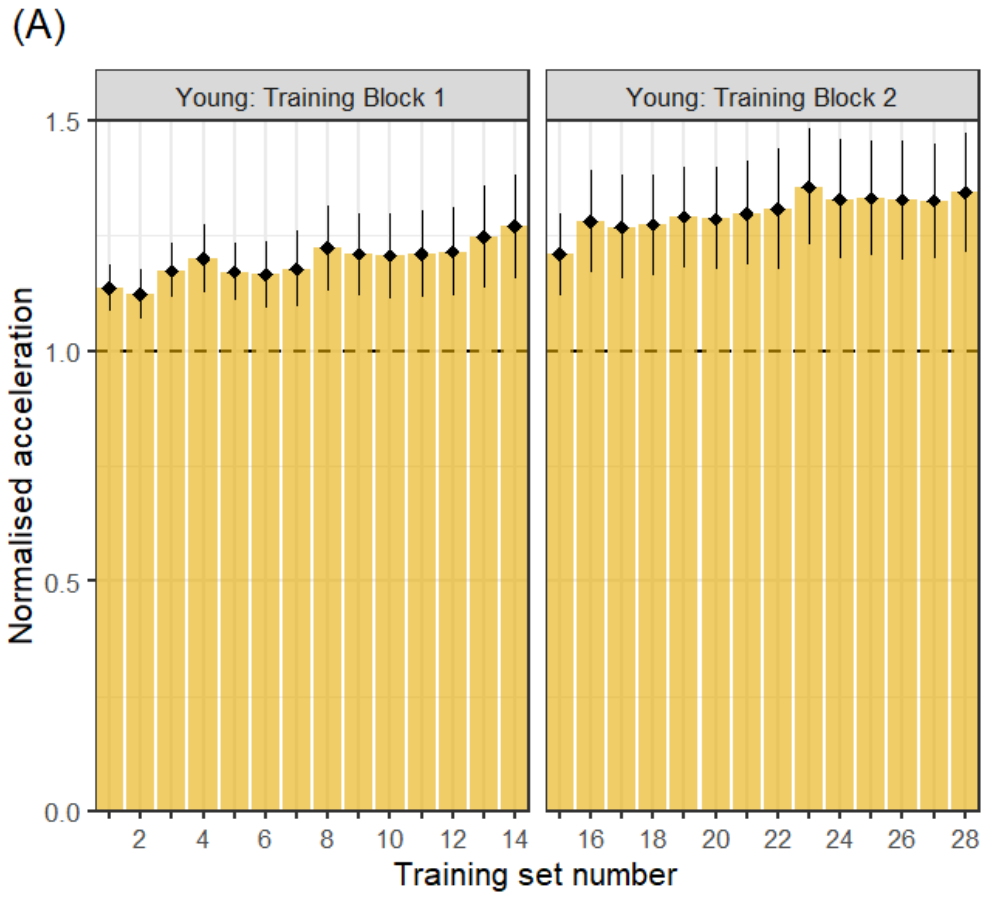
4.3.1 BEHAVIOURAL OUTCOMES: GENERAL OVERVIEW

We commence with an overview of the normalised performance of the trained limb (where the raw accelerations have been expressed relative to pre-training levels) as exhibited throughout the course of the two training blocks. This is followed by an assessment of age-related variations in the raw accelerations achieved with the trained and untrained limbs at pre-training, mid-training, post-training, and retention. A similar analysis is presented in respect of relative improvement (i.e., where the raw accelerations have been normalised with respect to pre-training levels) with the view of assessing the magnitude of training-related change in trained and untrained limb performance. The same analysis is then presented in respect of interlimb transfer. Training-related changes in short- and long-latency PMd-M1 IHI, and the extent to which these are modulated by age, are examined subsequently. A series of correlation analyses are then reported, which were undertaken with the view of relating training-related changes in short- and long-latency PMd-M1 IHI, to interindividual variations in CE.

4.3.2 BEHAVIOURAL OUTCOMES: PERFORMANCE OF THE TRAINED LEFT LIMB DURING TRAINING

Throughout the course of training, i.e., from one training set to the next, the peak angular acceleration of the wrist exhibited by young adults, when normalised with respect to pre-training levels, tended to increase in a non-

monotonic fashion (Figure 4.3A). Inspection of the lower limits of the confidence intervals associated with each training set suggested that training limb performance was consistently greater than baseline levels. In older adults, the normalised peak angular acceleration of the wrist tended to rise and fall throughout the course of training (Figure 4.3B). Towards the end of the initial training block, and throughout the entirety of that which succeeded it, the lower bounds of the confidence intervals associated with each set, overlapped increasingly with pre-training performance, suggesting that as training progressed, training limb performance could not be distinguished reliably from baseline performance in older volunteers.



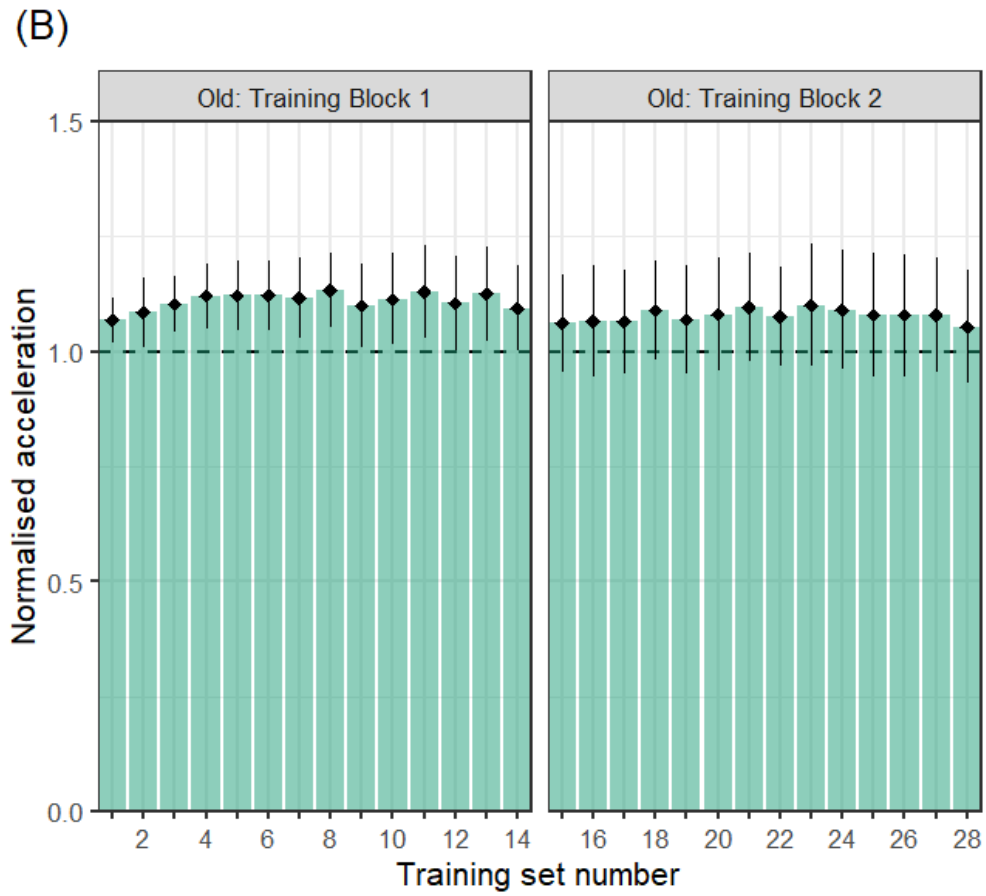


Figure 4.3: Normalised acceleration of the trained left limb as a function of training set. These data are provided separately for young (Panel A, orange bars) and older adults (Panel B, green bars). The black dots denote the trimmed means of the normalised acceleration values (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals. The acceleration values were normalised with respect to pre-training left limb performance (dashed black horizontal line at $y = 1$).

4.3.3 BEHAVIOURAL OUTCOMES: NON-NORMALISED GAINS IN PERFORMANCE

To examine age- and training-related variations in non-normalised ("raw") training limb performance (expressed in units of 10^{-3} ° s^{-2}), a robust two-factor mixed effects model was computed, in which age was included as a between-subjects factor (levels = young, old) and time as a within-subjects factor (levels = pre, mid, post, ret). This analysis revealed a significant main effect of age (F (1, 19.45) = 13.39, p = 0.002) and time (F (3, 13.07) = 5.39, p = 0.012), but no age x time interaction (F (3, 13.07) = 0.83, p = 0.500). In young adults, a robust one-factor repeated measures ANOVA indicated that the raw acceleration of the training limb varied significantly over the course of the intervention (F (2.72, 27.22) = 17.86, p < 0.001). Planned comparisons revealed that relative to pre-training levels ($mean_{tr}$ = 7.74, SD_w = 1.85), an increase in training limb acceleration was present at each point of measurement, including mid-training ($mean_{tr}$ = 9.16, SD_w = 2.35; t (10) = 3.28, p_{FDR} = 0.011, d_R = 0.83 (-0.03, 1.56)), post-training ($mean_{tr}$ = 10.46, SD_w = 2.30; t (10) = 4.56, p_{FDR} = 0.002, d_R = 1.16 (0.06, 2.62)), and retention ($mean_{tr}$ = 11.18, SD_w = 2.35; t (10) = 3.43, p_{FDR} < 0.001, d_R = 1.83 (0.90, 4.10)). There was no difference between the raw accelerations of the training limb at post-training and retention (t (10) = 1.28, p_{FDR} = 0.229, d_R = 0.19 (-0.64, 0.44)).

In older adults, a robust one-factor repeated measures ANOVA did not indicate the presence of reliable pairwise differences between the raw accelerations of the training limb at pre-training ($mean_{tr}$ = 13.54, SD_w = 2.69), mid-training ($mean_{tr}$ = 13.82, SD_w = 3.47), post-training ($mean_{tr}$ = 14.69, SD_w = 2.68), or retention ($mean_{tr}$ = 14.91, SD_w = 2.06) (F (2.87, 28.72) = 1.04, p = 0.388).

Thus, only in young adults did the raw accelerations of the training limb increase significantly over the course of the training session (i.e., relative to baseline levels). Somewhat surprisingly, the raw acceleration of the training limb in older adults, was significantly greater than that of young adults at each point of measurement, i.e., at pre-training (t (17.72) = 4.51, p_{FDR} = 0.001, d_R = 1.56 (0.75, 3.24)), mid-training (t (17.07) = 2.79, p_{FDR} = 0.012, d_R = 0.97 (0.19, 2.25)), post-training (t (19.25) = 4.23, p_{FDR} = 0.011, d_R = 1.05 (0.36, 2.00)), and retention (t (19.79) = 3.73, p_{FDR} = 0.011, d_R = 1.02 (0.25, 1.95)) (Figure 4.4).

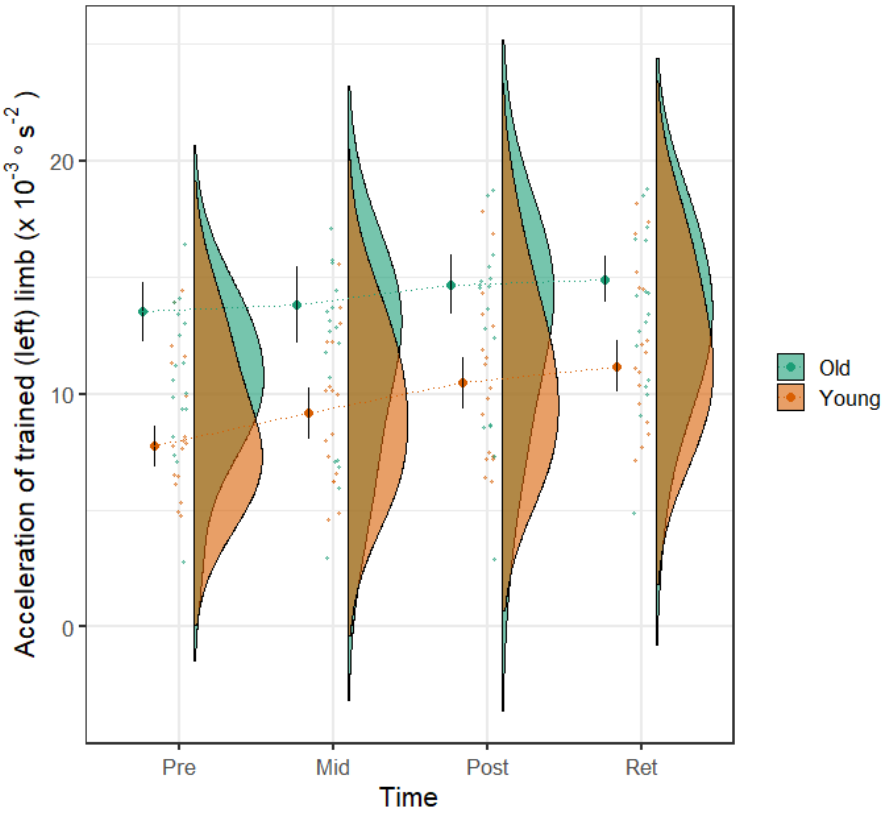


Figure 4.4: Non-normalised acceleration of the trained left limb as a function of age and time. These data are provided separately for young (orange) and older adults (green). The black dots denote the trimmed means of the raw

(i.e., non-normalised) acceleration values (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals.

In seeking to assess age- and training-related variations in the raw acceleration achieved by the untrained limb, a similar two-factor analysis as that above was undertaken. This analysis revealed a significant main effect of time (F (3, 15.98) = 9.58, $p < 0.001$); however, there was no effect of age (F (1, 19.94) = 3.64, $p = 0.071$) or an age x time interaction (F (3, 15.98) = 1.02, $p = 0.412$). In young adults, a robust one-factor repeated measures ANOVA indicated that the raw acceleration of the untrained limb varied appreciably over the course of training (F (2.35, 23.53) = 11.97, $p < 0.001$). Planned contrasts revealed that relative to pre-training levels ($mean_{tr}$ = 8.32, SD_w = 2.22;), there was no significant change in acceleration at mid- ($mean_{tr}$ = 9.22, SD_w = 2.44; t (10) = 1.37, p_{FDR} = 0.201, d_R = 0.17) or post-training (t (10) = 2.29, p_{FDR} = 0.060, d_R = 0.34). In the retention session undertaken one-week later ($mean_{tr}$ = 11.93, SD_w = 2.49), the acceleration values were elevated appreciably relative to pre- (t (10) = 4.63, p_{FDR} = 0.004, d_R = 0.58) and post-training ($mean_{tr}$ = 10.20, SD_w = 2.55; t (10) = 3.10, p_{FDR} = 0.022, d_R = 0.29) levels.

In older adults, a robust one-factor repeated measures ANOVA indicated that the raw acceleration of the untrained limb likewise varied throughout the intervention (F (2.20, 22.01) = 5.81, $p = 0.008$). Planned comparisons revealed that relative to pre-training levels ($mean_{tr}$ = 10.80, SD_w = 1.99), the raw acceleration of the untrained limb increased significantly at post-training ($mean_{tr}$ = 13.20, SD_w = 2.88; t (10) = 3.31, p_{FDR} = 0.032, d_R = 0.42) and retention ($mean_{tr}$

= 13.48, SD_w = 2.52; *t* (10) = 2.71, p_{FDR} = 0.044, d_R = 0.59). The increase in raw acceleration between pre- and mid-training ($mean_{tr}$ = 11.75, SD_w = 2.99) did not however achieve conventional levels of statistical significance (*t* (10) = 1.50, p_{FDR} = 0.218, d_R = 0.16). This was likewise the case between post-training and retention (*t* (10) = 0.44, p_{FDR} = 0.672, d_R = 0.05). Thus, while significant improvements in acceleration were demonstrated by both age groups in the retention session undertaken one-week later, only older adults exhibited a significant improvement within the course of the initial training session (i.e., from pre- to post-training). The raw accelerations of the untrained limb did not differ reliably between young and older adults at pre-training (*t* (19.88) = 2.13, p_{FDR} = 0.115, d_R = 0.74 (-0.02, 1.80)), mid-training (*t* (19.21) = 2.53, p_{FDR} = 0.140, d_R = 0.59 (-0.12, 1.81)), post-training (*t* (19.74) = 2.02, p_{FDR} = 0.115, d_R = 0.70 (-0.02, 1.90)), or retention (*t* (20) = 1.55, p_{FDR} = 0.274, d_R = 0.39 (-0.31, 1.26)) (Figure 4.5).

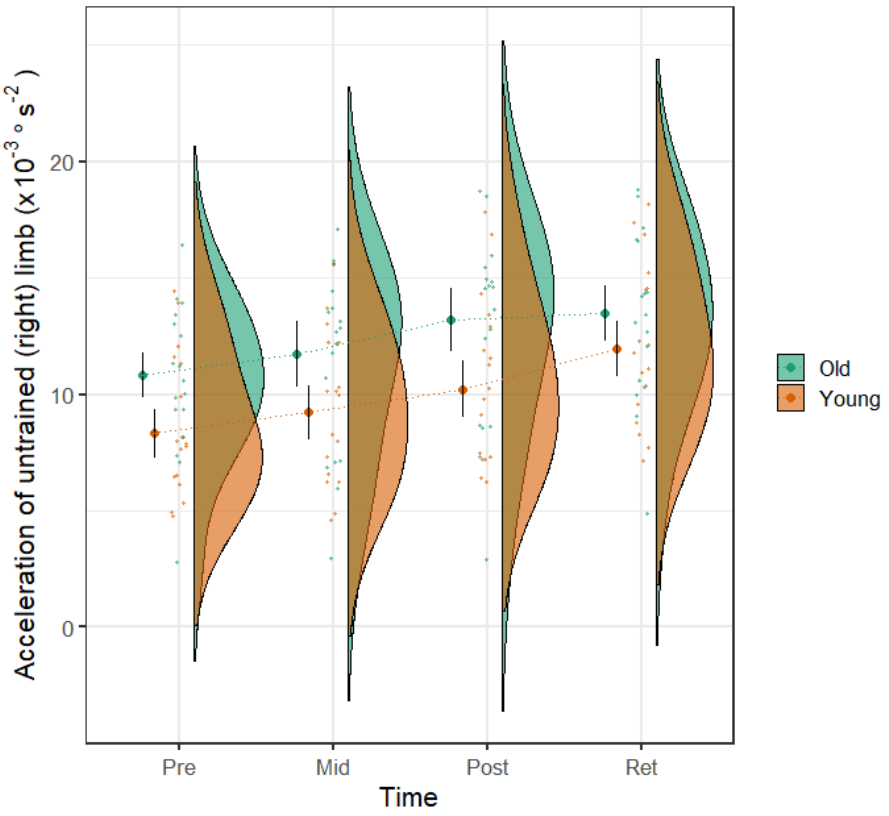


Figure 4.5: Non-normalised acceleration of the untrained right limb as a function of age and time. These data are provided separately for young (orange) and older adults (green). The black dots denote the trimmed means of the raw (i.e., non-normalised) acceleration values (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals.

4.3.4 Behavioural outcomes: Normalised (relative) gains in performance

To assess age- and training-related variations in the normalised performance of the training limb, a robust two-factor mixed effects model was computed, in which age was included as a between-subjects factor (levels = young,

old) and time as a within-subjects factor (levels = pre, mid, post, retention). This analysis revealed a significant main effect of age (F (1, 17.63) = 6.63, p = 0.019) and time (F (3, 14.98) = 7.21, p = 0.003) but no age x time interaction (F (3, 14.98) = 2.22, p = 0.129). In young adults, a robust one-factor repeated measures ANOVA indicated that the normalised performance of the training limb varied significantly over the course of the intervention (F (2.24, 22.38) = 13.43, p < 0.001). Planned comparisons revealed that relative to baseline performance, the normalised acceleration of the training limb was elevated appreciably by mid-training ($mean_{tr}$ = 1.20, SD_w = 0.155; t (10) = 3.39, p_{FDR} = 0.014, d_R = 0.81 (-0.01, 1.75)), post-training ($mean_{tr}$ = 1.37, SD_w = 0.254; t (10) = 3.70, p_{FDR} = 0.013, d_R = 0.97 (0.05, 1.89)), and retention ($mean_{tr}$ = 1.46, SD_w = 0.256; t (10) = 4.60, p_{FDR} = 0.005, d_R = 1.07 (0.39, 1.86)). There was not however any difference between the normalised accelerations registered at post-training and retention (t (10) = 0.09, p_{FDR} = 0.531, d_R = 0.21 (-0.69, 0.59)).

In older adults, the normalised acceleration of the training limb at mid-training ($mean_{tr}$ = 1.02, SD_w = 0.095), post-training ($mean_{tr}$ = 1.10, SD_w = 0.147), and retention ($mean_{tr}$ = 1.17, SD_w = 0.221), did not differ reliably from pre-training levels (F (1.71, 17.14) = 3.20, p = 0.072). This is consistent with the raw acceleration outcomes reported previously, in which only young adults exhibited a significant change in performance over the course of training. With respect to between-group differences, the normalised acceleration of the training limb in young adults, was significantly greater than that of older adults at each point of measurement, i.e., mid-training (t (16.46) = 2.58, p_{FDR} = 0.039, d_R = 0.89 (0.22,

2.15)), post-training (t (16.14) = 2.37, p_{FDR} = 0.039, d_R = 0.82 (0.08, 1.78)), and retention (t (19.57) = 2.21, p_{FDR} = 0.0392, d_R = 0.77 (0.04, 1.55)) (Figure 4.6).

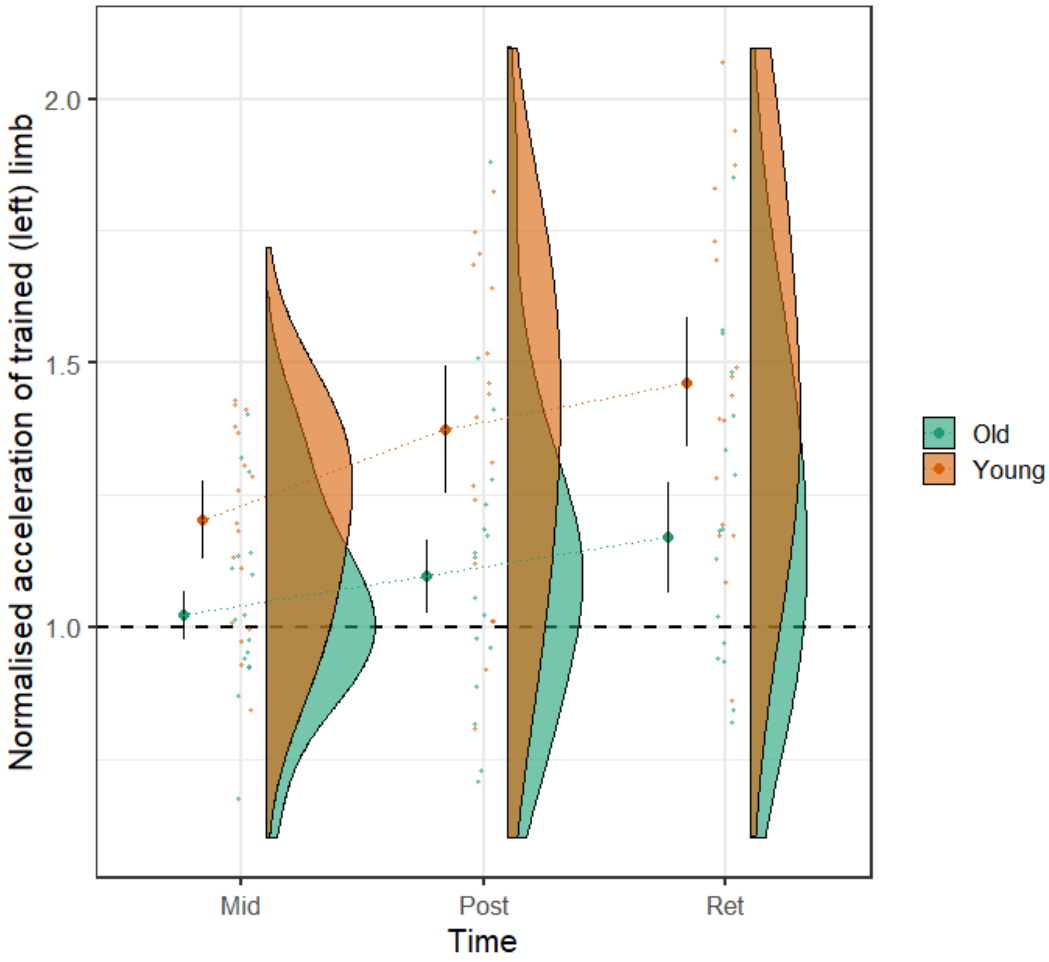


Figure 4.6: Normalised acceleration of the trained left limb as a function of age and time. These data are provided separately for young (orange dots) and older adults (green dots). The orange/green dots denote the trimmed means of the normalised acceleration values (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals. The acceleration values were normalised with respect to pre-training left (i.e., trained) limb performance (dashed black horizontal lines at y = 1).

To examine age- and training-related variations in the normalised acceleration of the untrained limb (i.e., "relative improvement"), a robust two-factor mixed effects model was computed, in which age was included as a between-subjects factor (levels = young, old) and time as a within-subjects factor (levels = pre, mid, post, retention). This analysis revealed a significant main effect of time (F (3, 15.41) = 8.87, p = 0.001); however, there was no effect of age (F (1, 18.58) = 0.18, p = 0.674) or an age x time interaction (F (3, 15.41) = 0.16, p = 0.919). In young adults, a robust one-factor repeated measures ANOVA indicated that the level of relative improvement expressed by the untrained limb varied significantly over the course of the intervention (F (2.35, 23.45) = 9.21, $p < 0.001$). Planned comparisons revealed that relative to pre-training performance, the normalised acceleration of the untrained limb was elevated significantly when assessed in the retention session undertaken one-week later ($mean_{tr}$ = 1.41, SD_w = 0.261; t (10) = 3.90, p_{FDR} = 0.012, d_R = 1.04 (0.42, 2.12)). There was no difference however between the normalised acceleration of the untrained limb at pre-training when compared to that registered at both mid- ($mean_{tr}$ = 1.07, SD_w = 0.144; t (10) = 1.30, p_{FDR} = 0.220, d_R = 0.23 (-0.39, 1.18)) and post-training ($mean_{tr}$ = 1.24, SD_w = 0.254; t (10) = 2.37, p_{FDR} = 0.056, d_R = 0.48 (-0.43, 0.99)). There was likewise no difference between the normalised accelerations of the untrained limb at post-training and retention (t (10) = 2.33, p = 0.056, d_R = 0.74 (0.22, 2.08)).

As with young adults, a robust one-factor repeated measures ANOVA indicated that the levels of relative improvement attained by older adults, varied appreciably over the course of training (F (1.94, 19.37) = 9.57, p = 0.001). Within this cohort, planned contrasts revealed that relative to baseline performance,

significant levels of relative improvement were evident at post-training ($mean_{tr}$ = 1.18, SD_w = 0.144; t (10) = 3.24, p_{FDR} = 0.027, d_R = 0.65 (0.18, 1.52)) and retention ($mean_{tr}$ = 1.34, SD_w = 0.240; t (10) = 3.58, p_{FDR} = 0.027, d_R = 1.02 (0.21, 1.84)). This was not however the case at mid-training ($mean_{tr}$ = 1.07, SD_w = 0.124; t (10) = 1.54, p_{FDR} = 0.165, d_R = 0.26 (-0.16, 1.12)). The increase in relative improvement between post-training and retention was not statistically significant (t (10) = 2.33, p_{FDR} = 0.165, d_R = 0.20 (-0.14, 1.07)). These findings are consistent with those reported in respect of raw acceleration, whereby significant increases in performance were evident at retention in both young and older adults, but at post-training in older adults only. With respect to between-group differences, the levels of relative improvement expressed in young adults, did not differ reliably from those observed in older volunteers when assessed at mid-training (t (19.58) = 0.02, p_{FDR} = 0.987, d_R = 0.01 (-0.71, 0.74)), post-training (t (15.56) = 0.06, p_{FDR} = 0.618, d_R = 0.18 (-0.52, 1.04)), or retention (t (19.83) = 0.47, p_{FDR} = 0.643, d_R = 0.16 (-0.60, 0.81)) (Figure 4.7).

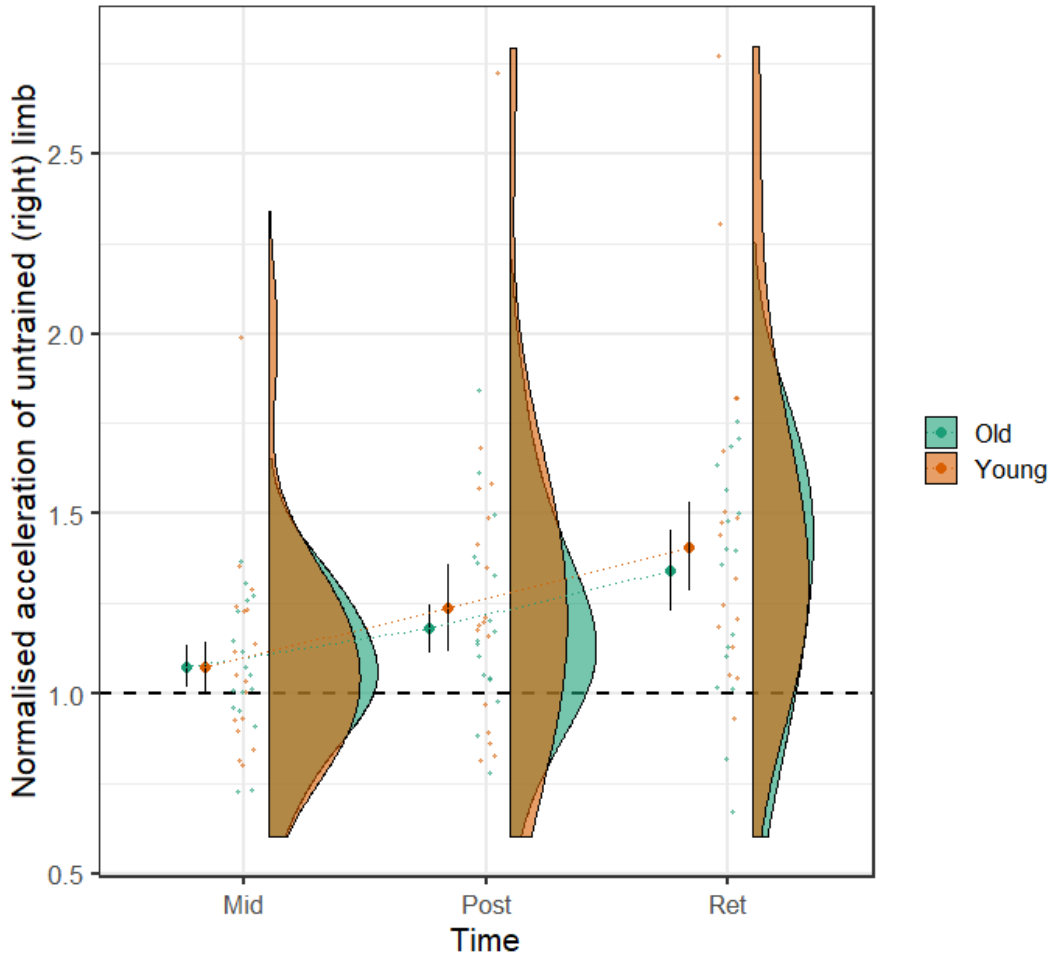


Figure 4.7: Normalised acceleration (relative improvement) of the untrained right limb as a function of age and time. These data are provided separately for young (orange dots) and older adults (green dots). The orange/green dots denote the trimmed means of the normalised acceleration values (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals. The acceleration values were normalised with respect to pre-training right (i.e., untrained) limb performance (dashed black horizontal lines at y = 1).

4.3.5 BEHAVIOURAL OUTCOMES: INTERLIMB TRANSFER

To assess age- and training-related variations in interlimb transfer, a robust two-factor mixed effects model was computed, in which age was included as a between-subjects factor (levels = young, old) and time as a within-subjects factor (levels = mid, post, retention). Based on this analysis, there were no significant effects of age (F (1, 18.40) = 3.51, p = 0.077), time (F (2, 15.74) = 0.70, p = 0.510), or an age x time interaction (F (2, 15.74) = 0.93, p = 0.42). Separately in each group, a robust one-factor repeated measures ANOVA indicated that levels of interlimb transfer did not vary significantly over the course of the intervention (Young: F (1.53, 15.28) = 1.14, p = 0.330; Old: F (1.76, 17.59) = 0.24, p = 0.764). There were no statistically significant differences in interlimb transfer between young and older adults at mid-training (Young: mean_{tr} = 0.92, SD_w = 0.054; Old: mean_{tr} = 1.04, SD_w = 0.121; t (13.92) = 2.32, p_{FDR} = 0.066, d_R = 0.80 (0.14, 1.45)), post-training (Young: mean_{tr} = 0.91, SD_w = 0.109; Old: mean_{tr} = 1.07, SD_w = 0.137; t (18.89) = 2.16, p_{FDR} = 0.066, d_R = 0.75 (0.03, 1.48)), or retention (Young: mean_{tr} = 0.99, SD_w = 0.160; Old: mean_{tr} = 1.06, SD_w = 0.142; t (19.58) = 0.85, p_{FDR} = 0.406, d_R = 0.29 (-0.47, 0.88)). The levels of interlimb transfer expressed by young and older adults were thus comparable between groups and across time (Figure 4.8).

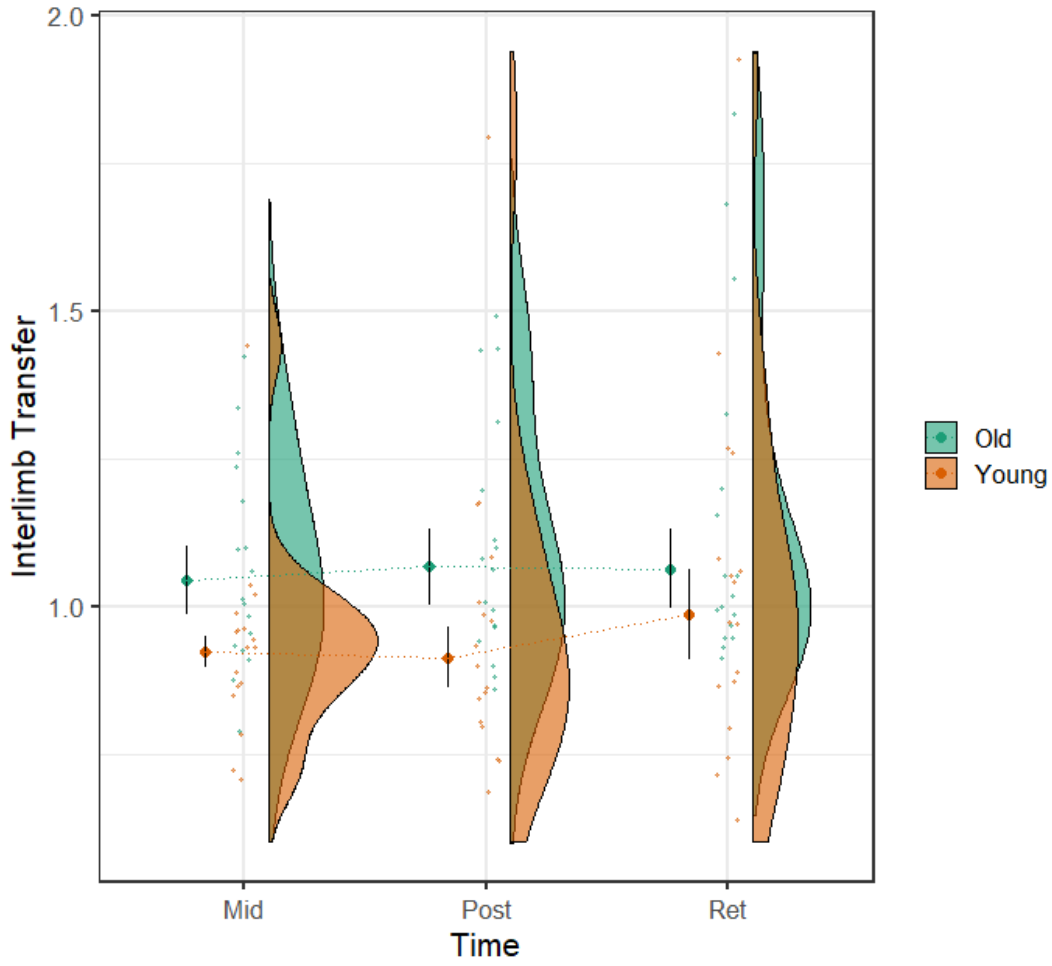


Figure 4.8: Interlimb transfer as a function of age and time. These data are provided separately for young (orange dots) and older adults (green dots). The orange/green dots denote the trimmed means of the normalised acceleration values (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals.

4.3.6 ELECTROPHYSIOLOGICAL OUTCOMES: TRAINING-RELATED CHANGES IN SHORT- AND LONG-LATENCY DORSAL PREMOTOR-PRIMARY MOTOR CORTEX INTERHEMISPHERIC INHIBITION

To assess age- and training-related changes (i.e., between pre- to mid-training and pre- to post-training) in short-latency PMd-M1 IHI, a robust two-factor mixed effects model was computed in which age was included as a between-subjects factor (levels = young, old) and time as a within-subjects factor (levels = mid, post). This analysis revealed no significant effects of age (F (1, 18.95) = 2.05, p = 0.169), time (F (1, 18.96) = 0.97, p = 0.338), or an age x time interaction (F (1, 18.95) = 0.03, p = 0.866). In both cohorts, there were no reliable differences between the percentage change in short-latency PMd-M1 IHI that was expressed at mid- and post-training (Young mid vs. post: t (10) = 1.11, p_{FDR} = 0.292, d_R = 0.42 (-0.10, 1.41); Old mid vs. post: t (9) = 2.98, p_{FDR} = 0.423, d_R = 0.32 (-0.29, 1.25)). There were no statistically significant differences in the percentage change in short-latency PMd-IHI between young and older adults at mid- (Young: $mean_{tr}$ = -0.65, SD_w = 8.10; Old: $mean_{tr}$ = -4.36, SD_w = 8.98; t (18.29) = 0.78, p_{FDR} = 0.444, d_R = 0.27 (-0.45, 0.96)) or post-training (Young: $mean_{tr}$ = -3.99, SD_w = 6.90; Old: $mean_{tr}$ = -8.72, SD_w = 9.71; t (18.29) = 0.99, p_{FDR} = 0.337, d_R = 0.38 (-0.33, 1.20)) (Figure 4.9).

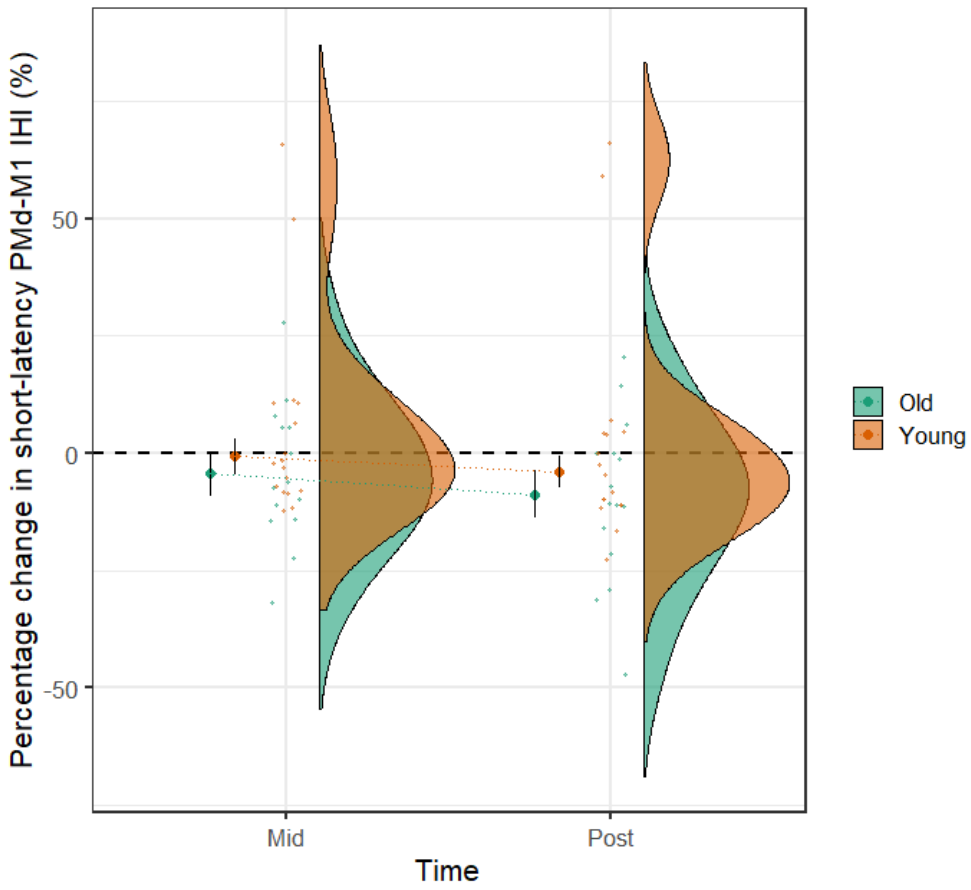


Figure 4.9: Percentage change in short-latency right dorsal premotor cortex-left primary motor cortex interhemispheric inhibition as a function of age and time. These data are provided separately for young (orange dots) and older adults (green dots). The large orange/green dots denote the trimmed means of the normalised acceleration values (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals. Each plot and the accompanying analyses are based only on data from those participants who attended both testing sessions. In one older adult, it was not possible to obtain a measure of IHI as the stimulation intensity associated with the conditioned threshold hunting target consistently exceeded the output capacity of the stimulator.

With respect to the percentage change in long-latency PMd-M1 IHI (again expressed relative to pre-training levels), a similar analysis as that above was undertaken. The results of the two-factor model revealed no effects of age (F (1, 14.46) = 0.77, p = 0.394), time (F (1, 14.46) = 0.35, p = 0.563), or an age x time interaction (F (1, 14.46) = 0.08, p = 0.780). There were no reliable pairwise differences between the percentage change in long-latency PMd-M1 at mid- or post-training in either young or older adults (Young mid vs. post: t (10) = 1.35, p_{FDR} = 0.207, d_R = 0.25 (-0.31, 0.80); Old mid vs. post: t (9) = 0.22, p_{FDR} = 0.831, d_R = 0.30 (-0.36, 1.05)). As with percentage changes in short-latency PMd-M1 IHI, there were also no statistically significant differences in the percentage change in long-latency PMd-M1 IHI between young and older adults at mid-training (Young: $mean_{tr}$ = -4.31, SD_w = 6.43; Old: $mean_{tr}$ = -2.56, SD_w = 9.61; t (15.86) = 0.372, p_{FDR} = 0.716, d_R = 0.14 (-0.69, 0.93)) or post-training (Young: $mean_{tr}$ = -7.29, SD_w = 6.43; Old: $mean_{tr}$ = -3.87, SD_w = 8.65; t (15.86) = 0.80, p_{FDR} = 0.435, d_R = 0.30 (-0.53, 1.11)) (Figure 4.10).

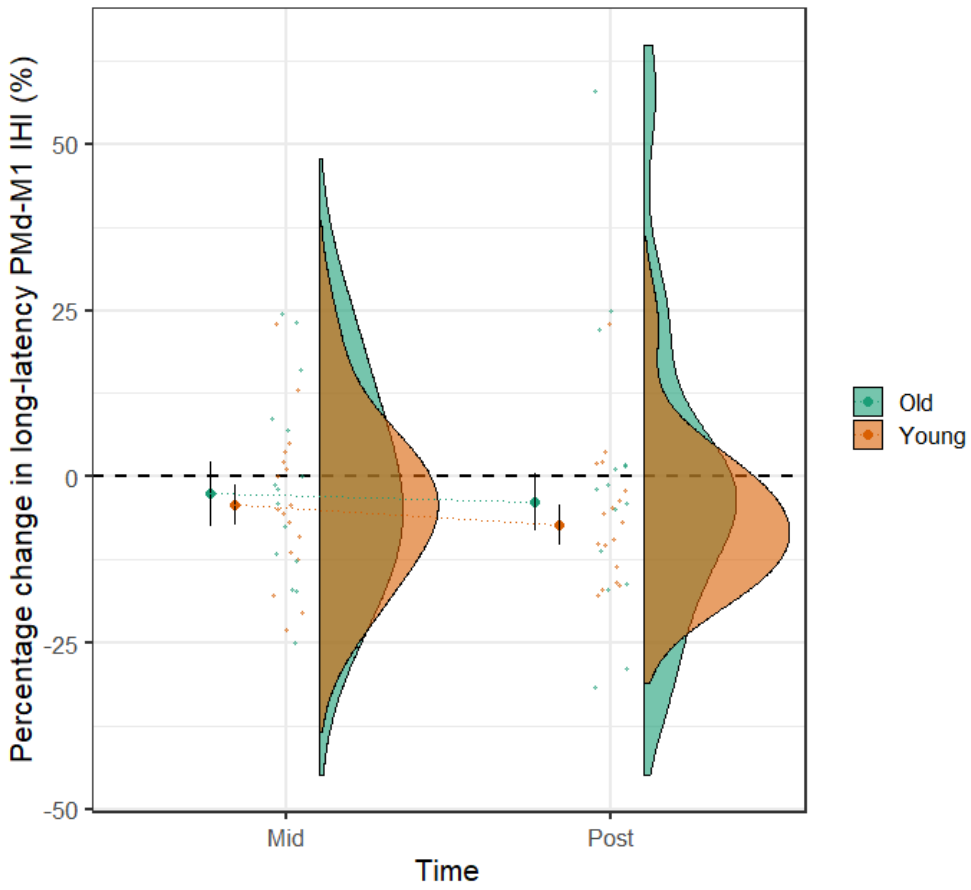


Figure 4.10: Percentage change in long-latency right dorsal premotor cortex-left primary motor cortex interhemispheric inhibition as a function of age and time. These data are provided separately for young (orange dots) and older adults (green dots). The orange/green dots denote the trimmed means of the normalised acceleration values (trimming interval = 0.2). The error bars represent the corresponding 95% confidence intervals. Each plot and the accompanying analyses are based only on data from those participants who attended both testing sessions. In one older adult, it was not possible to obtain a measure of IHI as the stimulation intensity associated with the conditioned threshold hunting target consistently exceeded the output capacity of the stimulator.

There was no difference between the rMTs of young ($mean_{tr}$ = 49.08, SD_w = 3.56) and older adults ($mean_{tr}$ = 52.33, SD_w = 3.62) in the conditioned hemisphere (t (22.66) = 1.73, p = 0.097, d_R = 0.42). The stimulation intensity required to elicit the THT (i.e., in the test hemisphere) was however significantly greater in the older adult group (t (22.66) = 3.07, p = 0.007, d_R = 0.65; older adults: $mean_{tr}$ = 61.08, SD_w = 9.85; young adults: $mean_{tr}$ = 48.31, SD_w = 5.34). All means and standard deviations are expressed as percentages of maximum stimulator output (MSO).

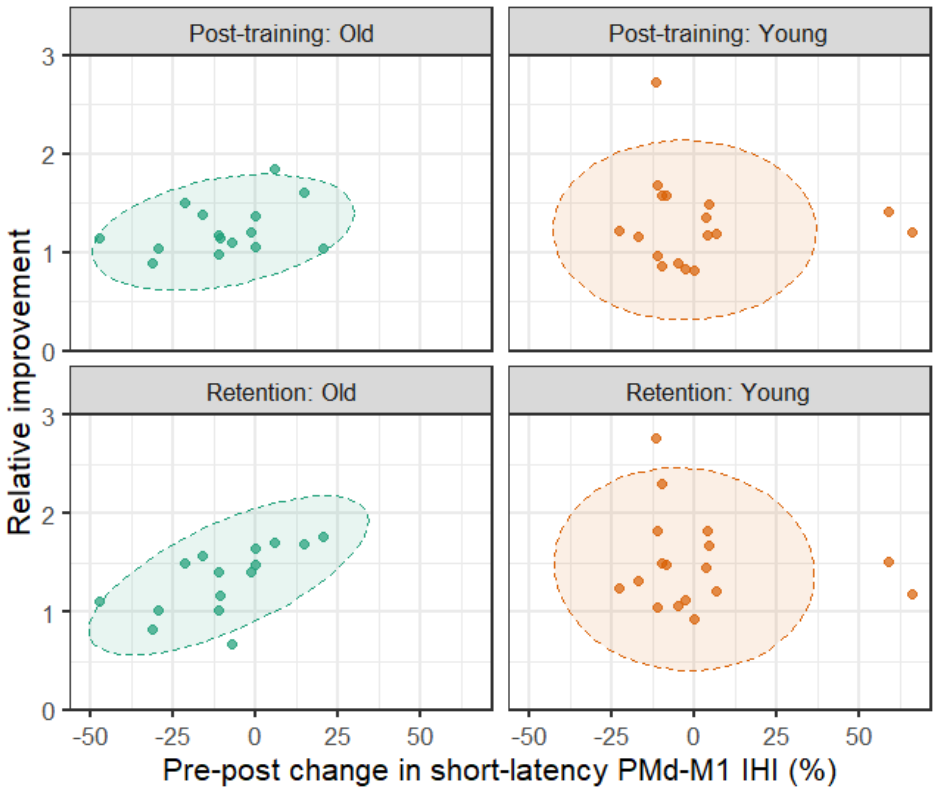
In seeking to establish whether the amplitudes of the "control" MEPs (i.e., those elicited during the course of each IHI measurement at the same intensity as that needed to evoke the THT in the absence of conditioning) were equivalent between testing intervals, a series of equivalence tests were undertaken based on the rTOST procedure. These analyses were performed separately by group and included only those participants for whom a minimum of five MEPs were obtained at each time point, to ensure sufficient within-session reliability of MEP amplitudes (Cavaleri et al., 2017). In applying these criteria, the effective sample size was 10 young adults and 9 older adults. In young adults alone, the rTOST analyses indicated that the control MEP amplitudes obtained at pre- ($mean_{tr}$ = 303.01, SD_w = 120.46), mid- ($mean_{tr}$ = 404.34, SD_w = 122.83), and post-training ($mean_{tr}$ = 402.36, SD_w = 143.59) were not statistically equivalent (pre vs. mid: t (5) = 1.10, p = 0.837; pre vs post: t (5) = 1.04, p = 0.853; mid vs. post: t (5) = 0.04, p = 0.509). A similar pattern was evident in the case of older adults, in respect of MEPs obtained at pre- ($mean_{tr}$ = 212.70, SD_w = 145.00), mid- ($mean_{tr}$ = 346.30, SD_w = 128.14), and post-training ($mean_{tr}$ = 328.22, SD_w = 112.50) (pre vs. mid: t

(6) = 3.28 p = 0.991; pre vs post: t (6) = 2.37, p = 0.972; mid vs. post: t (6) = 0.67, p = 0.727). All means and standard deviations are expressed in units of μV.

4.3.7 Correlation analyses: Relative improvement and training-related changes in dorsal premotor–primary motor cortex interhemispheric inhibition

In older adults, interindividual variations in the levels of relative improvement expressed at retention (i.e., one-week following the initial training session), were correlated positively with pre- to post-training changes in short-latency PMd M1 IHI (r_{pb} = 0.72 (0.33, 0.90), p_{FDR} = 0.024). No other correlations approached conventional levels of statistical significance (all ps > 0.05) (Figure 4.11). The results are summarized in Table 4.1.

(A)


Post-training: Old
Post-training: Young
Retention: Old
Retention: Young
Relative improvement
0
1
2
3
-50
-25
0
25
50
Pre-post change in short-latency PMd-M1 IHI (%)

(B)

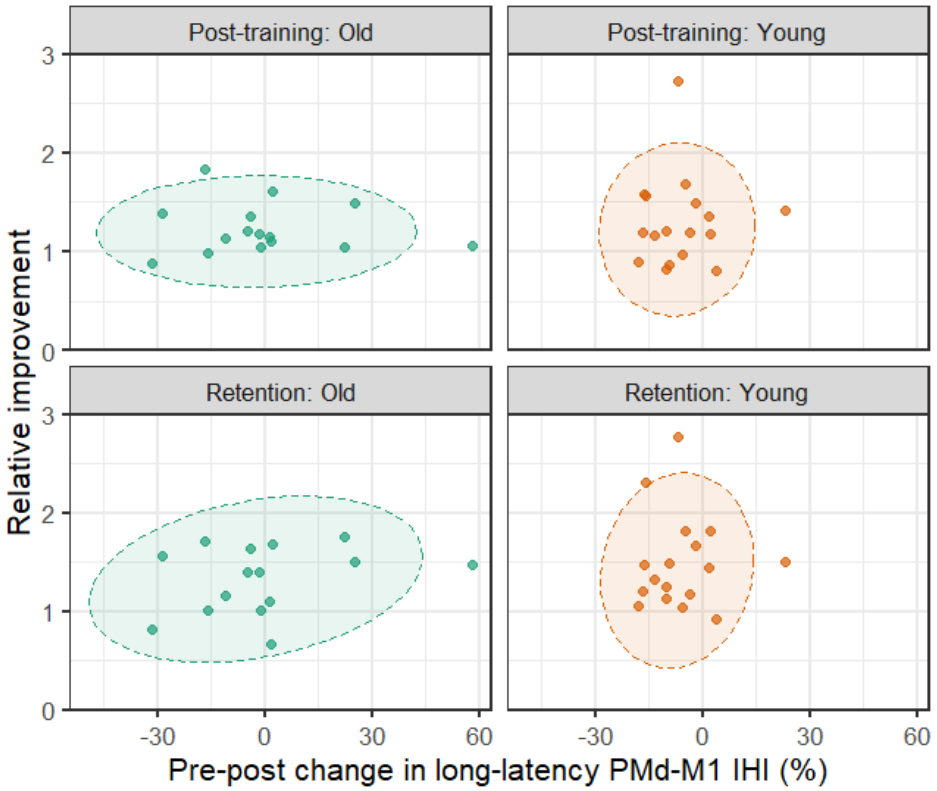

Post-training: Old
Post-training: Young
Retention: Old
Retention: Young
Relative improvement
0
1
2
3
-30
0
30
60
Pre-post change in long-latency PMd-M1 IHI (%)

Figure 4.11: Scatterplots depicting the relationship between training-related changes in short- (A) and long-latency (B) right dorsal premotor cortex-left primary motor cortex interhemispheric inhibition (from pre- to post-training) and levels of relative improvement attained at post-training and retention in young and older adults. In each panel, the topmost plots correspond to levels of relative improvement expressed at post-training while those at the bottom are concerned with levels registered at retention. Each plot and the accompanying analyses are based only on data from those participants who attended both testing sessions. In one older adult, it was not possible to obtain a measure of IHI as the stimulation intensity associated with the conditioned threshold hunting target consistently exceeded the output capacity of the stimulator. Young *n* = 17, old *n* = 15.

Table 4.1.

Percentage bend correlations between levels of relative improvement (attained at post-training and retention) and pre- to post changes in short- and long-latency dorsal premotor-primary motor cortex interhemispheric inhibition in young and older adults.

Age Group	IHI_{ISI}	Time	r_{pb} (95% CI)	*n*	p_{FDR}
Young	8 ms	Post-training	-0.05 (-0.51, 0.45)	17	0.947
		Retention	-0.08 (-0.54, 0.42)	17	0.947
	40 ms	Post-training	0.02 (-0.47, 0.49)	17	0.947
		Retention	0.17 (-0.34, 0.60)	17	0.947

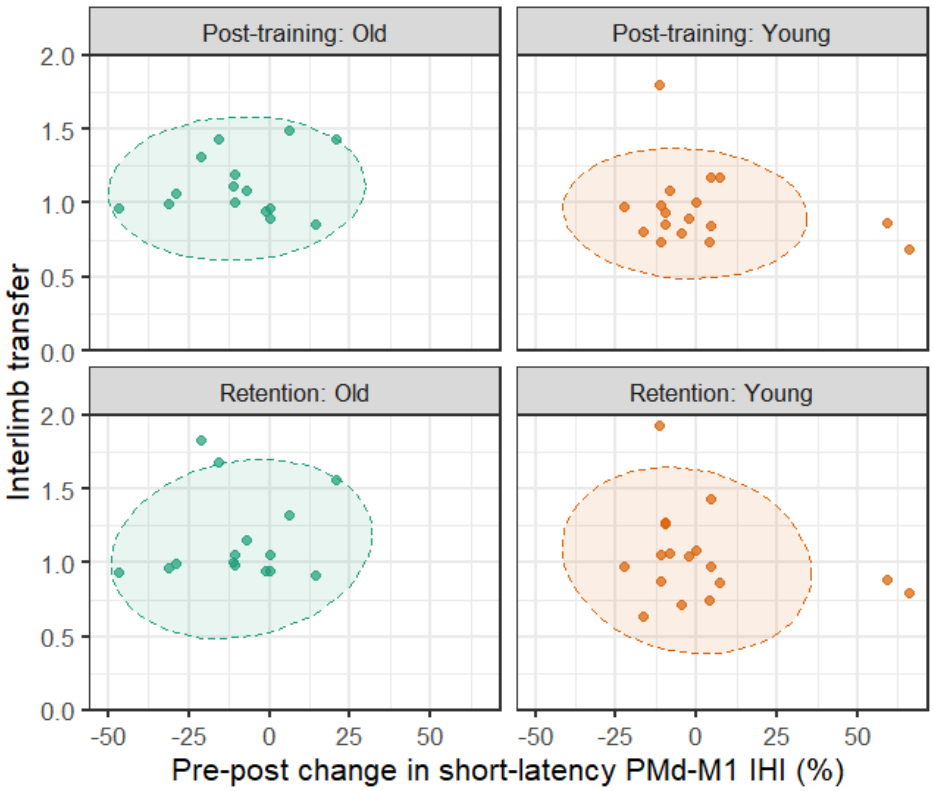
Old	8 ms	Post-training	0.34 (-0.21, 0.72)	15	0.741
		Retention	0.72 (0.33, 0.90)	15	0.024*
	40 ms	Post-training	0.04 (-0.49, 0.54)	15	0.947
		Retention	0.30 (-0.25, 0.70)	15	0.741

r_{pb} = *percentage bend correlation coefficient;* FDR = Benjamini-Hochberg false discovery rate; IHI_{ISI} = interhemispheric inhibition interstimulus interval; *$p_{FDR} < 0.05$.

4.3.8 CORRELATION ANALYSES: INTERLIMB TRANSFER AND TRAINING-RELATED CHANGES IN DORSAL PREMOTOR-PRIMARY MOTOR CORTEX INTERHEMISPHERIC INHIBITION

In both young and older adults, there was no correlation between interindividual variations in levels of interlimb transfer registered at post-training and retention, and the magnitudes of pre- to post-training changes in short- (Figure 4.12A) or long-latency PMd-M1 IHI (all *p*s > 0.05) (Figure 4.12B). The results are summarised in Table 4.2.

(A)


Post-training: Old
Post-training: Young
Retention: Old
Retention: Young
Interlimb transfer
2.0
1.5
1.0
0.5
0.0
-50
-25
0
25
50
Pre-post change in short-latency PMd-M1 IHI (%)

(B)

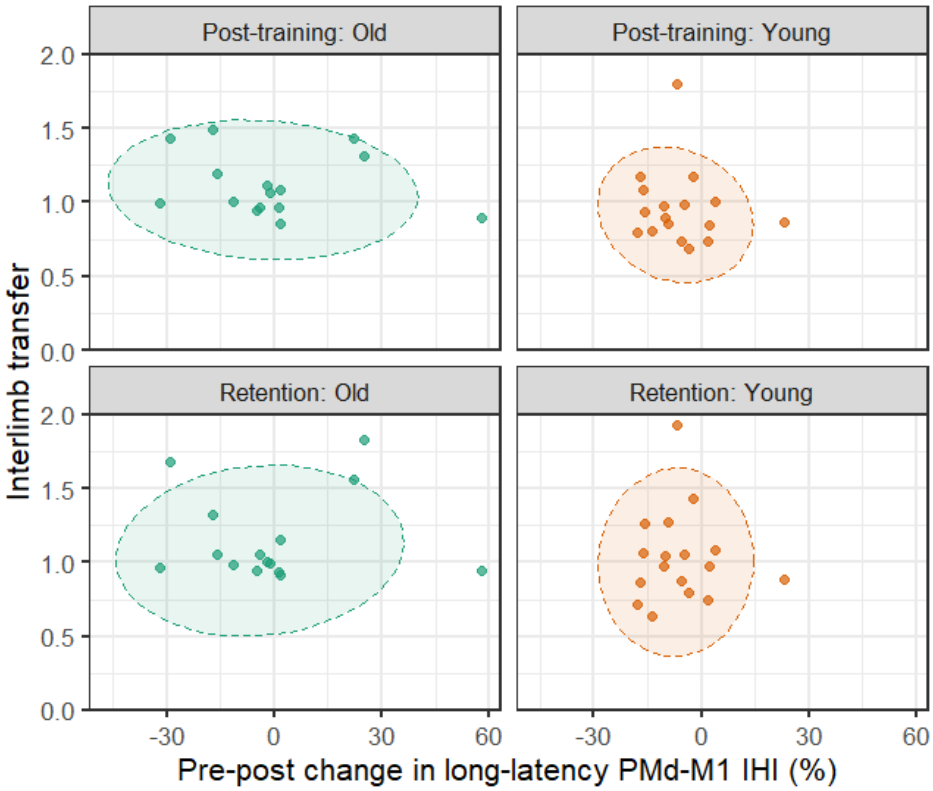

Post-training: Old
Post-training: Young
Retention: Old
Retention: Young
Interlimb transfer
2.0
1.5
1.0
0.5
0.0
-30
0
30
60
Pre-post change in long-latency PMd-M1 IHI (%)

Figure 4.12: Scatterplots depicting the relationship between training-related changes in short- (A) and long-latency (B) right dorsal premotor cortex-left primary motor cortex interhemispheric inhibition (from pre- to post-training) and levels of interlimb transfer attained at post-training and retention in young and older adults. In each panel, the topmost plots correspond to levels of interlimb transfer expressed at post-training while those at the bottom are concerned with levels registered at retention. Each plot and the accompanying analyses are based only on data from those participants who attended both testing sessions. In one older adult, it was not possible to obtain a measure of IHI as the stimulation intensity associated with the conditioned threshold hunting target consistently exceeded the output capacity of the stimulator. Young *n* = 17, old *n* = 15.

Table 4.2.

Percentage bend correlations between levels of interlimb transfer (attained at post-training and retention) and pre- to post changes in short- and long-latency dorsal premotor-primary motor cortex interhemispheric inhibition in young and older adults.

Age Group	IHI_{ISI}	Time	r_{pb} (95% CI)	*n*	p_{FDR}
Young	8 ms	Post-training	-0.08 (-0.54, 0.42)	17	0.952
		Retention	-0.21 (-0.63, 0.30)	17	0.952
	40 ms	Post-training	-0.22 (-0.63, 0.29)	17	0.952
		Retention	0.02 (-0.47, 0.49)	17	0.952
Old	8 ms	Post-training	0.03 (-0.49, 0.53)	15	0.952

	Retention	0.15 (-0.39, 0.62)	15	0.952
40 ms	Post-training	-0.06 (-0.56, 0.47)	15	0.952
	Retention	0.11 (-0.43, 0.59)	15	0.952

r_{pb} = *percentage bend correlation coefficient;* FDR = Benjamini-Hochberg false discovery rate; IHI_{ISI} = interhemispheric inhibition interstimulus interval; *$p_{FDR} < 0.05$.

4.4 DISCUSSION

Here, we demonstrated that a single session of unimanual ballistic wrist extension training undertaken with the non-dominant limb of right-handed participants, engendered comparable levels of CE (when expressed in terms of relative improvement and interlimb transfer) in both young and older adults. These effects were present both acutely, i.e., immediately after training, and one-week following its completion ("retention"). In both age groups, TMS-derived measures of short- and long-latency PMd-M1 IHI did not vary significantly over the course of training, nor did they differ appreciably between young and older adults when assessed at mid- or post-training. In light of failures in ensuring that the amplitude of the test response was maintained constant throughout the course of training, it was not however possible to interpret sensibly the functional significance of any variations in the measures of IHI that were obtained. More specifically, as it was not known whether equivalent populations of neurons were being stimulated by the TS at each point of measurement (due to substantial fluctuations in "control MEP" amplitudes, i.e., between pre-, mid-, and post-training), the possibility that the observed changes in IHI were driven mainly by changes in the excitability of corticospinal projections from the untrained M1 – rather than alterations in inhibitory drive from the contralateral PMd, could not be excluded. Necessarily therefore, an interpretation of the observed changes in IHI cannot be provided.

We have raised the point previously that the levels of CE expressed by young and older adults, and the extent to which these may differ between groups, may depend upon the characteristics of the specific training task (Calvert &

Carson, 2022). Although reference is made below to the meta-analytic estimates reported by Green and Gabriel (2018), it is important to emphasise that these estimates were based mainly on outcomes obtained from multi-session (>5) strength training paradigms which varied widely in respect of training load, rather than single sessions of ballistic movement training. While we retain these values to facilitate comparisons with levels of CE reported elsewhere in the literature, it is also necessary to consider the present findings with reference to the levels of CE that have been obtained in the context of similar training paradigms.

When expressed in terms of the level of relative improvement that was present immediately after training, the magnitude of CE exhibited by the older adults enrolled in the present study (~18%) was consistent with estimates derived from a recent meta-analysis (15%, see Green & Gabriel, 2018). It was also similar to that reported in a previous investigation in which a unimanual ballistic thumb abduction protocol was employed (~12.5%, see Dickins et al., 2015a). Although the levels of CE observed following a regimen of ballistic finger abduction training exceeded those obtained in the present study (26%, see Hinder et al., 2013), this was the case only when the non-dominant limb was trained (as was the case in the present study). When the same training regimen was undertaken with the dominant limb instead, significantly lower levels of CE were notably obtained (6%, see Hinder et al., 2011; *cf*. Parikh & Cole, 2013). This pattern of outcomes is reminiscent of the notion of "transfer asymmetries" whereby the performance gains derived by an untrained limb may depend specifically on which limb is trained (Sainburg, 2002). Although this effect is sometimes conceptualised in terms of "limb dominance" (i.e., handedness or footedness), an alternative

explanation is that different aspects of movement control (e.g., acceleration amplitude, duration) may be lateralised to different cerebral hemispheres (Sainburg et al., 2016). While transfer *symmetries* (i.e., where transfer occurs regardless of which limb is trained) are more characteristically observed in older adults, this effect is likely to be task-dependent (Graziadio et al., 2015b; Krishnan et al., 2018; Pan & Van Gemmert, 2013; Wang et al., 2011). A mechanism based on the notion of transfer asymmetries may therefore account for the abnormally low levels of CE observed by Hinder et al. (2011). Altogether, the levels of relative improvement attained by older adults enrolled in the present study was within the range of values reported previously by similar training paradigms.

While the level of relative improvement expressed by young adults immediately after training (~24%) was consistent with meta-analytic estimates (~18%, see Green & Gabriel, 2018), it was generally lower than that reported by other ballistic movement training studies in which a single session of ballistic finger abduction (~20-54%, see Hinder et al., 2013; Hinder et al., 2011; Parikh & Cole, 2013; Reissig et al., 2015), thumb abduction (~43%, see Dickins et al., 2015a), or wrist flexion training was undertaken (~23-41%, see Ruddy et al., 2017b; Ruddy et al., 2016). Although our young adults did not exhibit levels of relative improvement that were commensurate with these studies, the stated absence of age differences (i.e., when performance was contrasted with the older adult group) was nonetheless consistent with similar reports (Hinder et al., 2013; Parikh & Cole, 2013; Reissig et al., 2015). It was also accordant with the lack of age differences (i.e., in relative improvement) reported by several strength training studies (Bemben & Murphy, 2001; Ehsani et al., 2014; Hester et al., 2019a; Hester

et al., 2019b; Lemmer et al., 2000). As relative improvement may be bound intimately to the dimensions of motor training, the lack of age differences observed in ballistic movement and strength training protocols may share a common basis, in that both tasks necessitate that a high level of neural drive be directed to the limb engaged in training. This is unlikely to apply to tasks which place greater emphasis on such skills as visuomotor tracking, which have been shown previously to engender lower levels of relative improvement in older volunteers (Veldman et al., 2021). This reinforces a point which was raised previously, namely that the expression of age differences in relative improvement is likely to be task-dependent.

When expressed in terms of interlimb transfer, the level of CE attained by older subjects at post-training (~107%) and retention (~106%) was substantially greater than that reported by other ballistic movement training studies (11-36%, see Dickins et al., 2015a; Hinder et al., 2011; Parikh & Cole, 2013). It was also greater than estimates (~48%) derived from a recent meta-analysis of six ageing studies (Green & Gabriel, 2018). By contrast, although the level of interlimb transfer expressed by young adults at post-training (~91%) and retention (~99%) was larger than meta-analytic estimates (~70%, see Green & Gabriel, 2018), it was within the range of values reported by other ballistic movement training studies (73-110%, see Parikh & Cole, 2013; Ruddy et al., 2017b; Ruddy et al., 2016; *cf.* ~52% in Dickins et al., 2015a). Although there is some evidence that young adults tend to exhibit higher levels of transfer than older volunteers (young = 70%, old = 48%, see Green & Gabriel, 2018), this has been observed only inconsistently in the context of ballistic movement training studies (young > old, see Hinder et al.,

2011; Parikh & Cole, 2013; no difference, see Dickins et al., 2015a; Hinder et al., 2013). Altogether, the present findings are consistent with the view that young and older adults not only exhibit comparable levels of interlimb transfer, but that the degree of transfer present remains relatively stable throughout the course of the intervention (i.e., from pre-training to retention).

It is important to note that in contrast to previous studies (e.g., Hinder et al., 2013; Hinder et al., 2011; Parikh & Cole, 2013), the raw accelerations of the trained and untrained limbs observed in older adults, were appreciably greater than those exhibited by younger volunteers. It is therefore possible that the sample of older adults recruited in the present study was not necessarily representative of older adults generally. The notion of "super seniors" is a well-documented phenomenon in ageing research (e.g., Cabeza et al., 2018). It refers to the tendency in scientific studies to recruit older adults whose health status and educational attainment may differ (often in a positive fashion) from those of the reference population (Martinson et al., 2010). In seeking to generalise the behavioural outcomes observed in the present study, considerable circumspection may be therefore required.

As described previously, the stated failures in maintaining constant the amplitudes of the "control" MEPs between each testing interval (i.e., at pre-, mid-, and post-training) were such that it was not possible to ascribe any functional significance to any variations in IHI that were observed. More specifically, it was not possible to determine to what extent the observed changes in IHI were driven by changes in the excitability of corticospinal projections from the untrained M1, as opposed to alterations in inhibitory drive from the contralateral PMd. These

issues serve to highlight that, in the context of an intervention study, it is absolutely critical to track at each point of measurement, the TS intensity required to elicit the non-conditioned THT. The present findings perhaps also highlight a critical issue with the threshold tracking methodology. Apart from one exception, the amplitudes of the control MEPs obtained during the course of each IHI measurement differed dramatically from the expected THT (i.e., 200 μV). This was likewise apparent during the acquisition of pre-training measures of IHI in younger volunteers, despite the test stimulus intensity having been determined only a few minutes prior. If one cannot assume that the stimulation intensity determined by the PEST algorithm reliably elicits the non-conditioned response, how can we assume that its estimate of that required to elicit the conditioned THT is at all valid? This observation underscores the need to reassess the TS intensity required to elicit the THT at each point of measurement.

In summary, we demonstrated that comparable levels of CE are obtained in young and older adults (when expressed in terms of relative improvement and interlimb transfer), both immediately and one-week following a single session of unimanual ballistic wrist extension training.

Chapter 5

General Discussion

5.1 General discussion and closing remarks

The aim of this thesis was twofold:

(a) To examine age-related variations in the extent to which the phenomenon of cross education (CE) is manifested.

(b) To develop novel methods of non-invasive brain stimulation with which to elucidate the underlying neural mechanisms which mediate this effect.

In Chapter 1, an extensive review of the literature was presented that detailed several pathways that exhibit the potential to mediate the putative neural adaptations that underlie the expression of CE. A specific emphasis was placed upon the extent to which associated brain structures and networks may be affected by the neurodegenerative processes that are a feature of ageing. Several conclusions emerged from this analysis. In the first instance, there was little evidence that lifespan variations in CE (or in the mechanisms which mediate it) can be attributed to alterations in the states or structure of descending corticofugal projections to the untrained limb, irrespective of their origin. A similar conclusion was reached with respect to adaptations that occur within the 'untrained' primary

motor cortex (M1), which was based mainly on appraisal of evidence derived from transcranial magnetic stimulation (TMS)-based measures of inter- and intra-hemispheric M1 connectivity. The functional contributions of non-primary motor regions were then considered, which identified dorsolateral prefrontal cortex (dlPFC), dorsal premotor cortex (PMd), and supplementary motor area (SMA), as candidate structures which may be implicated in mediating CE. In older adults, the potential functional contributions of PMd were highlighted specifically.

This led to the formulation of a research agenda that was given effect through three experimental studies. In Chapters 2 and 3, novel methods of non-invasive brain stimulation were developed and refined, with the view of probing excitatory and inhibitory interhemispheric PMd-M1 interactions. The method developed in Chapter 3 was applied subsequently to a CE paradigm which sought to examine age-related variations in PMd-M1 connectivity and their ostensive association with various indices of CE, as described in Chapter 4. In the first experimental study (Chapter 2), a novel method of eliciting interhemispheric facilitation (IHF) was devised, in which the magnetic conditioning stimulus was replaced by a short burst of transcranial alternating current (tACS) or random-noise stimulation (tRNS). As IHF has been examined only sparingly with magnetic conditioning of non-primary motor regions (and elicited with even greater scarcity), we decided that in seeking to establish proof of principle, it was necessary to apply conditioning tACS and tRNS to M1 only. The intention of this approach was to enable comparisons with results obtained with other, more conventional methods of stimulation (i.e., dual-coil TMS) in which the conditioning and test stimuli have been applied almost exclusively to M1. We

hypothesised that the amplitudes of motor-evoked potentials (MEPs) elicited by TMS stimuli that were preceded 6 ms earlier by short bursts of tACS or tRNS applied to the opposite M1, would be significantly greater than those elicited by TMS alone. In the second experimental study (Chapter 3), a novel approach to eliciting interhemispheric inhibition (IHI) was presented, that incorporated a fully automated dual-coil adaptive threshold hunting (ATH) paradigm. Although PMd-M1 IHI has been investigated previously with dual-coil TMS approaches, variations in only a limited range of stimulation parameters (e.g., conditioning stimulus intensity, interstimulus interval, test coil orientation) have thus far been examined. The central objective of this study was to define a range of stimulation parameters that can be used reliably to elicit PMd-M1 IHI. In the third (and final) experimental study (Chapter 4), a unimanual ballistic wrist extension paradigm was employed to study age-related variations in the levels of CE expressed by young and older adults. In addition, using methods developed in Chapter 3, we also sought to establish whether changes in short- and long-latency PMd-M1 IHI occurred over the course of training. Altogether, the aim of this study was twofold: i) to examine differences in the levels of CE attained by young and older adults, both immediately and one-week following the initial training session; and ii) to ascertain whether the level of CE thus expressed was associated with the magnitude of change in PMd-M1 IHI.

5.2 SUMMARY OF EMPIRICAL FINDINGS

In Chapter 2, a novel method of eliciting IHF was trialled, in which the initial magnetic conditioning stimulus was replaced by a short burst of tACS or tRNS. Although this effect is typically obtained with dual-coil TMS, it is widely held that the poor spatial resolution of the transcallosal volley evoked by the magnetic conditioning stimulus, may activate a slew of inhibitory inputs that mask the focal facilitation expressed by the test MEP. We reasoned that this effect would be at least partially circumvented if the magnetic conditioning stimulus was replaced by a discrete (< 500 ms) electrical stimulus that engendered voltage gradients several orders of magnitude weaker than those induced by TMS. Using this approach, IHF was obtained between the primary motor cortices when a suprathreshold TMS stimulus that induced current flow in the anterior-to-posterior (AP) direction, was preceded 6 ms earlier by a 30 ms (but not 100 or 500 ms) duration burst of 1 mA (peak-to-peak) 140 Hz tACS applied to the opposite M1. The magnitude of this effect (an increase of ~12% in MEP amplitude, i.e., relative to that elicited by TMS alone) was within the range of values reported previously by dual-coil TMS studies in which the test stimulus induced current flow in the AP direction. The amplitudes of MEPs elicited by TMS 6 ms following 6, 12, 100, or 500 ms duration bursts of 670 Hz tACS or 100-640 Hz tRNS applied to the opposite M1, were not modulated reliably relative to a control condition in which TMS was delivered in the absence of conditioning stimulation. To the best of our knowledge, this study is the first to demonstrate that IHF may be obtained when the magnetic conditioning stimulus is replaced by a short duration (i.e., 30 ms)

burst of tACS. Whether there exists a specific combination of tACS stimulation parameters (e.g., current level, duration, frequency, interstimulus interval, phase) with which this form of IHF may be elicited more reliably than that obtained with conventional dual-coil TMS, remains to be determined.

In Chapter 3, a fully automated dual-coil ATH paradigm was devised, with the view of establishing a range of stimulation parameters that can be used reliably to elicit IHI between PMd and M1 (and also right and left M1). Although IHI is conventionally expressed as a percentage change in MEP amplitude when a fixed TS intensity is applied in the presence of conditioning stimulation, the ATH method quantifies IHI as the percentage change in stimulation intensity necessary to elicit a fixed MEP amplitude known as the threshold hunting target (THT). Several stimulation parameters were manipulated, including conditioning stimulus intensity, interstimulus interval, and test coil orientation. The major finding was that PMd-M1 IHI was obtained only with test stimuli that induced current flow in the posterior-to-anterior (PA) direction. Reversing the coil orientation such that the cortical eddy current flowed in the opposite (i.e., AP) direction, did not affect the stimulation intensity required to elicit the conditioned THT. The depth of PMd-M1 IHI that was obtained when the test stimulus was oriented to induce current flow in the PA direction, tended to increase as a function of conditioning stimulus intensity, but did not vary by interstimulus interval. When conditioning stimulation was applied to M1, IHI was obtained with test stimuli that induced current flow in either the PA or AP directions. As with PMd-M1 IHI, the magnitude of M1-M1 IHI tended to increase as a function of conditioning stimulus intensity, but only in circumstances in which the test coil

was oriented to induce current flow in the PA (but not AP) direction. The depth of M1-M1 inhibition was generally greatest when the test coil was oriented to induce current flow in the PA direction. There was no difference between the level of M1-M1 IHI obtained with short- (10 ms) or long-latency (40 ms) interstimulus intervals. As far as we are aware, this study constitutes one of the most comprehensive assessments of PMd-M1 IHI that have been undertaken to date. It is also the first to document a fully automated procedure with which the effect can be obtained.

In Chapter 4, a unimanual ballistic wrist extension paradigm was employed in which young and older adults completed a single session of non-dominant limb training. Performance of the trained and untrained limbs was assessed prior to ("pre"), midway through ("mid"), and immediately following ("post") the training regimen. In seeking to differentiate improvements in performance that were due to motor practice, from those which reflect the extent of motor learning, the same measures were also obtained one-week following the initial training session ("retention"). CE was expressed both in terms of relative improvement (i.e., the normalised gain in acceleration of the untrained limb relative to pre-training performance) and interlimb transfer (i.e., the relative improvement of the untrained limb expressed relative to that of the limb engaged in training). Although older adults tended to express lower levels of relative improvement than their younger counterparts (both at post-training and retention), the two groups did not differ significantly on this measure. In terms of interlimb transfer, the opposite effect was obtained, whereby older adults tended to exhibit higher levels of transfer than younger volunteers. Once again, however, these

differences were not statistically significant. The levels of relative improvement and interlimb transfer expressed at post-training were similar to those expressed in the retention session undertaken one-week later. Using methods devised in Chapter 3, a further aim was to establish whether there were accompanying (i.e., training-related) changes in short- and long-latency PMd-M1 IHI. In light of failures in ensuring that the amplitude of the test response was maintained constant throughout the course of training, it was not however possible to obtain interpretable measures of IHI. More specifically, as it was not known whether equivalent populations of neurons were being stimulated by the test stimulus at each point of measurement (due to substantial fluctuations in the amplitudes of "control MEP" amplitudes, i.e., when obtained at pre-, mid-, and post-training), it was impossible to determine the extent to which the observed changes in IHI were driven by changes in the excitability of corticospinal projections from the untrained M1, as opposed to alterations in inhibitory drive from the contralateral PMd.

5.3 GENERAL DISCUSSION OF FINDINGS IN RELATION TO EXISTING LITERATURE

It has been demonstrated previously that a short burst of 140 Hz tACS (~0.5 s, 1 mA peak-to-peak) can act as either the first or second element of paired associative stimulation protocols that induce changes in corticospinal tract excitability (Carson et al., 2021; McNickle & Carson, 2015). Although this form

of tACS may alter the states of neural circuits in the opposite hemisphere (Carson et al., 2021), it was not known whether the magnitude and focality of this effect lies within the "narrow window" (Bäumer et al., 2006) necessary for the invocation of IHF. In Chapter 2, we showed that pairing 30 ms (but not 100 or 500 ms) duration bursts of 1 mA (peak-to-peak) 140 Hz tACS applied to one M1, with AP TMS (at 120% rMT) delivered 6 ms later to the opposite M1, engendered significant facilitation of MEP amplitudes elicited in response to the latter. This effect was not however obtained by conditioning M1 with 6, 12, 100, or 500 ms duration bursts of 670 Hz tACS or 100-640 Hz tRNS.

Although it is widely believed that the effects of tACS on motor cortical output may be frequency-dependent, it is extremely challenging to state precisely the specific physiological mechanisms by which its effects are instantiated. It was proposed previously (Moliadze et al., 2010) that the facilitatory effects induced by 140 Hz tACS (i.e., on the amplitudes of MEPs elicited from the ipsilateral M1 following 10 min of tACS) may reflect interactions with parahippocampal ripples that engender selective activation of neocortical regions (Logothetis et al., 2012; Todorova & Zugaro, 2020). A key issue with this interpretation however is that there is no known association between the occurrence of ripple range discharges in mediotemporal areas (registered by means of intracranial recordings in humans) and corresponding changes in ripple band power in M1 (Vaz et al., 2019). An alternative explanation is that the effect may be instantiated by downregulating the firing rates of neurons in the subthalamic nucleus (STN). It has been demonstrated previously that the electric field induced in STN by 1 mA tACS (~0.08 V m^{-1}) may exceed the background activity recorded in this region by

several orders of magnitude (Ruhnau et al., 2018). In the indirect pathway of the basal ganglia, one would expect that a decrease in STN firing should engender disinhibition of both pallido- and nigro-thalamic afferents, leading to an ostensive increase in thalamocortical output. This effect may be present in patients with Parkinson's disease in whom deep brain stimulation is applied at frequencies > 100 Hz (Meissner et al., 2005). In principle therefore, it is conceivable that short bursts of 140 Hz tACS may increase the amplitudes of MEPs elicited from the contralateral M1 by decreasing the probability of STN firing, thereby facilitating thalamocortical drive to M1.

Although the discharge frequencies of corticospinal neurons that occur in response to magnetic stimulation of M1 vary in the order of ~670 Hz (Di Lazzaro et al., 2012), the amplitudes of MEPs elicited from M1 were unaffected by prior conditioning with short bursts (6-500 ms) of tACS delivered at this frequency. While various explanations have been proposed, the absence of effect attributable to ~670 Hz tACS may simply reflect the rarity with which discharge frequencies as high as these occur naturally in M1 (Lemon & Kraskov, 2019), or callosal neurons during the course of normal motor behaviour (Beloozerova et al., 2003; Soteropoulos & Baker, 2007). It is unlikely therefore that 670 Hz tACS exhibits the potential for entrainment of these cell types, other than at subharmonic frequencies. While the paucity of effect attributable to 6-500 ms duration bursts of 100-640 Hz tRNS may undermine a role for such mechanisms as stochastic resonance in facilitating the amplitudes of MEPs elicited from the contralateral M1, the point has been raised previously that the facilitatory effects of tRNS may vary as a parabolic function (i.e., in a ∩-shaped fashion) of the applied noise

intensity (Potok et al., 2021). In this regard, it should be noted that when short (3 s) bursts of (100-500 Hz) tRNS are applied with a peak-to-peak amplitude of 4 mA (but not 1 mA as that applied in the present study), the probability of eliciting MEPs with subthreshold TMS (i.e., < rMT) is increased significantly (Potok et al., 2021). It is possible therefore that the intensity of tRNS that we applied was simply insufficient to modify the discharge characteristics of neurons with the potential to influence (via callosal projections) the states of circuits in the opposite M1.

Overall, the findings of Chapter 2 provided partial support for our hypothesis that short bursts of tACS, when applied at interstimulus intervals (6 ms) shown previously to engender IHF, may increase the amplitudes of MEPs elicited from the opposite M1. There remains scope however to determine whether there exists a specific combination of stimulation parameters (e.g., tACS current, duration, frequency, phase, interstimulus interval) with which this form of IHF may be generated more reliably than that obtained with conventional dual-coil TMS methods (or indeed the parameters we employed).

In the second experimental study (Chapter 3), a fully automated dual-coil ATH paradigm was devised with the view of establishing a range of stimulator parameters (conditioning stimulus intensities, interstimulus intervals, and test coil orientations) that can be used reliably to elicit PMd-M1 (and M1-M1) IHI (Calvert et al., 2020). Although IHI is conventionally expressed as a percentage change in MEP amplitude when a fixed TS intensity is applied in the presence of conditioning stimulation, the ATH approach quantifies IHI as the percentage change in stimulation intensity necessary to elicit a fixed MEP amplitude known as the threshold hunting target (THT). The benefit of this approach is twofold.

First, by maintaining fixed the amplitude of the test response, the spinal, peripheral, and central mechanisms that mediate the expression of MEPs are held to exert a relatively consistent influence (Fisher et al., 2002; Opie & Semmler, 2014b). Secondly, if the THT lies on the appropriate portion of the nonlinear TMS intensity-MEP amplitude curve, the method is thought to reduce the influence of the trial-to-trial variability that is an inherent characteristic of magnetically evoked motor responses (Kiers et al., 1993; Vucic et al., 2006). This approach may be especially beneficial in testing older volunteers (Mooney et al., 2017), in whom greater variations in response amplitude are frequently evident (Pitcher et al., 2003).

When TMS is applied to M1, the magnetic stimulating coil is most frequently oriented such that the induced cortical eddy current travels in a latero-posterior to antero-medial (frequently termed the "PA") direction. At least partially distinct populations of fibres are excited when the TMS coil is instead oriented to induce current flow in the opposite (i.e., AP) direction (Di Lazzaro et al., 2001). It is widely believed that the magnitude of late indirect (e.g., I_3) waves generated by TMS, which are elicited preferentially by AP stimuli (Sakai et al., 1997), may reflect the states of excitation of pyramidal neurons with cells bodies in premotor cortex on the crown of the precentral gyrus, that project onto layer V cells in M1 via long-range corticocortical fibres (Laakso et al., 2014; Triesch et al., 2015). In a study that examined the relationship between the latencies of MEPs obtained with various test coil orientations and fMRI-derived measures of functional connectivity seeded on the M1 hotspot, Volz et al. (2014) concluded that MEPs elicited by AP TMS are more likely to reflect the contributions of short-

latency cortico-cortical inputs from premotor regions (including those relayed by interhemispheric projections) compared to those obtained with other coil orientations. As callosal fibres ramify in multiple layers (Cissé et al., 2003), it was not however known whether the effects of interhemispheric input to M1 following magnetic stimulation of the contralateral PMd, would be expressed most readily by test stimuli that induced current flow in the PA or AP directions.

In seeking to elicit M1-M1 IHI, it has been suggested (e.g., Mooney et al., 2018) that evoking the test response with AP TMS may enable a more sensitive measure to be obtained, as it is primarily the I_3 component (elicited preferentially with AP test stimuli, see Sakai et al., 1997) that is modulated by prior conditioning stimulation (Di Lazzaro et al., 1999). Our findings suggest however that in conditioning PMd, this line of reasoning does not necessarily apply. Indeed, while PMd-M1 IHI was expressed reliably across all conditions (n = 9) in which the test coil was oriented to induce current flow in the PA direction, it was conspicuously absent when current flow was induced in the opposite (i.e., AP) direction. While at first glance these findings may suggest that the sensitivity of afferent projections to AP and PA currents may depend upon their cortical origin, it is important to emphasise that the distributions of the cortical layers to which these fibres project may be likewise implicated. It is well established that callosal fibres ramify in multiple cortical layers including supragranular (II, III), intragranular (IV), and infragranular (V) layers (Cissé et al., 2003). While PA stimuli may thus provide the best means of eliciting PMd-M1 IHI in the context of dual-coil TMS, this does not imply that MEPs elicited in response to such stimuli necessarily provide the

most faithful representation of interhemispheric interactions between these brain regions.

The magnitude of IHI that was evoked when conditioning stimulation was applied to PMd tended to increase as a function of conditioning stimulus intensity. Although this effect was consistent with that obtained with test stimuli that induced current flow (i.e., in M1) in the lateromedial direction (Mochizuki et al., 2004; Ni et al., 2009b), it differs notably from the null effects reported by Fiori et al. (2017) who applied the same test stimuli (PA) as those used in the present work. This discrepancy is likely rooted in the ultra-long latencies (40-150 ms) at which IHI was assessed in the latter study, which exceeded the 8-40 ms window within which the present effects were obtained. Although precise mechanistic details have yet to be provided, it is acknowledged widely that short- and long-latency IHI may be mediated by interhemispheric pathways that are at least partially distinct (Ni et al., 2009b). It cannot be assumed that the effects of test coil orientation on the levels of IHI obtained at shorter interstimulus intervals necessarily hold at longer latencies. A similar effect of conditioning stimulus intensity was evident in respect of M1-M1 IHI, but only when PA (but not AP) test stimuli were applied, consistent with previous findings from our group (Ibey et al., 2015).

In summary, the findings from Chapter 3 established a range of stimulation parameters with which PMd-M1 (and M1-M1) IHI can be reliably obtained in the context of a novel, fully automated, dual-coil ATH procedure. Although it might have been expected that test stimuli that induced current flow in the AP direction may have been especially suited to capturing the interhemispheric effects of

conditioning stimulation applied to PMd, the complete absence of IHI observed in this context emphasises that the anatomical and physiological factors that determine the impact of test coil orientation on TMS-evoked potentials remain poorly understood.

Although the clinical applications of CE training have been studied most extensively in young adults (Haggert et al., 2020), the greatest therapeutic benefits are likely to be derived by older subjects in whom the incidence of unilateral impairment (e.g., following appendicular fractures, see Ensrud, 2013; or stroke, see Bejot et al., 2016) is most pronounced. As the brains of humans change profoundly as we age (Cox et al., 2016; Seidler et al., 2010) and vary accordingly in the adaptations that occur in response to motor training (Barry & Carson, 2004), two issues are thus presented. Firstly, are there age-related variations in the extent to which the phenomenon of CE is manifested? And secondly, do the neural mechanisms which meditate its expression also change with age? These questions formed the basis of the third (and final) experimental study presented in this thesis (Chapter 4).

Consistent with previous studies, our findings revealed that following a single session of unimanual ballistic wrist extension training undertaken with the non-dominant limb, similar levels of CE (expressed in terms of relative improvement and interlimb transfer) were present in young and older adults (Dickins et al., 2015a; Hinder et al., 2013; Reissig et al., 2015; *cf.* Hinder et al., 2011). In seeking to differentiate improvements in performance that were due to motor practice, from those which reflect the extent of motor learning, the same measures were also obtained one-week following the initial training session

("retention"). Although higher levels of CE were present in this second testing session, these did not differ appreciably from those observed immediately after training. While these findings may suggest that the contralateral benefits of unimanual limb training are preserved in later life (Barss et al., 2016), we have raised the point previously (Calvert & Carson, 2022) that the extent to which this holds may depend on the characteristics of the specific training task. Nonetheless, at least in the context of a ballistic movement training protocol, the present findings are supportive of the view espoused previously: that the levels of CE expressed by older adults are comparable to those attained by younger volunteers. It is important to emphasise however that in contrast to previous studies (Hinder et al., 2013; Hinder et al., 2011; Parikh & Cole, 2013), the raw accelerations exhibited by the older volunteers were appreciably greater than those of young adults. It is therefore possible that the sample of older adults recruited in the present study was not necessarily representative of older adults in general. Similar issues have been highlighted previously in other areas of ageing research (Cabeza et al., 2018; Martinson et al., 2010). In seeking to generalise the behavioural outcomes observed in the present study, considerable circumspection may thus be required.

In the course of executing unimanual actions, the level of effective connectivity that is registered interhemispherically between PMd and M1, is elevated markedly in the brains of older adults (Lariviere et al., 2019; Wang et al., 2019b). These changes are believed to drive age-related elevations in the level of activation that is manifest in the ipsilateral M1 during unimanual actions (Tak et al., 2021). This pattern of activation, in which there is increased symmetry of

motor cortical activation, is consistent with the "hemispheric asymmetry reduction in older adults" (HAROLD) model proposed by Cabeza (2002). The essence of this model is that increased levels of bilaterally symmetric functional brain activity may constitute a compensatory response that facilitates task performance, in light of age-related diminutions in grey and white matter structure. To the extent that these changes are adaptive and driven mainly by interhemispheric input from PMd to the opposite M1 (Tak et al., 2021), we applied a dual-coil TMS paradigm to obtain measures of interhemispheric inhibition (IHI) between these brain regions to determine whether training-related changes in the magnitudes of these measures, were related to interindividual variations in the levels of CE expressed by older adults.

Although in both age groups the magnitude of IHI present at mid- and post-training was marginally diminished relative to pre-training levels, the stated failures in maintaining constant the amplitudes of the "control" MEPs throughout the testing session (i.e., from pre- to post-training) were such that it was not possible to ascribe any functional significance to the changes that were observed. More specifically, we were unable to determine whether the observed changes in IHI were driven mainly by variations in the excitability of corticospinal projections from the untrained M1, or alterations in the level of inhibitory drive engendered by the contralateral PMd. These issues highlight that in the context of an intervention study, it is absolutely critical to track at each point of assessment, the TS intensity required to elicit the non-conditioned (THT) response. The present findings also highlight a potential limitation of the ATH methodology. With the exception of a single set of measurements, there was substantial deviation

in the amplitudes of the control MEPs from the expected THT amplitude (200 μV). This issue was apparent as early as the pre-training interval, despite the test stimulus intensity having been determined only a few minutes prior. If one cannot assume that the stimulation intensity determined by the PEST algorithm reliably elicits the non-conditioned THT, how can one assume that its estimation of that required to elicit the conditioned THT is at all valid? Put simply, the basic requirements of the threshold tracking paradigm were not satisfied.

Overall, the findings from Chapter 4 indicate that following a single session of unimanual ballistic wrist extension training, young and older adults exhibit comparable levels of CE (when expressed in terms of relative improvement and interlimb transfer). The benefits conferred by training remain present when assessed one-week later. It is possible however that in view of the superior accelerations generated by members of the older adult group, which unexpectedly exceeded those exhibited by young adults, that our sample of older adults was not necessarily representative of the reference population.

5.4 LIMITATIONS AND FUTURE DIRECTIONS

Although non-invasive brain stimulation in general, and TMS in particular, provide a simple means of probing motor cortical function, relating these measures (and in particular changes in their magnitude) to underlying physiological processes is not so easily achieved (Bestmann & Krakauer, 2015). While the use of such terms as IHF and IHI may be taken to imply that there is direct correspondence between TMS-derived measures of interhemispheric brain

function and the physiological processes with which they share their names, it is important to note that this association is both erroneous and misleading (Carson, 2020). In the context of IHI, the invocation of high-frequency repetitive discharges by TMS and the massed undifferentiated activity that arises consequently, cannot be assumed to provide a faithful representation of circuits which in normal physiological conditions, are precisely engaged and serve to refine the focus of motor cortical activation. In applying TMS to M1, it is important also to consider that the region of brain from which the motor potential is evoked, and the characteristics of cells from which this response is obtained, constitute only a small subset of circuits (Carson et al., 2016) that are sampled mainly from the posterior lip of the precentral crown (Dubbioso et al., 2021), and which are relayed primarily by fast-conducting corticospinal axons (Lemon et al., 2002). While it remains legitimate to enquire whether training-related changes in TMS-derived measures of IHI (or IHF) are manifested in circumstances in which CE has occurred, it is important to recognise that these methods yield only a narrow and highly partial index of interhemispheric function that does not necessarily reflect normal physiological activity. As a result, the physiological significance of any such changes (where these occur) will remain extremely challenging to determine (Calvert & Carson, 2022).

Although the amplitudes of MEPs increase monotonically with test stimulus intensity (Bawa & Lemon, 1993), the noise floor of the TMS-MEP input-output (IO) curve is known to overlap significantly with the resting background EMG, which may exceed levels as high as 10 μV (e.g., Goetz et al., 2014). In order to distinguish reliably the evoked response from the background noise which

masks it, a resting motor threshold (rMT) of ~50 μV is therefore frequently applied, that is closely associated with the initial rise of the IO slope. The consequence of this approach, however, is that it necessarily delimits the response amplitudes at which the effects of conditioning stimulation may be present. It is only by applying high intensity stimuli that these effects are thus discernible, with the caveat that a less focal response is consequently obtained. In short, the signal-to-noise ratio of the MEP response is such that it is not always possible to examine variations in MEP amplitudes that are contained within the lower segments of the IO curve. In a recent development, Li and colleagues devised an adaptive matched-filter approach that operationalises the MEP as a volley of multiple motor unit action potentials (which can be subsequently decomposed) of identical shape but variable amplitude and latency (Li et al., 2021). When applied to MEPs obtained in the context of an IO procedure, the matched-filter estimator yields an IO curve in which the lower limits are notably extended, insofar that the rMT is situated proximal to the point of inflection (i.e., the centre of the sigmoid) rather than the lower plateau. Critically, the signal-to-noise ratio may be increased more than fivefold when compared with conventional methods of detection. If applied in the context of a dual-coil TMS paradigm, the adaptive matched-filter approach may allow the effects of weak(er) conditioning stimuli (e.g., short duration tACS) to be studied with greater sensitivity, which may facilitate the detection of notoriously capricious measures such as IHF. It may also promote the use of lower THT amplitudes in threshold hunting paradigms, which not only improves participant comfort (as lower intensity TMS stimuli will be necessarily required), but also minimises the risk of ceiling effects (i.e., where the conditioned TS

intensity exceeds the output capacity of the stimulator) and coil overheating when measures of IHI are obtained. This may be especially beneficial in circumstances in which higher THT intensities are required, e.g., when testing older volunteers (Chapter 4) or when applying test stimuli that induce current flow in the AP direction (Chapter 3).

As we have noted previously, a critical limitation of the ATH methodology applied in Chapter 4, was that training-related variations in the excitability of corticospinal projections from M1 were not adequately controlled. The tests of equivalence indicated that the amplitudes of MEPs elicited by the TS alone varied significantly throughout the course of the intervention. With only one exception, the control responses obtained in the course of obtaining each IHI measurement also failed to accord with the expected THT amplitude, which raises concerns about the use of the methodology more generally. At a minimum, our findings emphasise that in seeking to apply ATH-based measures of IHI in an intervention context, it is absolutely crucial to reassess the TS intensity required to elicit the THT at each point of assessment. It cannot be assumed that the TS intensity that elicits the THT prior to commencing training, will necessarily remain the same during or following its completion. The deviation between the expected and observed amplitudes of the non-conditioned THT responses, although inconsistent with our previous work (Calvert et al., 2020), raises concerns that the threshold tracking method is not without deficiencies.

In seeking to apply CE training either alone or as a therapeutic adjuvant in clinical populations, it is important to consider both i) the extent to which the effect is manifest in specific training tasks, and ii) the magnitude of its expression in the

population of interest (as well as matched controls). Although various clinical applications have been proposed (for reviews, see Farthing & Zehr, 2014; Hendy et al., 2012; Sun & Zehr, 2019), a particular focus has hitherto been placed upon the attenuation of functional deficits that may arise during the course of unilateral limb immobilisation (Haggert et al., 2020), e.g., following a fracture of the distal radius (Magnus et al., 2013), and the promotion of functional recovery in the paretic limbs of stroke survivors (Dragert & Zehr, 2013; Sun et al., 2018; Urbin et al., 2015). In both instances, it should be emphasised that the incidence of each pathology is most pronounced in older populations (Bejot et al., 2016; Ensrud, 2013). To what extent therefore does the expression of CE and the mechanisms which mediate it, differ from those of the healthy young adults in which its effects have been studied customarily?

Relatedly, it is important to consider which training tasks should be considered apposite for functional rehabilitation. The answer to this question obviously depends on the nature of the clinical problem. In Chapter 4, we employed a ballistic movement training task as it is known that the generation of explosive strength is reliant upon a rapid rate of force development (RFD) (Duchateau & Baudry, 2014). Notably, the RFD is a key predictor of functional status in older adults (Aagaard et al., 2010; Hess et al., 2006; Rubenstein, 2006), and hence tasks which rely upon this measure are likely to be of relevance in promoting functional rehabilitation. In addition, and as noted by Hinder et al. (2011), ballistic movement tasks also have appeal in that relatively large effects can be observed in both the trained and untrained limbs following only a single session of training. While this is clearly convenient to the experimenter, it may

also be beneficial for the participant as a relatively large amount of gain can be derived following a short period of practice. Unfortunately, a comprehensive summary of which tasks are most appropriate for CE-based interventions in such settings as unilateral fracture or stroke, has yet to be provided.

It is likewise appropriate to consider the extent to which the benefits conferred by CE training may ameliorate the relatively large magnitude of dysfunction that accompanies serious injuries of the CNS or periphery. Another way of framing this question is to ask in which specific sets of circumstances might CE interventions be considered efficacious. In the case of an injury such as a unilateral rupture of the anterior cruciate ligament (ACL), it is known that supplementing standard therapies with CE training following ACL reconstruction does not improve early- or late-phase rehabilitation outcomes (Zult et al., 2018b) or neuromuscular function (Zult et al., 2018a). By contrast, supplementing standard therapy with CE training during a period of unilateral limb immobilisation following a distal radius fracture, engenders higher levels of strength and an increased range of motion in the fractured limb when assessed 12wks later, leading to a faster recovery when compared to standard therapy alone (Magnus et al., 2013). It is thus apparent that the benefits conferred by CE training are present in some instances but not others. Unfortunately, there is a paucity of high-quality evidence (e.g., randomised controlled trials) concerning the utility of CE training in these and other populations, especially stroke survivors (for a review, see Lim & Madhavan, 2022). As a consequence, it remains at present difficult to state in which circumstances in particular CE training may confer therapeutic benefit, and also those in which it may be considered frivolous.

A final issue concerns the difficulty of generalising findings from studies conducted in healthy volunteers to populations in whom alterations in brain structure and function may be present (e.g., stroke survivors). This of course was a key motivation that underpinned the present work, which was focused exclusively upon age-related neurodegeneration (Calvert & Carson, 2022). Although it is always difficult to generalise findings from 'healthy' to 'pathological' populations, the value of work undertaken in healthy volunteers is that it helps to define the characteristics of the 'normal' reference population. As the therapeutic applications of CE training apply most readily to older adults (Calvert & Carson, 2022), the objective of this thesis was to establish whether CE was manifest in this reference population. As we and others have shown, this is indeed the case. That which remains to be determined is the specific mechanism by which CE is given effect. If these mechanisms can be formulated precisely, there may exist an opportunity to select patients in whom the mediating pathways are preserved, for appropriate intervention (i.e., CE-based therapies). In the case of stroke survivors, this process of selection may depend upon the vascular territories affected by an infarct. In patients with multiple sclerosis, it may instead depend upon the location of demyelinating plaques. In circumstances such as these, in which the disorder is characterised by considerable heterogeneity, the aim is not to generalise findings to clinical 'populations' (e.g., all stroke survivors), but to use them to tailor treatments for individual patients (i.e., those in whom the mechanisms are preserved). It is important to emphasise however that this can only be achieved by understanding which brain regions and networks

are instrumental in mediating CE. Despite more than a century of research, and the best efforts of this thesis, this matter has however yet to be resolved.

5.5 CONCLUDING REMARKS

The original contributions arising from the investigations presented in this thesis were firstly that, in applying a short duration burst of transcranial alternating current stimulation unilaterally to M1, the amplitude of the motor potential evoked by TMS delivered 6 ms later to its homologue, was elevated considerably. The extent of interhemispheric facilitation (IHF) obtained with this methodology was within the range of values reported previously by dual-coil TMS studies. We also describe a fully automated dual-coil threshold tracking methodology, with which it may be possible to obtain measures of interhemispheric inhibition between the primary motor cortices, as well as between PMd and M1. Lastly, we show that following a regimen of unimanual ballistic wrist extension training, comparable levels of CE (expressed in terms of relative improvement and interlimb transfer) are obtained in young and older adults, which remain present one-week following the initial training session. Although corresponding variations in PMd-M1 IHI were observed in this context, it was not possible to relate these unambiguously to interindividual variations in the magnitude of the interlimb effect.

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