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Neurophysiological effects of arm weight support: Implications for stroke rehabilitation

Keith David Runnalls

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Exercise Sciences, the University of Auckland, 2017.
Abstract

Arm weight support may be used as an adjuvant to increase training dosage and improve movement quality during upper limb stroke rehabilitation. However, the underlying neurophysiological effects of weight support are not well understood. The aim of this thesis was to investigate the neurophysiological effects of arm weight support in healthy adults and chronic stroke patients. Four experiments examined the effects of weight support on muscle activation and corticomotor excitability across the upper limb using multiple gradations of supportive force. Transcranial magnetic stimulation and electromyography were employed during different movement tasks. For muscles that generate shoulder abduction (anti-gravity) torque, muscle activity responded linearly to gradations of supportive force. For distal muscles, a trend between nonessential tonic muscle activity and the degree of weight support provided evidence in support of a common neural drive to the upper limb. Modulation of corticomotor excitability was muscle-specific and discontinuous with respect to linear gradations of supportive force. Therefore, weight support may interact with thresholds in multiple modulatory mechanisms. During a separate rhythmic movement task, an improvement in biceps brachii selectivity with greater weight support was revealed by task-dependent modulation of corticomotor excitability preceding agonist or antagonist contractions. The results indicate that weight support may interact with excitatory mechanisms linking muscle representations as well as local inhibitory circuits. In a comparison of sitting and standing postures, there were small but significant differences in corticomotor excitability across the upper limb. During a reaching task, patients with moderate-severe upper limb impairment were able to hit more targets with greater weight support. Muscle activity tended to decrease with more supportive force; however, the response depended on impairment severity. Weight support had an influence on corticomotor excitability in control, mild, and moderate-severe impairment groups. The pattern of modulation was not consistent and likely reflects individual differences in lesion extent and location. Several novel findings
contribute to our understanding of upper limb control. Arm weight support appears to have direct mechanical effects and indirect neurophysiological effects. Chronic stroke patients respond to changes in weight support at behavioural and neurophysiological levels. The responses vary with the severity of motor impairment.
Acknowledgments

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<tr>
<td>AD</td>
<td>anterior deltoid</td>
</tr>
<tr>
<td>ADM</td>
<td>abductor digiti minimi</td>
</tr>
<tr>
<td>AMT</td>
<td>active motor threshold</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>APB</td>
<td>abductor pollicis brevis</td>
</tr>
<tr>
<td>ARAT</td>
<td>Action Research Arm Test</td>
</tr>
<tr>
<td>ASH</td>
<td>modified Ashworth Spasticity Scale</td>
</tr>
<tr>
<td>BB</td>
<td>biceps brachii</td>
</tr>
<tr>
<td>BRD</td>
<td>brachioradialis</td>
</tr>
<tr>
<td>CM</td>
<td>corticomotoneuron</td>
</tr>
<tr>
<td>CME</td>
<td>corticomotor excitability</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CS</td>
<td>conditioning stimulus</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CST</td>
<td>corticospinal tract</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion-weighted imaging</td>
</tr>
<tr>
<td>ECR</td>
<td>extensor carpi radialis</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>EPSP</td>
<td>excitatory post-synaptic potential</td>
</tr>
<tr>
<td>FA</td>
<td>fractional anisotropy</td>
</tr>
<tr>
<td>FCR</td>
<td>flexor carpi radialis</td>
</tr>
<tr>
<td>FDI</td>
<td>first dorsal interosseous</td>
</tr>
<tr>
<td>FM</td>
<td>Fugl-Meyer assessment</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
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<tr>
<td>ICA</td>
<td>independent component analysis</td>
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<tr>
<td>iEMG</td>
<td>integrated EMG area</td>
</tr>
<tr>
<td>M1</td>
<td>primary motor cortex</td>
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<tr>
<td>MD</td>
<td>middle deltoid</td>
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<tr>
<td>MEPs</td>
<td>motor evoked potentials</td>
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<tr>
<td>MN</td>
<td>motoneuron</td>
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<tr>
<td>mod-sev</td>
<td>moderate-severe</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MSO</td>
<td>maximum stimulator output</td>
</tr>
<tr>
<td>MVC</td>
<td>maximum voluntary contraction</td>
</tr>
<tr>
<td>NC</td>
<td>non-conditioned</td>
</tr>
<tr>
<td>PD</td>
<td>posterior deltoid</td>
</tr>
<tr>
<td>PLIC</td>
<td>posterior limb of the internal capsule</td>
</tr>
<tr>
<td>PM</td>
<td>pectoralis major</td>
</tr>
<tr>
<td>PMC</td>
<td>premotor cortex</td>
</tr>
<tr>
<td>PMd</td>
<td>dorsal premotor area</td>
</tr>
<tr>
<td>PMv</td>
<td>ventral premotor area</td>
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<tr>
<td>Pre-PMd)</td>
<td>pre-dorsal premotor area</td>
</tr>
<tr>
<td>Pre-SMA</td>
<td>pre-supplementary motor area</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PSTH</td>
<td>post-stimulus time histogram</td>
</tr>
<tr>
<td>PT</td>
<td><em>pronator teres</em></td>
</tr>
<tr>
<td>RF</td>
<td>radio frequency</td>
</tr>
<tr>
<td>rmsEMG</td>
<td>root mean squared EMG</td>
</tr>
<tr>
<td>RMT</td>
<td>resting motor threshold</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>SICI</td>
<td>short-latency intracortical inhibition</td>
</tr>
<tr>
<td>SMA</td>
<td>supplementary motor area</td>
</tr>
<tr>
<td>SR</td>
<td>stimulus-response</td>
</tr>
<tr>
<td>TB</td>
<td><em>triceps brachii</em></td>
</tr>
<tr>
<td>TE</td>
<td>echo time</td>
</tr>
<tr>
<td>TES</td>
<td>transcranial electrical stimulation</td>
</tr>
<tr>
<td>TMS</td>
<td>transcranial magnetic stimulation</td>
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<tr>
<td>TR</td>
<td>repetition time</td>
</tr>
<tr>
<td>TS</td>
<td>test stimulus</td>
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<tr>
<td>UE-FM</td>
<td>upper extremity Fugl-Meyer</td>
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<tr>
<td>WS</td>
<td>arm weight support</td>
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<tr>
<td>ΔINH</td>
<td>change score for inhibition</td>
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| Extent of contribution by PhD candidate (%) | 75 |

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1 Introduction

This chapter provides background information for context, outlines the research objectives, and presents an overview of the thesis.

1.1 Context for upper limb control and arm weight support

Movement is the primary means by which we interact with our environment. Complex and adaptable upper limb movement is ubiquitous in daily life. For example, reaching forward and manipulating objects with the hand is the basis for much fundamental human behaviour. However, the mechanisms by which the nervous system encodes movement information to produce coordinated output remain unresolved. An abundance of neuro-musculo-skeletal degrees of freedom facilitates the remarkable variety of tasks performed with the upper limbs. The numerous movement possibilities afforded by a system with many elements entail a need for an efficient control architecture (Bernstein, 1967; Latash, 2012).

Converging lines of evidence suggest the central nervous system (CNS) structures control of movements by grouping muscle activity into functional units, herein termed synergies (Turvey, 2007). Synergies might arise from internal constraints within the nervous system, or as the result of an optimisation process within the task-organism system (Diedrichsen et al., 2010). In this thesis, synergies refer to stable spatiotemporal patterns of activity across muscles that may arise through anatomical and physiological linking of elements at multiple levels of the CNS.

Further knowledge of the anatomical substrates of synergies, the physiological mechanisms of binding, and the regulation of behavioural consequences are key to understanding issues of upper limb movement in both health and disease.
Stroke is a leading cause of acquired adult disability (Mendis, 2013). Upper limb motor impairment is a frequent complication, occurring in more than three-quarters of stroke survivors and becoming chronic for two-thirds of patients (Sunderland et al., 1989; Rathore et al., 2002; Feigin et al., 2010). Upper limb motor deficits are a key indicator as to whether or not patients will engage in independent activities of daily living (Kwakkel et al., 1996; Patel et al., 2000; Meijer et al., 2003; Schiemanck et al., 2006; Veerbeek et al., 2011). The most common impairment after stroke is hemiparesis; a collective term for several positive and negative motor symptoms including muscle weakness, spasticity, and dyscoordination in the form of abnormal synergies (Wolfe, 2000; Krakauer, 2005). A positive relation between functional status and quality of life underscores the importance of upper limb function as a rehabilitation goal (Samsa and Matchar, 2004; Dobkin, 2005; Stinear, 2010). Targeting therapeutic interventions to specific aspects of motor impairment may better promote recovery of function.

Abnormal synergies emerge spontaneously early during recovery and contribute to impairment by limiting independent joint control and constraining limb function to a subset of the normal workspace (Twitchell, 1951; Brunnstrom, 1970). The paretic limb exhibits less focal mapping of muscle activation to force direction, and greater coactivation between shoulder and elbow (Tang and Rymer, 1981; Bourbonnais et al., 1989; Dewald et al., 1995; Beer et al., 1999). Furthermore, altered shoulder-elbow coordination is implicated in the disruption of multi-joint movement kinematics and dynamics (Levin, 1996; Beer et al., 2000). Despite their prevalence, our understanding of abnormal synergy aetiology and the underlying mechanisms is limited. It is unclear whether abnormal synergies represent an optimal adaptation to the damaged motor system (Latash and Anson, 1996), or locally stable patterns in
a landscape of possibilities that may be amenable to modification through 
neuroplastic mechanisms.

Efforts to reduce the global burden of stroke-related disability have prompted the 
development of novel rehabilitation technologies to act as adjuvants or 
complements to conventional therapy. Arm weight support (WS) involves the 
application of assistive forces to the upper limb to compensate for the effect of 
gravity. The gravity compensation forces can be applied as a component of robotic-
aided therapies, which typically involve additional assistive or resistive forces, or in 
isolation through dedicated WS devices (Johnson, 2006; Stienen et al., 2007; 
Loureiro et al., 2011). In this thesis, WS refers to the use of a dedicated passive 
mechanical device to provide gravity compensation.

WS may benefit upper limb rehabilitation through multiple means; such as 
facilitating an increase in the intensity or volume of therapeutic exercises (Kwakkel 
and Meskers, 2014), or improving movement quality (Prange et al., 2009a; 2009b). 
Changes in movement quality may result from interactions with the mechanisms 
responsible for integrated limb control and synergy expression. Gravity-
compensated movements require less shoulder activation to perform abduction, 
which reduces involuntary elbow flexion and permits hemiparetic patients a greater 
range of motion (Dewald et al., 2001; Beer et al., 2004). Moreover, the effect appears 
independent of proximal weakness or strength imbalances (Beer et al., 2007). While 
it is evident that WS can transiently mitigate the deleterious effects of abnormal 
upper limb synergies, the neurophysiological underpinnings are unclear.

The CNS may integrate upper limb control such that proximal muscle activation (e.g. 
shoulder abduction) influences corticomotor recruitment of task-relevant distal 
muscles through neural linkages in the motor cortex or spinal cord (Devanne et al.,
Disruption of the corticospinal tract following stroke may give rise to upper limb dyscoordination through several mechanisms: interruption of monosynaptic connections to proximal muscles, up-regulation of alternate descending pathways, and altered modulation of segmental circuits (Krakauer, 2005). As many of the putative anatomical substrates for normal and abnormal synergy formation are shared, it stands to reason that investigating the neurophysiological effects of WS may provide insight into both healthy and post-stroke synergies of the upper limb. A better understanding of WS may also contribute to a more informed and individualised approach to its application in stroke rehabilitation.

1.2 Research objectives

i. Explore how the degree of weight support affects corticomotor recruitment of distal forearm and hand muscles in healthy adults.

ii. Determine if weight support affects the selectivity of *biceps brachii* activation in healthy adults.

iii. Investigate how weight support affects corticomotor recruitment of arm and forearm muscles in healthy adults, and whether there is an interaction between sitting and standing postures.

iv. Examine how weight support affects muscle activity during reaching in chronic stroke patients.

v. Examine how weight support affects corticomotor recruitment of arm and forearm muscles in chronic stroke patients.

1.3 Overview of thesis

Chapter 2 presents a literature review of three central topics: first, neural basis of upper limb control; second, the effects of stroke on upper limb control; and third, arm weight support. Chapter 3 presents an overview of the techniques used in the experiments reported in subsequent chapters.
Chapters 4–7 describe four separate experiments utilising transcranial magnetic stimulation (TMS) and analyses of electromyograms (EMG) to assess the effect of WS manipulation on corticomotor excitability (CME) and muscle activity. It was hypothesised that WS might have remote or indirect influences on muscle recruitment through interactions with neurophysiological mechanisms that integrate upper limb control. The experiments in Chapters 4–6 were performed in healthy adults while Chapter 7 incorporated chronic stroke patients and age-similar healthy controls. Chapter 4 explores how the degree of WS affects CME to the forearm and hand. Five gradations of supportive force, or levels of WS, are employed to manipulate tonic shoulder abduction activity while TMS is used to elicit motor-evoked potentials (MEPs) across the limb. Chapter 5 examines whether WS influences the selective recruitment of biceps brachii by comparing CME preceding agonist elbow flexion and antagonist forearm pronation at three levels of WS. Chapter 6 investigates if WS interacts with whole-body posture, i.e. sitting or standing, to influence CME to upper limb muscles. Chapter 7 examines the effects of WS in chronic stroke patients in two parts. First, muscle activation patterns from a dynamic reaching task employing an array of targets are analysed. Second, CME is assessed in a static shoulder abduction task. Modulation with WS is examined for different levels of impairment severity. Chapter 8 concludes the thesis by summarising the experimental findings and suggesting directions for future research.
2 Review of Literature

This chapter reviews literature relating to the neural basis of upper limb control, the effects of stroke on upper limb control, and arm weight support.

2.1 Neural basis of upper limb control

Upper limb movements are a primary means by which we interact with the world around us. Purposeful motor behaviours require the coordinated activation of multiple muscles in precise spatiotemporal patterns. A network of cortical regions, descending pathways, and spinal circuits mediate sensorimotor transformations that generate motor output.

2.1.1 Motor cortex and descending motor pathways

The localisation of motor functions to the caudal sector of the frontal lobe was recognised following original studies by Fritsch, Hitzig, and Ferrier in the 1870s (Taylor and Gross, 2003). This caudal region, now identified as motor cortex, is histologically distinct because it lacks granular cells and has a five-layered structure. Early cytoarchitectonic studies distinguished regions of precentral cortex: Brodmann’s area 4, or primary motor cortex (M1), and Brodmann’s area 6, or premotor cortex (PMC) (Rizzolatti and Luppino, 2001). Subsequent work has revealed subdivisions of premotor cortex including supplementary motor area (SMA), pre-supplementary motor area (Pre-SMA), dorsal premotor area (PMd), pre-dorsal premotor area (Pre-PMd), and ventral premotor area (PMv) (Dum and Strick, 2002). Primary motor cortex (M1) and the caudal premotor regions (SMA, PMd, PMv) receive sensory input from parietal areas whereas the rostral premotor regions (Pre-SMA, Pre-PMd) receive higher order cognitive information from pre-frontal areas (Rosén and Asanuma, 1972; Kwan et al., 1978; Murphy et al., 1978;
Interconnections between the regions facilitate the integration of movement intentions with sensory feedback. Collectively the motor cortical network selects, plans, and executes actions (Shen and Alexander, 1997; Kalaska, 2009).

The lateral corticospinal tract (CST) is the primary descending motor pathway for volitional movement in humans (Lemon, 2008). Pyramidal neurons that modulate upper limb activity originate in layer V of M1, SMA, PMd, PMv, and somatosensory cortex, and project to the intermediate zone of cervical spinal segments (Dum and Strick, 2002). Axons originating in M1 comprise the greatest proportion of fibres (Seo and Jang, 2013). Corticomotoneuronal (CM) cells originate in layer V of M1 and project directly to the ventral horn of the spinal cord where they make monosynaptic connections with spinal motoneurons (Kuypers, 1981; Rathelot and Strick, 2006). These CM connections underlie individuated dextrous movements in hand and fingers but also innervate proximal muscles (Colebatch et al., 1990; Maier et al., 1993). Axons exiting the cortex converge caudally to form the posterior limb of the internal capsule before continuing through the brain stem to the medullary pyramid where the majority of fibres decussate and continue descending via the contralateral dorsolateral column. These crossed fibres may synapse directly onto spinal motoneurons, or onto segmental interneurons in the dorsolateral intermediate zone. Uncrossed axons form the ventral CST and descend via the ipsilateral ventral column, synapsing bilaterally onto interneurons in the ventromedial intermediate zone.

The ventromedial and dorsolateral brainstem pathways also receive cortical output and project to the spinal cord. The ventromedial pathway descends via the ventral and ventrolateral funiculi of the spinal cord and terminates bilaterally in the
ventromedial intermediate zone. The dorsolateral brainstem pathway descends via the contralateral dorsolateral funiculus and terminates in the dorsolateral intermediate zone (Kuypers, 1981; Lemon, 2008). The uncrossed CST parallels the ventromedial brainstem pathway and may project onto long propriospinal neurons that act to link widely separated spinal segments bilaterally. These pathways tend to be involved in postural and proximal muscle activation. In contrast, the crossed CST parallels the dorsolateral brainstem pathway and may project onto short propriospinal neurons that act to link more local segments unilaterally. These pathways are thus more suited to activation of more distal muscles (Molenaar and Kuypers, 1978; Kuypers, 1981; Pierrot-Deseilligny and Burke, 2012).

Interhemispheric motor pathways are critical for coordinating bimanual movements. Motor cortical regions reciprocally project to the homologous region in the contralateral hemisphere. Callosal motor fibres that transit through the posterior midbody and isthmus of the corpus callosum are structured somatotopically and are the primary path for interhemispheric connections (Wahl et al., 2007). Inhibitory transcallosal projections act to suppress bilateral mirroring when only unilateral upper limb movement is desired (Bloom and Hynd, 2005). There is also evidence to support a component of the transcallosal pathway that acts to facilitate the contralateral region. However, its role in natural motor behaviours is less clear (Bäumer et al., 2006; Morishita et al., 2012).

2.1.2 Neuroanatomical substrates for synergies
As discussed briefly in Chapter 1, synergies are a natural phenomenon of motor behaviour. Synergy is defined as a stable spatiotemporal pattern of activity across muscles simultaneously involved in the performance of a movement. Synergies may be considered a basic unit of motor behaviour (Turvey, 2007; Kelso, 2009).
Synergies may originate at several levels of the neuraxis. Because synergies are fundamental patterns of relative neuromuscular activity, any neural structure with connectivity between muscle representations or motor neurons may function as a synergy substrate.

Cortically mediated synergies are supported by the intrinsic connectivity of motor cortical regions. Capaday and colleagues have advanced an argument for the primary motor cortex as the neural substrate of functionally integrated muscle control (synergies), particularly for proximal-distal coordination in the forelimb (Capaday et al., 2013). They hypothesise that primary motor cortex is the site in which motor commands from premotor and thalamic areas are synthesised into synergetic patterns and dispatched. The idea appears to be based upon the early views of Hughlings Jackson (1882) and Walshe (1943) who argued the motor cortex represents complex patterns of movements in an overlapping and integrated fashion. This is contrasted with the punctate localisation theory advocated by Leyton and Sherrington (1917) that argued motor cortex representations have a one-to-one mapping with muscles.

Neuroanatomical studies of the motor cortical structure have utilised both microstimulation and cell tracing techniques. The forelimb areas (in monkeys and cats) are interconnected to respective antagonists via horizontal projections (Huntley and Jones, 1991; Keller, 1993; Tokuno and Tanji, 1993; Capaday et al., 1998). Huntley and Jones originally suggested these horizontal connections within motor cortex could be the substrate of multi-joint coordination synergies (Huntley and Jones, 1991). These horizontal connections are glutamatergic and communicate with cells in their local neighbourhood via numerous synaptic boutons along their axon collaterals (Capaday et al., 1998). For example, a cortical point that primarily
represents the brachialis muscle has horizontal projections that course through, and synapse onto cells within, both wrist and shoulder representations. A distal thumb muscle was also found to have connections to a proximal shoulder muscle. The same study also reported intracortical connections between agonist-antagonist pairs and postulated this communication could be layered upon reciprocal inhibition mediated within the spinal cord and give rise to triphasic bursting patterns during ballistic movements or co-contraction activity. Thus it appears there are anatomical features of motor cortex that have the potential to link muscle representations together across cortical space for functions related to reaching and grasp.

Widespread distributions of muscle representations may also provide opportunities for intracortical linking. Microstimulation of points in the cat motor cortex, even at threshold intensity, elicits widespread muscle responses (Armstrong and Drew, 1985). Similar results have been observed in other species (Donoghue et al., 1992; Capaday et al., 1998; Schneider et al., 2001). The cortical sites at which microstimulation can elicit a response in a particular muscle are not contiguous and are spread across a region of the motor cortex with a weak correlation between anatomical location and peak response (Schneider et al., 2001). The gradual somatotopic gradient of the classical homunculus describes mapping on a macro scale; however, within a region of the motor cortex, such as the upper limb area, individual muscles have multiple non-contiguous overlapping representations (Schieber, 2001; Rathelot and Strick, 2006). The overlap of finger and wrist muscle representations in the human motor cortex has also been reported in studies utilising fMRI (Sanes et al., 1995; Sanes and Schieber, 2001).

Further evidence in support of functionally linked cortical points comes from studies that observed and artificially stimulated motor behaviours. Poliakov and
Schieber conducted a cluster analysis in which neurons that were behaving similarly while the animal performed individuated finger movements were grouped together (Poliakov and Schieber, 1999). They reported there were fewer neural clusters than there were finger movements, indicating a one-to-one somatotopic mapping was unlikely, and finger movements were the product of interacting cortical representations. More causal evidence for a cortical basis of movement specific synergies results from the work of Graziano and colleagues who utilised prolonged microstimulation to the macaque cortex (Graziano et al., 2002). Pulse widths of 300–500 ms, which are intentionally approaching the duration of natural movements, evoke patterns of muscle contractions that resemble natural motor behaviours. The preceding studies provide an evidence base for an anatomical structure of motor cortex that could support coordinated muscle activity through the linking of muscle representations into networks of cortical points.

Functional linking of motor cortical points is dependent on intracortical inhibitory mechanisms. As demonstrated by Schneider and colleagues, disinhibition of a test point within motor cortex using bicuculine, a GABA\textsubscript{A} antagonist, resulted in stimulus evoked responses in both control and test muscles. Without the artificial lifting of inhibition at the test point, stimulation at the control point only evoked a response in the respective control muscle (Schneider et al., 2002). These findings were interpreted as evidence of artificial synergy formation because under normal conditions the two sites did not exhibit overlapping responses. The specificity of inhibitory mechanisms was further confirmed by an absence of combined responses to either glutamate application or suprathreshold electrical microstimulation. The authors demonstrated that the coupling was mediated synaptically, and not due to electrical current spread, by interrupting the coupling of stimulus-evoked responses through chemical blockade of excitatory glutamate receptors after disinhibition. The
release of a motor cortical point into a synergy thus appears to be dependent on disinhibition, allowing horizontal excitatory connections to couple muscle activity.

Functional binding of muscle activity may also result from a divergence of corticospinal neurons within the spinal cord (Shinoda et al., 1976; 1981; 1986; Tantisira et al., 1996; McKiernan et al., 1998). McKiernan and colleagues reported that in rhesus monkeys approximately half of corticospinal neurons in forelimb areas project to the motoneuron pools of at least a proximal and a distal muscle (McKiernan et al., 1998). Selectivity and superposition of descending signals would be required to take advantage of this structure. Divergent cortical projections have been proposed as an anatomical basis for reaching synergies (Scott and Kalaska, 1997; Scott et al., 1997; Graziano and Aflalo, 2007).

2.1.3 Modular theory of motor control and muscle synergies
The idea that movements may be constructed from the additive effect of multiple neurally-based synergistic modules has existed in some form since the time of Sherrington (1906) (Lee, 1984). Modern versions of the theory posit that interneuron networks in the spinal cord produce stable ratios of output to a set of muscles in response to descending input (Tresch et al., 2002; Flash and Hochner, 2005; Ting and McKay, 2007; Bizzi et al., 2008; Tresch and Jarc, 2009). Combinations of the spinal interneuron network modules can be selectively activated and scaled to produce various motor behaviours. Recognising that the concept of primitive neuroanatomical constraints is not imperative for the production of synergistic behaviour, a modular control architecture comprised by spinal synergies can account for a variety of phenomena within the nervous system (Flash and Hochner, 2005; Ting and McKay, 2007; Tresch and Jarc, 2009).
At the level of muscle synergies, several studies have demonstrated that neural networks within the spinal cord of various animals produce stable patterns of muscle activation that can be combined to produce natural motor behaviours (Tresch et al., 2002; Bizzi et al., 2008). Other work has also reported that modules exist as anatomical structures in the spinal cord (Tresch et al., 1999; Dietz, 2003; Cheung et al., 2005; d'Avella and Bizzi, 2005; McCrea and Rybak, 2007; Kargo and Giszter, 2008). Notably, intraspinal microstimulation in the cat demonstrated that interneuronal networks are highly dependent on descending input and the state of the spinal cord (Mushahwar et al., 2004).

These motor primitives are one possible neural substrate of synergies. In support, direct microstimulation of the motor cortex produced synergies consistent with those identified during the voluntary hand and finger movements (Overduin et al., 2012). A variety of related analytical techniques has been employed to identify synergies by reducing the dimensionality of recorded electromyograms. Methods such as non-negative matrix factorisation (NMF) model recorded myoelectric data sets as the linear combination of a smaller number of basis vectors (Tresch et al., 2006). Each basis vector specifies a relative weighting of muscle activity, which is multiplied by a time-varying input signal. The term ‘muscle synergy’ has been used to label estimates of synergies derived from quantitative matrix factorization methods. The outputs of each synergy are summed linearly into a signal for each muscle. Factorisation analyses have been used to investigate spinal cord function (Tresch et al., 1999; Saltiel et al., 2005; Hart and Giszter, 2010; Roh et al., 2011), postural control (Ting and Macpherson, 2005; Torres-Oviedo and Ting, 2010), and motor development (Monaco et al., 2010; Dominici et al., 2011). In this framework, synergies are linked together in the spinal cord. This concept is not mutually exclusive to synergies represented in the motor cortex or descending pathways.
2.1.4 Proximal-distal interactions in the upper limb

Devanne and colleagues investigated the cortical control of task related muscles by measuring the recruitment properties of upper limb muscles during various contraction tasks (Devanne et al., 2002). Compared to an isolated contraction of extensor carpi radialis (ECR), co-contraction with anterior deltoid (AD), such as when pointing, resulted in a greater plateau value of both the ECR and triceps brachii stimulus-response curves. The effect was asymmetrical with respect to the proximal-distal axis as co-contraction of distal muscles did not affect the stimulus-response curve of the AD. The increased plateau value of elbow and wrist muscles in the presence of AD contraction was absent when near-threshold anodal transcranial electrical stimulation (TES) was used instead of TMS. This finding suggests an intracortical site of facilitation. This conclusion is corroborated by an absence of significant differences in H-reflex amplitude, indicating proximal-distal co-contraction did not alter the gain of the motoneuron pool. The effect appears to be mediated by a reduction of intracortical inhibition when AD was co-contracted. An anatomical basis for proximal-distal interaction is supported by evidence from macaques and humans. In macaques, synergies binding proximal and distal muscles of the forelimb may be mediated in the motor cortex via an intermediate zone between a horseshoe shaped representation of proximal muscles surrounding circular representations of distal hand muscles (Park et al., 2001). Additional studies have supported a proximal-distal surround structure (Sanes and Schieber, 2001).

The influence of shoulder position on pathways to distal muscles has also been explored. Forward adduction of the shoulder in the horizontal plane resulted in steeper slopes and elevated plateaus of the stimulus-response curves for both flexor carpi radialis (FCR) and ECR muscles in the forearm. Paired-pulse stimulation
revealed no change in intracortical inhibition but some differences in the intracortical facilitation of FCR between the shoulder positions. H-reflex amplitudes in FCR remained unchanged lending further corroborating evidence to an intracortical mechanism of proximal-position dependent recruitment of forearm muscles (Ginanneschi et al., 2006). This group also assessed the effect of shoulder position on the recruitment of the abductor digiti minimi (ADM) muscle, which is typically active to open the hand at the end of a reach in preparation for grasping. A similar pattern of a steeper stimulus-response slope and elevated plateau were found as a function of horizontally adducting the shoulder forward; presumably, peripheral information specifying a forward shoulder position would be transferred to the forearm and hand in order to increase excitability of their corticospinal pathways in preparation for prehensile activities. In line with findings related to the forearm, the ADM representation displayed altered levels of intracortical facilitation, but not inhibition, as a function of shoulder position. However, both F-waves and H-reflexes were observed to change as a function of the shoulder angle, thus implicating modulation of recruitment gain at both the spinal and cortical levels. Interestingly, no effect of shoulder position was observed for the first dorsal interosseous (FDI) muscle (Dominici et al., 2005; Ginanneschi et al., 2006). Collectively these techniques suggest the musculature of the arm is coordinated as a functional unit with a degree of a hierarchical structure along the proximal to distal axis.

2.1.5 Typical kinematic, kinetic, and EMG features of reaching
Studies of goal-directed reaching have described invariant features at the kinematic and kinetic levels of analysis. From point to point, the hand follows a relatively straight path and exhibits a single peak in its tangential velocity profile (Morasso, 1980). The velocity of the movement can be scaled without altering the trajectory of
the hand path (Soechting and Lacquaniti, 1981). Similarly, different loading of the arm can be compensated for without altering the hand path (Lacquaniti et al., 1982). The bell-shaped velocity profile is maintained under different loads, velocities, and trajectories (Atkeson and Hollerbach, 1985). Angular kinematics of the shoulder and elbow are tightly coupled, and their peak angular velocities coincide (Soechting and Lacquaniti, 1981; Lacquaniti et al., 1986). During reaching movements, generated torques must compensate for gravitational and inertial forces. The dynamic component (with the effect of gravity removed) of generated torque at the elbow and shoulder are linearly related (Gottlieb et al., 1997). Somewhat paradoxically, early attempts to find similar regularities or invariances in muscle activity were less successful. The phasic electromyograms from elbow and shoulder muscles display complex spatiotemporal patterns during reaching movements to different targets in the sagittal plane (Flanders et al., 1994). Elbow and shoulder kinematics are coupled (Soechting, 1984). The limb is not necessarily obligated to exhibit these consistent features, owing to the abundant degrees of freedom discussed in Chapter 1. Instead, invariant features of motor behaviour can be thought of as optimal solutions that emerge given a particular set of anatomical and task constraints. In this sense, invariant features of motor behaviour are consistent with the concept of synergies as stable spatiotemporal patterns of activity. When anatomy is disrupted, as is the case in stroke, new movement features emerge.

2.2 Effects of stroke on upper limb control
As discussed in Chapter 1, upper limb impairments resulting from stroke contribute significantly to the global burden of disability. Although strokes can affect any part of the brain, the discussion here will be limited to deficits affecting upper limb function.
### 2.2.1 Hemiparetic motor deficits

Damage to the motor cortex or descending motor pathways, as is commonly the case in stroke, can result in both positive and negative motor symptoms (Krakauer, 2005). A loss of CST input can result in muscle weakness (paresis) or complete paralysis, whereas disruption of modulatory input from brain stem pathways can lead to an increase in muscle tone (spasticity). A loss of corticomotoneuronal input in particular affects fractionated movements of the fingers and limits dexterity. The altered motor network also tends to lose independent joint control, leading to impaired coordination of multi-joint movements. These motor deficits, collectively termed hemiparesis, are not unlike the pyramidal syndrome induced by lesions to the primate motor system (Lawrence and Kuypers, 1968a; 1968b).

The loss of independent joint control frequently manifests in stereotyped patterns of muscle coactivation termed abnormal synergies (Twitchell, 1951). These patterns typically emerge spontaneously early during recovery. The more common flexor synergy primarily presents as an involuntary coupling of elbow flexion and forearm supination to shoulder flexion and abduction. The extensor synergy involves a coupling of the opposite actions; elbow extension and forearm pronation to shoulder extension and adduction (Brunnstrom, 1970). Both patterns constrain individuals’ functional range of motion to a subset of the normal workspace.

Several features of upper limb coordination in stroke patients have been characterised. The direction that muscles are tuned to shifts (Tang and Rymer, 1981), and becomes less focal (Bourbonnais et al., 1989). These changes may reflect an adaptation for the spared motor fibres to assume a broader role for force generation. Elbow flexion becomes abnormally coupled to shoulder flexion-abduction. This is evident in correlated muscle activity (Dewald et al., 1995), and
coupled joint torques (Dewald and Beer, 2001). These aspects are consistent with the flexor synergy. They represent a loss of anatomical substrate for healthy proximal-distal synergies and an increased reliance on spared anatomical substrates. Stroke also results in abnormal inter-joint coordination (Levin, 1996), and altered control of limb dynamics (Beer et al., 2000). These changes reflect deficits in sensorimotor transformations and highlight the networked nature of the motor system.

Despite the prevalence of abnormal synergies and disrupted coordination, our understanding of their aetiology and underlying mechanisms is limited. The compound effects of disrupted corticomotoneuronal connections, a shift to control via alternate descending pathways, and modifications to spinal reflex circuits are contributing mechanisms to hemiparetic impairments (Krakauer, 2005; McMorland et al., 2015). At a macroscopic scale, damage to the crossed corticospinal tract is thought to promote an increase in reliance upon alternative descending motor pathways such as ipsilateral projections from motor cortex to propriospinal neurons in the cervical spinal cord. Owing to highly divergent patterns of innervation, an upregulation of ipsilateral brainstem pathways has been implicated as a factor giving rise to involuntary co-contraction of muscles following stroke (Schwerin et al., 2007; Bradnam et al., 2013).

At present, there is no accepted method of classifying abnormal synergies in an objective and quantitative way. It is plausible that qualitatively similar movement patterns may have heterogeneous aetiology however the extent to which this is the case is unknown. The relationship between the size and location of a lesion and the expression of abnormal synergies has not been adequately explored. Ineffective cortical remapping (Chollet et al., 1990; Cao et al., 1994; Loubinoux et al., 2003),
inappropriate inhibitory regulation (Huynh et al., 2013), an upregulation of pathways with more divergent projections (Bradnam et al., 2013), a greater reliance on other descending pathways for motor control (Dewald and Beer, 2001; Lum et al., 2003), and dysregulation of segmental reflex circuits (Trumbower et al., 2008; Bhagchandani and Schindler-Ivens, 2012) may all play a role. These factors suggest a more ‘hard wired’ view of abnormal synergies. An alternative, but not mutually exclusive, ‘soft’ view posits that abnormal movement patterns may emerge as a result of altered upstream planning, or from compensatory strategies involving the recruitment of atypical degrees of freedom (Cirstea and Levin, 2000). While both types of problems may be amenable to improvement through appropriate therapy, a paucity of knowledge regarding the complex aetiology and pathophysiology of abnormal synergies hinders the development of targeted and individualised rehabilitation therapies.

2.2.2 Muscle synergy structure following stroke
How stroke affects muscle synergies has been the subject of relatively few studies. Data obtained during dynamic upper limb tasks suggest that the internal structure of synergies is preserved despite altered movement performance (Cheung et al., 2009). Synergy structures were found to be similar between the affected and unaffected arms of stroke patients and these were congruent with those identified in healthy adults. A subsequent study involving a larger sample corroborated the finding of preserved synergy structure, but only in individuals with mild impairment (Cheung et al., 2012). More impaired patients exhibited a merging of synergies, and in some very chronic patients a fractionation into simpler synergies was observed. A greater probability of certain synergies merging could explain the stereotyped patterns of co-contraction following stroke. A more recent study utilised an isometric force production task to eliminate differences in movement
performance as a confounding variable in their synergy analysis (Roh et al., 2013). The patterns of co-contractions that impair function were not reflected in the structure of individual synergies, however some synergy structures were altered. The three heads of the *deltoid* muscle were consistently expressed as a single synergy and the extent of its activation was related to the degree of impairment. These findings highlight both the potential for proximal-distal regulation of the arm to interact with altered synergies, and the importance of controlling and measuring the movement task in experiments designed to examine synergies.

In addition to voluntary arm movements, abnormal co-contractions are also present in reflex responses. Trumbower and colleagues identified synergies of the shoulder and elbow muscles using independent component analysis (ICA) and found they were activated by both voluntary activity and by stretch reflexes elicited by multi-joint arm perturbations (Trumbower et al., 2008). Reflex activation of the module involving elbow flexion and shoulder abduction was significantly greater in the stroke group and tended to be greater in more impaired subjects. Voluntary background activity in the *deltoid* muscles, including the generation of anti-gravity torques, increased the gain of the stretch reflexes in a load-dependent fashion. Multi-joint reflex coupling, biased to express the flexor synergy may contribute to upper limb impairment after stroke. These results indicate that proprioceptive processing may play a role in generating synergy patterns and deficits in sensory processing could contribute to abnormal co-contractions post-stroke.

### 2.3 Arm weight support

A key quantitative study of abnormal synergies in stroke patients demonstrated an involuntary coupling of isometric shoulder abduction torques to elbow flexion torques (Dewald and Beer, 2001). Given that reaching movements require shoulder
abduction, reducing the shoulder torque requirements through arm weight support can instantaneously mitigate the effects of the involuntary coupling and facilitate a greater range of elbow extension (Beer et al., 2004). Findings from this planar reaching task were supported by a study using a dedicated arm weight support device for three-dimensional reaching (Prange et al., 2007). These authors found a similar increase in maximal reaching distance and decrease in muscle activity. Subsequent studies found reaching with arm weight support resulted in reduced muscle activity but no change in activation patterns in healthy older adults (Prange et al., 2009b) and stroke patients with mild upper limb impairment (Prange et al., 2009a). Coscia and colleagues performed a muscle synergy analysis on reaching data and reported that WS reduced the activation signals but did not alter the underlying synergies (Coscia et al., 2014). The increase in reaching distance facilitated by a reduction of shoulder abduction is not related to elbow flexor–extensor strength imbalances or proximal weakness (Beer et al., 2007). This suggests the benefit of arm weight support for stroke patients is mediated through the neural coupling of shoulder and elbow activity.

Studies of robotic-aided therapy, which often includes a gravity-compensation component, are relatively numerous (Johnson, 2006; Loureiro et al., 2011; Mehrholz et al., 2015). However, evaluating the application of arm weight support alone has been less common. Reach training using arm weight support alone has resulted in modest improvements in motor status and maximum reaching distance (Sanchez et al., 2006; Amirabdollahian et al., 2007; Housman et al., 2009). Dipietro and colleagues have argued that improvements in supported planar circle drawing were due to a reduced impact of abnormal coupling that reflected tuning of existing abnormal synergies (Dipietro et al., 2007). By permitting practice of movement patterns distinct from the abnormal synergies, it is thought that training with arm
weight support may allow processes of use-dependent plasticity to reinforce neural networks sub-serving functional movements.

In summary, a diverse body of research supports the notion that control of the upper limb is integrated as a functional unit. Evidence from behavioural, neurophysiological, and anatomical studies suggests several non-exclusive mechanisms may underlie functional integration along the proximal-distal axis and facilitate stable patterns of motor activity. In parallel, stroke rehabilitation research has identified motor impairments resulting from dysfunctional coordination along the proximal-distal axis. Results of studies investigating the use of WS for stroke rehabilitation indicate it may be of benefit by ameliorating aspects of dysfunctional coordination. The neurophysiological effects of arm weight support that may mediate improved upper limb function are unknown. It was hypothesised that WS might have remote or indirect influences on muscle recruitment through interactions with neurophysiological mechanisms that integrate upper limb control.
3 Experimental Techniques

This chapter provides background information about transcranial magnetic stimulation, the analysis of motor evoked potentials, magnetic resonance imaging, and clinical assessments.

3.1 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a technique used to stimulate the brain noninvasively (Barker et al., 1985). The method was first reported in the mid-1980s as an alternative approach to transcranial electrical stimulation, which due to the high resistance of the skull, typically requires a stimulus voltage that is painful for subjects (Merton et al., 1982). During TMS, a pulsed magnetic field is created by discharging a high voltage capacitor through a coil of wire held against the scalp. When the coil is positioned over the motor cortex, a stimulus of sufficient strength will evoke muscle action potentials that can be measured using electromyography. Changes in the amplitude and latency of these motor evoked potentials (MEP) can be interpreted in both experimental and clinical studies.

Single-pulse TMS, when applied to the motor cortex, can be used to assess the excitability of descending motor tracts, primarily the corticospinal pathway. A stimulus of a given intensity will evoke MEPs of greater size if the membrane of a neural element, or elements, along the pathway has been depolarised closer to its activation threshold at the time of stimulation. The converse is also true; a relatively less excitable, or hyperpolarised element will result in a smaller MEP. Importantly, changes in excitability may occur in any component of the corticospinal pathway, including cortical interneurons, corticomotoneuronal (pyramidal) cells, spinal
interneurons, and alpha-motoneurons. When used in isolation, single-pulse TMS cannot differentiate the site at which excitability has changed.

The time-varying nature of the electric current through the coil, via electromagnetic induction, causes a potential difference that results in ionic flow in the cerebral tissues underneath the coil. The magnetic field is not significantly attenuated as it passes through the extracerebral layers and results in little activation of pain receptors. The induced current is proportional to the magnitude of the magnetic field, which can be controlled by the stimulator unit. The current induced in tissues flows parallel, but in the opposite direction to the current in the coil. Depending on the relative orientation of the ion flow and the respective cell structure, a TMS pulse may result in local depolarization or hyperpolarization of an excitable membrane.

The temporal structure of descending neural activity can provide insight into the mechanisms of transcranial stimulation. Rothwell and colleagues reported that a percutaneous electrical stimulus delivered to the motor cortex could elicit a muscle twitch response that is larger than the response evoked by a supramaximal stimulus delivered to the peripheral nerve (Rothwell et al., 1987). Further investigation concluded that cortical stimulation must activate spinal motoneurons via multiple descending volleys (Day et al., 1987). Analysis of the post-stimulus time histogram (PSTH) of a single motor unit revealed two distinct peaks separated by 4.5 ms. Each peak is attributed to a distinct excitatory post-synaptic potential (EPSP). When electrical stimulation of the motor cortex was delivered while subjects voluntarily contracted the target muscle, the evoked muscle response was found to be significantly greater in amplitude and slightly shorter in latency (Rothwell et al., 1987). Pre-activation of a muscle would result in a greater proportion of its motor unit pool being closer to their threshold potential and thus more likely to fire after
the first EPSP. This mechanism can explain why pre-activation of a target muscle can shorten the response latency to a cortical stimulus.

More invasive studies have provided a window into the form of the descending volleys responsible for the distinct peaks in the PSTH. Direct recordings from the pyramidal tract of cats, monkeys, and baboons demonstrated multiple descending volleys result from a single electrical shock delivered to the motor cortex (Patton and Amassian, 1954; Kernell and Chien-Ping, 1967). The first volley, termed the D-wave, results from direct depolarization of the corticomotoneuronal cell. Subsequent volleys, termed I-waves, occur at approximately 1.5 ms intervals and are due to trans-synaptic activation of the same corticomotoneuronal cell by repetitive excitatory inputs from cortical interneurons. Direct evidence in support of this hypothesis was obtained by performing both magnetic and electrical stimulation in human subjects and recording from electrodes implanted in the spinal cord both during surgery (Burke et al., 1993) and in awake human subjects (Kaneko et al., 1996; Nakamura et al., 1996; Di Lazzaro et al., 1998). This technique has also added direct support for the original hypothesis of Day and colleagues who proposed that compared to TES, which tends to recruit D-waves, TMS preferentially recruits I-waves by activating the corticomotoneuronal cells trans-synaptically (Day et al., 1989; Di Lazzaro et al., 2004). This conclusion was made after the observation that TMS typically resulted in longer response latencies consistent with the arrival of the first I-wave, rather than the earlier D-wave. Importantly, TMS is biased towards activation of fast conducting cells, which comprise only a small portion of the corticospinal tract (Edgley et al., 1997). The extent to which results from TMS experiments can be used to draw inference about principles of motor control is further limited by its mechanism of activation. While TMS does activate corticomotoneuronal cells through a cortically mediated, trans-synaptic mechanism,
the patterns of evoked activity do not resemble those observed during natural voluntary muscle activation (Di Lazzaro et al., 2008).

The size and shape of the TMS coil are also an important stimulation parameter. In general, larger coils generate stronger magnetic fields while smaller coils allow more focal stimulation and permit the simultaneous placement of multiple coils. Circular TMS coils, which were the type originally introduced by Barker and colleagues, produce a magnetic field that results in a wider area of activation (Barker et al., 1985). More focal stimulation can be achieved using a figure-of-eight coil, which consists of two adjacent circular coils with current flowing in opposite directions (Ueno et al., 1988). A double-cone style coil can achieve greater stimulation depth and is commonly used to activate the lower limb areas of the motor cortex that reside on the medial wall of the interhemispheric fissure.

The orientation of the TMS coil, and thus the direction of the induced current, has marked effects on the evoked responses. With a monophasic pulse delivered through a focal figure-of-eight coil to the arm and hand areas, the lowest threshold is typically obtained with a current flowing in the posterior to an anterior direction (Di Lazzaro et al., 2008). Neurons are most readily activated by TMS when current flows parallel to the long axis of either their dendrites or axons, thus at threshold intensities, this coil orientation is thought to preferentially act on the axons of interneurons which synapse onto corticospinal cells. Evidence in support of this comes from experiments in which recordings were made directly from the epidural space of the spinal cord. This technique permits one to distinguish between components of the descending volley resulting from a TMS pulse. At low suprathreshold stimulation intensities, the latency of responses is compatible with an $I_1$-wave. Stronger stimuli shorten the latency by 1–1.4 ms to that of a D-wave.
elicited by anodal TES, indicating the lowest threshold elements activated by TMS are pre-synaptic to corticomotoneuronal cells (Di Lazzaro et al., 1998).

The threshold for D-waves is relatively stable in a given corticomotoneuronal cell; however, this is not the case for I-waves, which show considerable variability in response to a constant stimulus (Edgley et al., 1997). Variability in the recruitment of I-waves has been implicated as a source of trial-to-trial variability of MEP size (Burke et al., 1995). This variability has necessitated the threshold intensity for TMS to be defined as the intensity which elicits reproducible MEPs in approximately half of series of stimuli (Rossini et al., 1994). A primary use of TMS is to probe the excitability of neural elements comprising the pathway to a given muscle. Any ion flow induced by TMS will interact with existing membrane potentials. The excitability of stimulated neurons will thus be reflected in the size of the motor evoked potential. Because the excitability of any element along the conduction pathway can impact the size of the response, it is necessary to experimentally control for differences in background muscle activity, which reflects pre-activation of alpha-motoneurons and a ‘subliminal fringe’ or population of neurons in the motor pool that are partially depolarised but not yet active.

Volitional background activity in a muscle will decrease the response threshold from the resting motor threshold (RMT) to the active motor threshold (AMT). This effect typically reaches maximum effect by 10–15% of the maximum voluntary contraction (MVC), beyond which no further reductions in threshold are observed. Voluntary contractions also have the effect of increasing MEP size. Epidural recordings from the cervical spinal cord have demonstrated that a voluntary contraction increases the size and number of descending volleys, but does not alter their threshold. This result indicates that the increased cortical excitability
associated with voluntary movement is reflected in increased cortical output from a TMS pulse (Di Lazzaro et al., 1998). Indirect descending pathways between motor cortex and spinal cord via the brainstem also have a modulatory influence on spinal interneurons and the motoneuron pool. The initial reduction in threshold resulting from low levels of muscle pre-activation can be attributed to an increase in excitability of motoneurons in the spinal cord. Further increases in the strength of voluntary contractions facilitate the size of MEPs through increased cortical output, reflecting differences in cortical excitability post-synaptic to the site of activation.

3.2 Input-output properties of the corticospinal pathway

The study of the corticospinal pathway using stimulus-response curves is based on original work by Devanne and colleagues (Devanne et al., 1997). These authors characterised several properties of the corticospinal pathway by analysing the magnitude of motor-evoked potentials in response to different TMS intensities. The resulting stimulus-response relation is best modelled as a sigmoidal response function with three parameters: the plateau value, or maximum MEP amplitude obtainable under the task conditions (MEP_max); the slope value, which reflects the steepness or gain of the function (k); the inflection point, or stimulus intensity at which the maximum steepness occurs (s50); and the threshold value (Carroll et al., 2001). The threshold value, or minimum TMS intensity required to elicit a response, is not explicitly represented within the sigmoidal response function but may be determined as the intercept of the function with an arbitrary amplitude value.

Introducing voluntary tonic background activity at approximately 10–20% of maximum had the effect of reducing the threshold intensity. Further increasing levels of tonic background activity to 30–40% of maximum had the additional effect of increasing the steepness of the response function four to seven times that
observed in the resting muscle. Because a different amount of tonic background activity was required to elicit these effects, they are presumably mediated via different neural mechanisms along the corticospinal pathway.

3.3 The use of TMS during movement

TMS can be used to probe the state of the corticomotor system at various phases of a voluntary movement. The excitability of cortical elements has, for example, been shown to increase preceding muscle activation. This muscle specific facilitation of MEPs has been demonstrated to progressively increase through the 100 ms preceding the onset of a voluntary movement of the hand (Rossini et al., 1988). However, as a consequence of modulation and change at multiple levels, interpretation of MEPs recorded during movement is more difficult. The size of motor evoked potentials has for example, been shown to change independently of background activation in a manner that is unique to both the phase of a reach to grasp task (Lemon et al., 1995), as well as to task objective (i.e. precision grip versus power grasp) (Schieppati et al., 1996).

Capaday and colleagues (Capaday, 1997) have provided recommendations for the use of cortical stimulation during movement; the general aim of which is to detect task-dependent changes of the functional connection between motor cortex and alpha-motoneurons. Such changes are assumed to adapt the control system to expected biomechanical requirements. As shown by Devanne and colleagues (Devanne et al., 1997), for a given level of background contraction, the corticospinal pathway is characterised by three parameters of its input-output function: the inflexion point, maximum slope, and plateau value. Demonstrating a task dependent change requires at least one of these parameters change independently of the background activity. This condition ensures that any observed differences in the
amplitude of evoked responses are due to mechanisms pre-synaptic to the alpha-motoneurons. The modulation may be mediated intracortically, via spinal interneurons, or a combination of both. Further elucidation of the site of modulation requires an assessment of cervicomedullary-evoked potentials or H-reflex facilitation at a latency that precludes effects due to sources other than the monosynaptic corticospinal connection (Ugawa et al., 1991; Taylor and Gandevia, 2004).

The tasks being compared must be similar enough that the muscles of interest are not organised into qualitatively different modes of contraction. For example, comparisons of input-output properties drawn between a task in which the muscle was co-contracting with its antagonist and a task in which they were reciprocally active would be inconclusive. Because of the nonlinearities involved, it is important to define the input-output curve on which the system is operating at each level of background activity and for each task. Furthermore, there is no plateau on the sensitivity function (first derivative) of a given sigmoid input-output relation. Thus test stimuli intensities should be adjusted to the same size to draw valid inferences when the test responses are conditioned.

### 3.4 Statistical analysis of motor-evoked potentials

The experiments presented in this thesis utilise TMS to evoke MEPs under varying task conditions with the aim of detecting changes in corticomotor excitability. Changes in corticomotor excitability can be observed as a shift of the stimulus-response curve or its parameters (Capaday et al., 1999). However, the experimental conditions examined here introduce differences in background muscle activity that are a feature of the task and cannot be eliminated. Owing to the influence of muscle activity on MEP size discussed in sections 3.1–3.3, it is necessary to account for task-
related differences in background muscle activity in the statistical analysis. A novel application of linear mixed models is used to capture the relation between background muscle activity (as a continuous covariate) and MEP size (as the dependent variable) within the experimental factors (independent variables) (Pinheiro and Bates, 2000; Gałecki and Burzykowski, 2013). In this approach, the units of observation are individual MEPs. After accounting for the variance in MEP size due to background EMG, factors can be evaluated using analysis of variance tables to test for effects of independent variables. Furthermore, the model can be used to predict MEP size at specified values of the factors and covariates (Welham et al., 2004). Thus valid estimates of MEP size can be compared or carried forward to further analysis. Throughout the methods and results sections, text in SMALL CAPS is used to designate model terms.

3.5 Magnetic resonance imaging

Magnetic resonance imaging (MRI) refers to a family of non-invasive tomographic imaging techniques that are used to measure the internal structure and function of the body. All MRI techniques are based on the phenomenon of nuclear magnetic resonance. When exposed to a strong magnetic field, atomic nuclei absorb and re-emit electromagnetic waves at a resonant frequency (Storey, 2006; Filomena Santarelli, 2009). In this thesis, MRI was used to obtain structural, and diffusion weighted images of the brain for the chronic stroke participants in Chapter 7.

3.5.1 Structural MRI

Structural MRI is used to obtain high-resolution images of the brain. The tissues and fluids in the brain (cerebrospinal fluid (CSF), bone, white matter, grey matter) are distinguished based on differences in their hydrogen content. Hydrogen nuclei, primarily found in water and fat, undergo longitudinal alignment of their magnetic
moment to the permanent magnetic field $B_0$ created by the scanner. Application of a transverse radio frequency (RF) pulse $B_1$ tips the magnetisation out of alignment with $B_0$. The nuclei return to longitudinal alignment over time $T_1$ in a process termed longitudinal or spin-lattice relaxation. As they relax, the nuclei emit RF waves that can be measured. The relaxation time $T_1$ depends on the tissue, and these differences are exploited to create contrast on MR images. $T_1$ weighted imaging utilises short repetition times (TR) and short echo times (TE). Fat, notably in myelin of white matter, appears the brightest because it has the shortest $T_1$ relaxation time. The grey matter appears an intermediate shade of grey while CSF appears darkest. High contrast makes $T_1$ weighted images suitable for applications requiring high anatomic detail (Katti et al., 2011).

3.5.2 Diffusion weighted imaging

Diffusion-weighted imaging (DWI) can be used to assess the structural integrity of white matter tracts. Within axons, the cellular membranes restrict diffusion of water to the axis. This diffusion anisotropy can be represented as an ellipsoid. Unrestricted diffusion occurs in regions where lesions have disrupted cellular structures. Ellipsoids representing less anisotropic diffusion are more spherical. Each voxel of interest can be characterised by the principal direction of diffusion and the fractional anisotropy (FA), which represents the shape of diffusion (Hagmann et al., 2006). The mean FA within the posterior limb of the internal capsule can be used as a measure of CST integrity. Asymmetry of FA values between the ipsilesional and contralesional PLIC can serve as a biomarker for motor impairment following stroke (Stinear et al., 2007).
3.6 Clinical assessments

Clinical assessments of upper limb function and impairment were used to characterise the stroke patients who participated in Chapter 7. The following section will provide a brief overview of the Fugl-Meyer Assessment (FM), Action Research Arm Test (ARAT), and Modified Ashworth Spasticity Scale (ASH). These tools are included in Appendices H, I & J.

The FM is a multi-domain assessment of sensorimotor impairment based on the stages of motor recovery after stroke (Brunnstrom, 1970; Fugl-Meyer et al., 1975). The complete assessment includes motor, sensory, balance, range of motion, and joint pain domains. Of interest here is the upper extremity component of the motor domain (UE-FM). Items assess voluntary movement, coordination, and reflexes. An assessor scores each item on a three-point scale where 0 = cannot perform, 1 = performs partially, 2 = performs fully. The maximum score is 66. Lower scores indicate more severe upper limb impairment. The UE-FM is valid and reliable (Duncan et al., 1983; Sullivan et al., 2011). However, there is a lack of consensus regarding threshold values used to group patients based on the severity of impairment (Duncan et al., 1994; Woodbury et al., 2013; Pang et al., 2006).

The ARAT is an observational test that was developed to assess recovery of upper limb function after stroke (Lyle, 1981). The ARAT consists of 19 items from four subscales: grasp, grip, pinch, and gross movement. The items assess the ability to move objects of different size, weight and shape. Items are rated by an assessor on a four-point scale where 0 = no movement possible, 1 = movement partially performed, 2 = movement performed but abnormal, 3 = normal movement. A maximum score of 57 indicates normal function. The ARAT is valid and reliable for stroke patients (van der Lee and Beckerman, 2001; van der Lee et al., 2001).
The ASH is an assessment of muscle spasticity that is commonly used after stroke. An assessor scores the level of muscle tone while passively moving the joint through its range of motion. The ASH is a six-point scale that grades the severity of spasticity from 0 (no increase in muscle tone) to 4 (affected parts rigid) (Ashworth:1964ta; Bohannon and Smith, 1987).

3.7 Safety considerations for TMS and MRI

TMS is considered safe for both healthy adults, and patient populations provided standard usage guidelines be observed (Rossi et al., 2009). The TMS safety checklist (Appendices E & F) was used to screen for contraindications to TMS. The most serious risk of TMS is the accidental induction of a seizure. However, the risk is very low for single and paired-pulse stimulation. The TMS safety checklist is used to identify risk factors for seizure, such as a family history of epilepsy, previous concussion, certain medications, and implanted electronic devices.

MRI is a non-invasive technique that presents no health risks given adherence to appropriate safety precautions. The main safety concern is ferromagnetic objects becoming projectiles in the vicinity of the scanner. The MRI safety form (Appendix G) was used in Chapter 7 to screen stroke participants for metallic or electronic implants and other contraindications to MRI.
Partial weight support differentially affects corticomotor excitability across muscles of the upper limb

This experiment has been reported in Physiological Reports 2014; 2(12): e12183. Published under the terms of the Creative Commons Attribution License. The final publication is available via http://dx.doi.org/10.14814/phy2.12183.

4.1 Abstract

Partial weight support may hold promise as a therapeutic adjuvant during rehabilitation after stroke by providing a permissive environment for reducing the expression of abnormal muscle synergies that cause upper limb impairment. We explored the neurophysiological effects of upper limb weight support in thirteen healthy young adults by measuring motor-evoked potentials (MEPs) from transcranial magnetic stimulation (TMS) of primary motor cortex and EMG from anterior deltoid (AD), biceps brachii (BB), extensor carpi radialis (ECR), and first dorsal interosseous (FDI). Five levels of weight support, varying from none to full, were provided to the arm using a commercial device (Saebo Mobile Arm Support). For each level of support, stimulus-response (SR) curves were derived from MEPs across a range of TMS intensities. Weight support affected background EMG activity in each of the four muscles examined (p < 0.0001 for each muscle). Tonic background activity was primarily reduced in the AD. Weight support had a differential effect on the size of MEPs across muscles. After curve fitting, the SR plateau for ECR increased at the lowest support level (p = 0.004). For FDI, the SR plateau increased at the highest support level (p = 0.0003). These results indicate that weight support of the proximal upper limb modulates corticomotor excitability across the forearm and hand. The findings support a model of integrated control of the upper limb and may inform the use of weight support in clinical settings.
4.2 Introduction

Functional linkages of muscles, or synergies, have been proposed as a biological mechanism for controlling complex motor systems (Kelso et al., 1980). For upper limb movements, such as reaching, relative joint motions along the proximal-distal axis are strongly correlated (Lacquaniti and Soechting, 1982; Soechting, 1984). The neurophysiological basis of synergies linking distal and proximal muscles and their physiological regulation remains an open question. For example, these may be embedded as circuits in the primary motor cortex (M1) (Park et al., 2001; Capaday et al., 2013). In humans, functional magnetic resonance imaging shows an overlap of muscle representations in M1 consistent with integrated control of upper limb muscles (Sanes et al., 1995). From TMS studies, the extent of activation of shoulder muscles can regulate healthy reach to grasp synergies by modulating the corticomotor excitability of task-relevant distal muscles (Devanne et al., 2002). If muscles involved in reaching movements are activated as a functional unit, it is possible that the organisational structure of the synergy places proximal muscles such as the anterior deltoïd in a regulatory role within a hierarchy.

Understanding how synergies are organised and regulated is fundamental to developing better diagnostic tools and therapies for those with movement disorders or acquired deficits due to brain injury such as stroke. For stroke survivors, the central feature of the stereotyped flexor synergy pattern is an involuntary coupling of elbow flexor activity to anti-gravity torques at the shoulder (Dewald and Beer, 2001). This loss of independent joint control restricts access to the normal workspace and compromises the ability to perform activities of daily living independently. At present, our understanding of the aetiology and mechanisms of synergy expression in stroke survivors is limited. One promising approach may be to reduce shoulder torque requirements during reaching through partial weight
support (Stienen et al., 2009; Prange et al., 2009a; 2009b). Partial weight support of the upper limb seems to reduce the deleterious effects of abnormal synergies, and permit patients a greater range of motion. However, the neurophysiological underpinning of these benefits is not yet known.

In healthy participants corticomotor excitability (CME) to forearm muscles increase with anterior deltoid activation and this occurs at least in part, via disinhibition within the primary motor cortex (Devanne et al., 2002). Shoulder posture can also increase CME directed to distal hand muscles. For example, a horizontally adducted posture increases CME of hand and forearm extensors that serve to open the hand during grasping (Dominici et al., 2005). These findings are consistent with the hypothesis of a proximal-distal reaching synergy that is at least partly mediated by the primary motor cortex.

In this study, we sought to probe CME of descending motor pathways that comprise a putative upper limb synergy in healthy adults using transcranial magnetic stimulation (TMS). We expected that isometric contraction of anterior deltoid would modulate CME of forearm muscle, extensor carpi radialis. We investigated parametric weight support of the arm using a commercially available rehabilitation device that provided an upward force to the arm through a forearm brace. To provide a reference, tonic background activity and motor-evoked potentials were analysed from muscles across the upper limb. We then examined CME and short-latency intracortical inhibition (SICI) in forearm and hand muscles and hypothesised that an increase in support would lead to a decrease in CME distally. The hypothesis was examined using TMS-derived stimulus-response curves, and paired-pulse TMS for SICI as evidence in support of a cortical mechanism underlying upper limb synergy formation.
4.3 Methods

4.3.1 Participants
Thirteen right-handed healthy young adults (6 female) without a history of upper limb injury or neurological illness participated in this study. The study was approved by the University of Auckland Human Participants Research Ethics Committee in accordance with the Declaration of Helsinki. Participants gave written informed consent and were screened for contraindications to TMS by a neurologist.

4.3.2 Design
We utilised a single-session repeated measures design in which all participants completed all task conditions. All muscles were examined simultaneously. Single-pulse TMS was used to obtain stimulus-response curves at five levels of weight support. Paired-pulse TMS was used to measure SICI at the minimum and maximum levels of weight support. The order of weight support was randomised between participants for stimulus-response curves and counterbalanced for SICI collection. Each session lasted approximately two hours.

4.3.3 Posture and arm support
The experimental arrangement is illustrated in Figure 4.1A. Participants were comfortably seated with their left arm resting on a cushion on their lap. The right arm was supported by a SaeboMAS dynamic mobile arm support system (Saebo Inc., Charlotte, NC). The SaeboMAS provided continuously adjustable weight support through a brace that cradled the proximal forearm. A rigid extension of the brace supported the wrist and hand. We utilised additional foam padding to support the forearm, wrist, and hand. All TMS was delivered in a standardised static posture that was voluntarily maintained by the participant. The shoulder was abducted 90° into the transverse plane and horizontally abducted 45° forward. The elbow was flexed to 90° and the forearm pronated. The SaeboMAS was set to prevent rotation of the
brace in the vertical plane thus ensuring the forearm was always parallel to the floor. The wrist was neutral, and the hand was relaxed. Joint angles were set using a goniometer. Participants would return to this set position by aligning a pointer that extended forward from the brace to a target.

The SaeboMAS permitted continuous manipulation of supportive force. We defined five equally spaced support levels from level 1, in which the device only compensated for its own weight and provided no significant support, to level 5, in which the device fully compensated for the weight of the arm. To determine the setting for level 5, we monitored activity in the anterior deltoid muscle in real-time and incrementally decreased the supportive force from a high setting until root mean squared EMG (rmsEMG) was observed to deflect away from the baseline.

Figure 4.1 A: Example of experimental arrangement. B: Background muscle activity as a function of support level, ranging from minimal support (1) to full support (5). Average root mean square EMG of anterior deltoid (AD), biceps brachii (BB), extensor carpi radialis (ECR), and first dorsal interosseous (FDI) muscles from the pre-stimulus interval. Error bars represent ± SEM.
4.3.4 Electromyography and transcranial magnetic stimulation

Surface electromyography data were recorded from the right anterior deltoid (AD), biceps brachii (BB), extensor carpi radialis (ECR), and first dorsal interosseous (FDI) muscles. Following skin preparation, self-adhesive 10 mm diameter Ag-AgCl electrodes (BlueSensor N; Ambu, Denmark) were arranged in a belly-tendon montage for FDI and ECR, and a belly-belly montage for BB and AD. A common ground electrode was placed over the acromion process (Red Dot: 3M Health Care, Canada). Signals were amplified (Grass P511AC, Grass Instrument Division, RI, USA) with 1000x gain, band-pass filtered (3–1000 Hz), sampled at 2 kHz using a 16-bit A/D acquisition system (National Instruments, Austin, USA) and saved to disc for subsequent offline analysis.

Single- and paired-pulse TMS of left M1 was delivered using two MagStim 200 magnetic stimulators connected to a BiStim unit (Magstim, Dyfed, UK). A figure-of-eight coil (Magstim D70²) was held tangentially to the scalp and perpendicular to the central sulcus, with a posterior to anterior induced current flow. The coil was positioned at the site eliciting maximal motor-evoked potentials (MEPs) in the resting right ECR muscle, and the location was marked on the scalp. Consistent coil position and orientation were maintained through alignment of a template to the scalp markings prior to each stimulus. Resting motor threshold (RMT) was defined as the minimum stimulus intensity that elicited a 50 µV MEP in four out of eight trials. Active motor threshold (AMT) was defined as the minimum stimulus intensity that elicited an MEP in four out of eight trials while maintaining wrist extension against gravity.

A stimulus-response curve was collected at each of the five arm support levels. A single stimulation site was used to concurrently elicit MEPs in all muscles. Ten
stimulus intensities were set relative to RMT of ECR (-5, 0, +5, +10, +15, +20, +25, +30, +35, +40% of maximum stimulator output). For each curve, six stimuli were delivered at each intensity in a block-randomised order. Rest breaks were given following every three stimuli to mitigate fatigue.

For paired-pulse TMS the test stimulus (TS) intensity was set to produce non-conditioned (NC) MEPs of approximately half the observed maximum amplitude at rest. The conditioning stimulus (CS) intensity was set equivalent to AMT and delivered 2 ms preceding the TS. Sixteen stimuli (8 C & 8 NC) were delivered in a randomised order at both the minimum and maximum levels of arm support.

**4.3.5 Data analysis**

The average MEP area was used as the primary dependent measure. For each trial, baseline area was calculated as the integral of EMG over a 20 ms interval immediately preceding stimulation. Baseline area was subtracted from the area integrated over a 20 ms MEP window. MEP onset was determined manually for each muscle for each participant. As a secondary dependent measure, background EMG was calculated as the average pre-trigger root mean squared EMG activity for each trial. MEPs were normalised relative to the largest mean MEP recorded in that muscle to account for differences in MEP size between participants. Statistical analyses were then carried out using mean normalised MEP area and mean background EMG at each combination of stimulus intensity and support level. Mean normalised MEP areas were averaged across participants, and the group level data were fit with three-parameter sigmoidal Boltzmann functions using nonlinear regression (Devanne et al., 1997). The slope, s50, and plateau parameters collectively describe the recruitment properties of the pathway. While motor threshold is not explicitly represented, changes in CME of the most excitable
neurons are captured by a shift in the s50 parameter. The regression procedure
does not assume the plateau of the function exists within the range of sample data.
For SICI, mean conditioned (C) and non-conditioned (NC) MEP areas were
calculated and inhibition calculated as %SICI = 100 – (%NC × 100). A change score for
inhibition (ΔINH) was determined between the minimum and maximum levels of
support.

4.3.6 Statistical analysis
Isometric muscle activity and MEP area were analysed separately for each muscle
using R 3.0.2 (R Core Team, 2014) with the Linear and Nonlinear Mixed Effects
Models package (Pinheiro et al., 2015). For isometric muscle activity, we performed
a linear mixed effects analysis of the relationship between average root mean
squared EMG and support level. We modelled SUPPORT LEVEL and STIMULATION
INTENSITY as fixed effects with interaction terms, and SUBJECTS as a random intercept
effect.

For normalised MEP area, data were logit transformed to meet the assumption of
homoscedasticity. For normalised MEP area, a linear mixed effects analysis with
SUPPORT LEVEL, STIMULATION INTENSITY, and BACKGROUND EMG as fixed effects and
SUBJECTS modelled as a random intercept effect. To understand the effect of
background EMG values on normalised MEP area for the ECR and FDI, pairwise
comparisons were conducted on interpolated means from the statistical model at
specified values of the background EMG covariate (Luo et al., 2014).

Group stimulus-response curves for ECR and FDI were analysed using extra sum-of-
squares F-tests in Prism (GraphPad, San Diego, CA) to assess whether individual
curves for each support level fit the data significantly better than a single global
curve for all support levels (Capaday et al., 1999). Differences in specific fit
parameters of the group curves were analysed using corresponding procedures to compare curves fit with independent parameters to those constrained to share the parameter of interest.

To examine SICI, conditioned MEP areas were analysed using a linear mixed model. Two levels of support (min, max) and two levels of stimulation (conditioned, non-conditioned) were modelled as fixed effects with background EMG as a covariate. Subjects were modelled as a random intercept effect. In a second analysis, we tested whether SICI differed between the maximum and minimum support levels with a one-sample t-test to determine if ΔINH deviated from zero.

An alpha level of 0.05 was adopted as the criterion for statistical significance. Multiple pairwise comparisons were evaluated by applying a modified Bonferroni procedure, correcting only for comparisons with p ≤ 0.05 (Rom, 1990). Means and standard errors (SE) are reported in the text.

4.4 Results

4.4.1 Effect of weight support on muscle activity
The effect of the weight support manipulation on isometric muscle activity was confirmed in the ANOVA for background EMG (Figure 4.1B, Table 4.1). For all muscles, there was a main effect of support level. There were no effects of stimulation intensity or support by stimulation intensity interactions. All muscles exhibited a decrease in tonic activity as the external supportive force was increased from level 1, in which no support was applied, to level 5, in which the SaeboMAS balanced the weight of the arm. Muscle activity appears to scale linearly with support level for AD, BB, and ECR as indicated by R² values of 0.99, 0.99, and 0.94 respectively. For the FDI muscle, an R² value of 0.47 likely reflects fluctuations about a resting state of muscle activity as all mean rmsEMG values were ≤ 6 µV.
Table 4.1 ANOVA of linear mixed effects models for background EMG

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Model Term</th>
<th>F</th>
<th>DF_{num}</th>
<th>DF_{den}</th>
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4.4.2 Effect of weight support on motor-evoked potentials in FDI

Example MEP traces are shown in Figure 4.2. For the FDI muscle, the linear mixed effects analysis of mean MEP area revealed main effects of both SUPPORT LEVEL and STIMULUS INTENSITY (Table 4.2). There was no significant effect of BACKGROUND EMG on mean MEP area, nor were there significant interaction effects. There was a trend towards an interaction between SUPPORT LEVEL and BACKGROUND EMG. To conduct pairwise comparisons of MEP area at different support levels, the linear mixed effects model was used to predict these values at specified levels of the background EMG covariate (Figure 4.3C & D). The consistent finding at both specified values of background EMG was a greater predicted mean MEP area at support level 5.

Table 4.2 ANOVA of linear mixed effects model for FDI MEP area

<table>
<thead>
<tr>
<th>Model Term</th>
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<th>DF_{num}</th>
<th>DF_{den}</th>
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<td>Support × Background EMG</td>
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<td>0.0542</td>
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Figure 4.2 Example EMG traces showing motor-evoked potentials (MEPs) from a single representative subject. Each trace is the average of four trials collected at an intensity 25% MSO above rest motor threshold of ECR. Support level is shown on the left. MEP areas in AD, BB and ECR were reduced with increased weight support. For FDI, MEP area increased with increased weight support.

4.4.3 Stimulus-response curves in FDI

Stimulus-response curves fit to group mean MEP areas using nonlinear regression are shown in Figure 4.4. The omnibus extra sum-of-squares F-test indicated that individual SR curves for each support level fit the data better than a single global curve ($F_{(12,35)} = 5.96, p < 0.0001$). Follow-up pairwise tests revealed that the curve for support level 5 was shifted upward compared to those for all other levels (4, $F_{(3,14)} = 5.57, p = 0.0100$ | 3, $F_{(3,14)} = 10.81, p = 0.0006$ | 2, $F_{(3,14)} = 15.90, p < 0.0001$ | 1, $F_{(3,14)} = 8.43, p = 0.0019$). Furthermore, the curve for level 3 was shifted significantly upward compared to level 1 ($F_{(3,14)} = 5.63, p = 0.0096$). When the slope parameter was constrained to be shared among the curves for each support level, the extra sum-of-squares F test revealed no difference compared to the curves in
which slope was unconstrained \( (F_{4,35} = 0.39, p = 0.8165) \). There was also no difference in the s50 parameter \( (F_{4,35} = 0.13, p = 0.7259) \). The plateau was found to be different between support levels \( (F_{4,35} = 6.88, p = 0.0003) \). Follow-up comparisons revealed the plateau of level 5 \((0.7878 \pm 0.028)\) was greater than the plateaus of all other support levels \((4, 0.6693 \pm 0.019, F_{1,14} = 10.59, p = 0.0058 | 3, 0.6609 \pm 0.017, F_{1,14} = 13.59, p = 0.0024 | 2, 0.6289 \pm 0.027, F_{1,14} = 12.44, p = 0.0033 | 1, 0.6631 \pm 0.023, F_{1,14} = 9.83, p = 0.0073)\).

Figure 4.3 Predicted mean MEP areas for different support levels at specified values of background EMG activity. A: For ECR at 10 µV, pairwise tests showed comparisons 1 \((p = 0.0013)\), 2 \((p=0.0011)\), and 3 \((p = 0.0009)\) to be significant after correction. B: For ECR at 17 µV, the mean value of background EMG, pairwise tests showed comparisons 4 \((p = 0.0121)\), 5 \((p = 0.0004)\), and 6 \((p = 0.0007)\) to be significant after correction. C: For FDI at 5.3 µV, the mean value of background EMG, pairwise tests showed comparisons 7 \((p = 0.0006)\), 8 \((p < .0001)\), and 9 \((p = 0.0068)\) to be significant after correction. D: For FDI at 10 µV, pairwise tests showed comparisons 10 \((p = 0.0041)\) and 11 \((p = 0.0194)\) to be significant after correction. All MEP areas are normalised relative to maximum. Error bars represent standard error of the mean.
4.4.4 Effect of weight support on motor-evoked potentials in ECR

For the ECR muscle, the linear mixed effects analysis of mean MEP area revealed main effects of SUPPORT LEVEL, STIMULUS INTENSITY, and BACKGROUND EMG and an interaction between STIMULUS INTENSITY and BACKGROUND EMG (Table 4.3). To conduct pairwise comparisons of MEP area at different support levels, the linear mixed effects model was used to predict these values at specified levels of the background EMG covariate (Figures 4.3A & B). There was a similar trend at both specified values of background EMG. Predicted mean MEP area was greater at support level 1, with no differences between the higher levels of support.

<table>
<thead>
<tr>
<th>Model Term</th>
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4.4.5 Stimulus-response curves in ECR

Following nonlinear regression (Figure 4.4), the omnibus extra sum-of-squares F-test indicated that individual curves for each support level fit the data better than a single global curve ($F_{(12,35)} = 5.91, p < 0.0001$). Follow-up pairwise tests revealed that the curve for support level 1 was different than those for all other levels ($F_{(3,14)} = 5.79, p = 0.0087$ | 3, $F_{(3,14)} = 13.30, p = 0.0002$ | 4, $F_{(3,14)} = 7.72, p = 0.0028$ | 5, $F_{(3,14)} = 18.51, p < 0.0001$). When the slope parameter was constrained to be shared among the curves for each support level, the extra sum-of-squares F test revealed no difference compared to the curves in which slope was unconstrained ($F_{(4,35)} = 0.22, p = 0.9282$). There was similarly no difference in the s50 parameter ($F_{(4,35)} = 1.16, p = 0.3438$). However, the plateau parameter was found to be different between
support levels \( (F_{(4,35)} = 4.75, p = 0.0036) \). Follow-up comparisons revealed the plateau of level 1 \((0.8332 \pm 0.026)\) was significantly greater than the plateaus of level 3 \((0.719 \pm 0.019, F_{(1,14)} = 10.79, p = 0.0054)\) and level 5 \((0.686 \pm 0.026, F_{(1,14)} = 11.20, p = 0.0048)\).

Figure 4.4 Stimulus-response regression curves fit to group mean MEP area. For ECR (bottom-left), the plateau of the curve for support level 1 was shifted significantly upward compared to curves for support levels 3 and 5. For FDI (bottom-right), the plateau of the curve for support level 5 was shifted significantly upward compared to curves for all other support levels. Stimulus intensities are expressed in units of stimulator output as the difference between test stimulus and RMT of ECR.

4.4.6 Effect of weight support on motor-evoked potentials in BB
For the biceps brachii, the linear mixed effects analysis of mean MEP area revealed main effects of support level, stimulus intensity, and background EMG and two-way
interactions between all factors (Table 4.4). Stimulus-response curves fit to group means show incremental upward shifts with decreasing levels of support and associated increases in background activity (Figure 4.4).

*Table 4.4* ANOVA of linear mixed effects model for BB MEP area

<table>
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<td>***</td>
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<tr>
<td>Stimulus × Background EMG</td>
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<td>0.0082</td>
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<td>0.9557</td>
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4.4.7 Effect of weight support on motor-evoked potentials in AD

For the *anterior deltoid*, the linear mixed effects analysis of mean MEP area revealed main effects of SUPPORT LEVEL, STIMULUS INTENSITY, and BACKGROUND EMG, and two-way interactions between all factors (Table 4.5). Stimulus-response curves fit to group means show incremental upward shifts with decreasing levels of support and associated increases in background activity (Figure 4.4).

*Table 4.5* ANOVA of linear mixed effects model for AD MEP area

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<td>***</td>
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<td>508</td>
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<tr>
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<td>&lt; .0001</td>
<td>***</td>
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<tr>
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<td>0.7079</td>
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4.4.8 Effect of weight support on SICI

Short latency intracortical inhibition of FDI was measured at the minimum and maximum levels of support. Initial tests confirmed that background EMG ($F_{(1,38)} = 0.32, p = 0.5754$) and non-conditioned MEP area ($F_{(1,12)} = 0.06, p = 0.8039$) did not differ between the SUPPORT LEVELS. An analysis of MEP area revealed a main effect of
CONDITIONING STIMULUS ($F_{(1,36)} = 29.61, p < 0.0001$), but no effect of SUPPORT LEVEL ($F_{(1,36)} = 0.20, p = 0.6578$), or SUPPORT by CONDITIONING STIMULUS interaction ($F_{(1,36)} = 0.08, p = 0.7786$). After calculating %SICI, we excluded one subject from further analysis because values less than 20% indicated the protocol was unsuccessful at eliciting SICI for this individual. At support level 1, the mean amount of inhibition (70.7%) was greater than that at support level 5 (56.0%), whereas ΔINH was not different than zero ($t_{(11)} = 0.89, p = 0.39$).

Short latency intracortical inhibition of ECR was assessed in the same manner as for FDI. There was more background EMG activity at support level 1 (22.3 ± 2.4 µV) than support level 5 (11.0 ± 2.0 µV, $F_{(1,38)} = 23.28, p < 0.0001$). Similarly, non-conditioned MEP area was greater at support level 1 (0.0122 ± 0.0018 mV·s) than support level 5 (0.0081 ± 0.0009 mV·s, $F_{(1,12)} = 10.66, p = 0.0068$). The analysis of MEP area revealed main effects of the CONDITIONING STIMULUS ($F_{(1,36)} = 40.00, p < 0.0001$), and SUPPORT LEVEL ($F_{(1,36)} = 16.77, p = 0.0002$), but no SUPPORT LEVEL by CONDITIONING STIMULUS interaction ($F_{(1,36)} = 1.05, p = 0.3113$). The same subject was excluded from ECR SICI analysis because SICI was not successfully elicited. At support level 1, the mean amount of inhibition (48.9%) was less than that at support level 5 (58.5%). The direct test of change in inhibition (ΔINH) revealed a main effect of support on the amount of SICI ($t_{(11)} = 2.63, p = 0.023$). Because the direction of ΔINH differed between ECR and FDI, we compared ΔINH between the two muscles using a paired sample t-test. This revealed a nonsignificant trend ($t_{(11)} = 2.15, p = 0.055$).
4.5 Discussion

This study is the first to examine corticomotor excitability and M1 intracortical inhibition across the forearm and hand during systematic variation in weight support of the proximal upper limb. Consistent with our hypothesis, we observed increased corticomotor excitability (CME) in ECR at the lowest level of weight support. In contrast, CME in FDI displayed the opposite trend, being elevated at the highest level of weight support. Modulation in CME occurred independently of any differences in task requirements for these muscles. Modulation of SICI with weight support equivocally supported the CME data in both muscles. Overall, these results support a model of integrated control of the upper limb that is mediated at least in part via cortical mechanisms. These novel results may inform clinical applications of weight support such as upper limb rehabilitation after stroke (Prange et al., 2009a).

4.5.1 Interactions between weight support, EMG activity and MEP size

Weight support affected tonic muscle activity across the upper limb. Briefly, tonic activity across muscles decreased in a linear manner with weight support (Figure 4.1B), with anterior deltoid having the greatest amplitude of activity and largest difference between low and high levels of weight support. This finding is consistent with its role as the prime mover for shoulder flexion and principal anti-gravity muscle for the posture examined. Elbow flexion occurred in the horizontal plane at the same height as the shoulder. Biceps brachii, while bi-articular, thus acted perpendicular to gravity. The effect of weight support on biceps brachii activity, therefore, cannot be explained by mechanical task requirements. Similarly, extensor carpi radialis had no differential mechanical requirements and still exhibited a trend of increased tonic activity as support decreased, despite instructions to maintain relaxation. Furthermore, the differences in BB and ECR activity across support levels cannot be explained by the requirement to stabilise the arm position on target;
horizontal forces did not change across conditions and successful maintenance of arm position in the horizontal plane was accomplished when muscle activity was at its minimum. The overall trend for weight support to decrease tonic activity in BB and ECR reflects a common drive across the upper limb including forearm. Conversely, FDI did not share any common drive as it remained at resting levels across all support levels. The functional consequence of relatively small differences observed in the distal muscles, i.e. whether they constitute a synergy, is unclear.

The effect of weight support on MEP area in AD and BB indicates a progressive increase in CME above and beyond the effect of increased tonic background activity. This finding implies that excitability of motor neurons in M1 is modulated in response to weight support. This inference was made after including background EMG as a covariate factor in our linear mixed effects analyses of MEP area, which showed a separate effect of support level as well as an interaction with background EMG. Thus an upregulation of CME appears to subserve both voluntary contractions in AD and nonessential tonic activity in BB.

In ECR, increasing weight support resulted in a similar pattern of decreasing tonic activity, but a dissimilar pattern of CME changes. Although MEPs were largest in ECR at the lowest level of support as observed for AD and BB, ECR MEP areas did not decrease progressively with increased weight support (Figure 4.3). With no significant differences between the higher support levels. It is not known why the extent of tonic activity in ECR and increase in MEP area with partial weight support dissociate. The separation may reflect a failure to experimentally detect a small effect or the activity of a separate neural circuit. Nevertheless, the mechanism facilitating greater CME in ECR with low levels of support is not strictly related to tonic background activity or task requirements.
The pattern of CME modulation in FDI differed to that of the more proximal muscles with the greatest CME observed at the highest support level. The difference in MEP size across support levels is particularly interesting because FDI played no role in the task and remained at rest throughout the experiment. It is unlikely that recruitment of the FDI motoneuron pool differed substantially across support levels, as there was no effect of background EMG on MEP area. Pairwise comparisons of predicted mean MEPs corroborate the finding that CME was particularly elevated with support level 5. As was the case in ECR, the irregular change of CME across support levels implicates a threshold effect in the modulatory mechanisms. If FDI was not integrated as part of the muscle linkage in the examined task, it could be subject to surround inhibition within M1 (Beck and Hallett, 2009; 2011). The increase in CME with support level 5 is consistent with a lifting of surround inhibition after the activity of nearby CM neurons projecting to proximal muscles dropped below a threshold (Capaday et al., 2013). In short, the absence of substantial changes in tonic activity is indicative that FDI was not subject to a common drive with the proximal muscles (Devanne et al., 2002; Dominici et al., 2005). However, modulation of CME across support levels suggests an interaction between proximal and distal muscle representations at least in part via intracortical mechanisms.

4.5.2 Neural mechanisms for integrated control of the upper limb
In the present study, decreasing weight support reduced the amount of SICI acting on ECR representations. If this is indeed a dynamic functional linkage between ECR and proximal muscle representations in M1, its emergence only at the lowest support level is indicative of its functional role. That is, there may be a threshold of AD activity that is required to activate the intracortical networks responsible for lifting inhibition of other components like ECR. Similar thresholds have been
observed in the context of other studies examining proximal-distal linkage in the upper limb (Park et al., 2001; Devanne et al., 2002). For example, Devanne and colleagues also reported a facilitation of CME in ECR when AD was active in a pointing task (Deanne et al., 2002). The present findings indicate that this threshold may be similar to the activity required for an unsupported natural forward reach.

The functional linkage between muscles across the upper limb may arise from both subcortical and cortical mechanisms (Bizzi and Cheung, 2013; Capaday et al., 2013). For example, common neural drive to multiple muscles may be mediated subcortically through divergence of descending corticomotor pathways (McKiernan et al., 1998), or via spinal interneuron networks (Bizzi et al., 1991). In theories that espouse modular motor control, spinal interneuron networks constrain muscle synergies by producing relatively stable patterns of activity across a subset of muscles (Lee, 1984; Bizzi and Cheung, 2013). Such neuroanatomical constraints may be unnecessary or suboptimal but persist as a result of phylogenetic inertia. At the cortical level, a common neural drive may arise via dynamic linking of points within M1. For example, Schneider and colleagues demonstrated the formation of a functional linkage between remote motor areas of cat motor cortex using microstimulation that emerged with the blockade of GABA\(_A\) receptors from a focal application of bicuculine (Schneider et al., 2002). In the hemiparetic upper limb, EMG biofeedback training can facilitate relaxation of flexors and recruitment of extensors during resting gravity-compensated conditions. However, during unsupported reaching movements agonist-antagonist coactivation is scaled down but not eliminated by the same biofeedback (Wolf and Binder-MacLeod, 1983; Wolf et al., 1994). These previous findings are indicative that additional linking mechanisms are recruited as a function of overall muscle activity. Taken together,
the effects of weight support on proximal-distal linkages are likely mediated through both cortical and subcortical mechanisms.

Reduced intracortical inhibition may also have contributed to the CME increases observed in FDI with weight support. Previous studies have concluded FDI is not part of a proximal-distal functional linkage (Devanne et al., 2002; Dominici et al., 2005). Thus the present pattern of CME modulation suggests that FDI was subject to a non-specific surround inhibition. Such local cortical interactions in M1 may be mediated by the topography of muscle representations. In animals, the forelimb area contains multiple representations of a given muscle that are non-contiguous and overlap those of other muscles (Donoghue et al., 1992; Schneider et al., 2001; Rathelot and Strick, 2006). Similar overlapping architecture has been observed in humans (Sanes et al., 1995; Devanne et al., 2006). It is, therefore, possible that in the absence of a dynamic linkage, the activity of an AD cortical point resulted in inhibition of a nearby FDI representation (Stinear and Byblow, 2003). Although the modulation of SICI was not statistically significant, the trend in these data is consistent with a lifting of surround inhibition of FDI when activity in nearby cortical points for proximal muscles dropped below a threshold value at a high level of support.

4.5.3 Potential limitations

There are limitations of the present study. First, we did not make direct measurements of peripheral reflex or motoneuron excitability. Single-pulse TMS probes the cumulative excitability of all neural elements along the corticomotor pathway. Therefore, any combination of cortical, subcortical or segmental circuits may contribute to observed differences in MEP area. Some modulation may have occurred at the spinal level. For example, the C3-C4 propriospinal system integrates
a variety of afferent information and modulates cortical output to forearm muscles (Pauvert et al., 1998; Pierrot-Deseilligny, 2002). Even though the static nature of the task precluded substantial differences in muscle spindle afferents from modulating the excitability of interneurons and motoneurons, it may be the case that input from cutaneous pressure receptors and Golgi tendon organs varied with weight support and impacted on motoneuron excitability directly or via propriospinal neurons (Garnett and Stephens, 1981; Rossini et al., 1996; Tokimura et al., 2000).

Second, we did not test multiple arm positions or a dynamic task. Across the upper limb, the accessibility of a given muscle to recruitment depends upon static limb position (Dominici et al., 2005; Ginanneschi et al., 2005; 2006; Mogk et al., 2014). In dynamic tasks, pre-movement facilitation of CME across the hand and forearm is highly specific, both temporally and spatially (Rossini et al., 1988; Lemon et al., 1995). Intracortical inhibition as assessed with SICI can shape motor cortical output in a spatially and temporally specific manner during movement production (Stinear and Byblow, 2003). Thus, the overall profile of CME and SICI across the upper limb might interact with weight support differentially depending on arm position and movement phase. The extent to which our results reflect a task-specific functional linkage, as opposed to a more persistent pattern of modulation, remains a topic for future study.

Third, the paired-pulse stimulation parameters were optimised for eliciting SICI in the resting ECR and examined at only a single interstimulus interval. Different stimulation parameters may have yielded different results across muscles. Withstanding limitations, the present results provide valid observations about CME in the upper limb during weight support.
4.5.4 Implications for the clinical application of weight support
Partially weight support may have relevance to upper limb rehabilitation after stroke (Prange et al., 2006). By globally reducing the amount of required activity in the weak or paretic upper limb, weight support facilitates movement repetition, which is known to promote adaptive cortical reorganisation (Nudo and Milliken, 1996). Additionally, our results indicate that partial weight support has potential to influence CME throughout the upper limb independently of its immediate mechanical effects on muscle activity. By creating unique neuromechanical control profiles, weight support may permit access to a range of motion otherwise unavailable to an individual with upper limb impairment resulting from stroke. Weight support has already shown promise as a therapeutic adjuvant after stroke (Amirabdollahian et al., 2007; Housman et al., 2009; Prange et al., 2009a; Krabben et al., 2012). A promising avenue for future research could be to determine how best to optimise weight support to mitigate the expression of stereotyped flexor and extensor synergy patterns common in stroke survivors with lingering upper limb impairment.
Partial weight support of the arm affects corticomotor selectivity of biceps brachii

This experiment has been reported in Journal of NeuroEngineering and Rehabilitation 2015; 12(94). Published under the terms of the Creative Commons Attribution License. The final publication is available via http://dx.doi.org/10.1186/s12984-015-0085-6.

5.1 Abstract

Weight support of the arm (WS) can be used in stroke rehabilitation to facilitate upper limb therapy, but the neurophysiological effects of this technique are not well understood. While an overall reduction in muscle activity is expected, the mechanism by which WS may alter the expression of muscle synergies has not been examined until now. We explored the neurophysiological effect of WS on the selectivity of biceps brachii (BB) activation in healthy adults. Thirteen participants completed counterbalanced movement tasks in a repeated measures design. Three levels of WS (0, 45, and 90% of full support) were provided to the arm using a commercial device (Saebo Mobile Arm Support). At each level of WS, participants maintained a flexed shoulder posture while performing rhythmic isometric elbow flexion (BB agonist) or forearm pronation (BB antagonist). Single-pulse transcranial magnetic stimulation of primary motor cortex was used to elicit motor-evoked potentials (MEPs) in BB 100–300 ms before muscle contraction. Baseline muscle activity and MEP amplitude were the primary dependent measures. Effects of movement task and support level were statistically analysed using linear mixed-effects models. As expected, with increased support tonic activity was reduced across all muscles. This effect was greatest in the anti-gravity muscle anterior deltoid, and evident in biceps brachii and pronator teres as well. For BB MEP
amplitude, task and support level interacted such that for elbow flexion, MEP amplitudes were smaller with incrementally greater WS. For forearm pronation, MEP amplitudes were smaller only at high WS. Weight support of the arm influences corticomotor selectivity of biceps brachii. WS may impact coordination independently of a global reduction in muscle activity. The amount of supportive force applied to the arm influences the neuromechanical control profile for the limb. These findings may inform the application of WS in upper limb stroke rehabilitation.

5.2 Introduction

Weight support of the arm (WS) can be used during stroke rehabilitation therapy to reduce the difficulty, and increase the quality and quantity of movements made by patients with upper limb impairment (Prange et al., 2006; Brewer et al., 2007; Mehrholz et al., 2012). A variety of devices, ranging from spring-based supports to robotic systems, have been employed to entirely or partially compensate for the weight of the arm (Loureiro et al., 2011). By lessening the magnitude of antigravity torques required for the performance of gross functional movements, WS improves execution of individual movements and may facilitate movement repetition. For example, WS mitigates the reductions in reaching work area observed in stroke patients with upper limb impairment (Sukal et al., 2007). WS is thought to benefit upper limb rehabilitation primarily by increasing capacity in terms of intensity or volume of therapeutic exercises (Kwakkel and Meskers, 2014).

While the dosage of training is a critical factor driving use-dependent plasticity and adaptive cortical reorganisation (Nudo et al., 1996; Woldag and Hummelsheim, 2002; Kleim and Jones, 2008), little is known about what patterns of neuromuscular activity are being expressed and learned under gravity compensated conditions. The application of WS can immediately reduce abnormal joint torque coupling between
the shoulder and elbow, permitting hemiparetic individuals a greater range of elbow extension during forward reaching tasks (Dewald and Beer, 2001; Beer et al., 2004). The effects of WS on movement kinematics are related to an overall reduction in the muscle activity needed to perform reaching tasks, which is evident in both healthy older adults and chronic stroke patients (Prange et al., 2009a; 2009b). Although it is apparent that WS can influence the motor behaviour of the upper limb, the mechanisms by which WS influences intra-limb coordination at the neural level remain unclear.

We previously examined the effects of WS on muscle activation, and corticomotor excitability to proximal and distal upper limb muscles using motor-evoked potentials from transcranial magnetic stimulation (TMS) in healthy adults (Runnalls et al., 2014). As expected, tonic activity in the anterior deltoid (AD) responded linearly to WS. However, a modulation of tonic activity in more distal muscles indicated that WS also interacted with proximal-distal neural linkages. Additionally, corticomotor excitability (CME) to distal muscles was modulated by WS. In the forearm muscle extensor carpi radialis, CME decreased with the application of any WS. A different pattern of modulation was observed in the first dorsal interosseous of the hand, where CME increased, but only at a high level of WS. Nonlinear muscle-dependent CME responses suggest that under static conditions, the neural linkages with which WS interacts are not generalised across the limb and involve both excitatory and inhibitory mechanisms. Here we examine how WS impacts coordination via CME modulation in the context of movement.

The neurophysiological mechanisms of selective muscle recruitment can be examined using TMS (Gerachshenko and Stinear, 2007; Gerachshenko et al., 2008; Bradnam et al., 2010; 2012). In healthy adults, motor-evoked potentials (MEPs)
elicited in the antagonist *biceps brachii* (BB) are suppressed at a cortical level prior to forearm pronation. In contrast, suppression of BB MEPs is drastically reduced or absent in stroke patients with more severe upper limb impairment (Gerachshenko et al., 2008; Bradnam et al., 2013). The ratio of MEP amplitude preceding forearm pronation relative to the amplitude preceding elbow flexion has been shown to be correlated with upper limb impairment (Gerachshenko et al., 2008; Bradnam et al., 2012). This selectivity ratio can be interpreted as a neurophysiological measure of upper limb coordination that is sensitive to the coupling of elbow flexion and shoulder abduction that typifies the abnormal flexor synergy (Dewald et al., 1995; Dewald and Beer, 2001). The effects of WS on selective muscle recruitment and suppression of antagonist muscles may provide insights into the underlying pathophysiology of dysfunctional synergies and inform the clinical use of WS.

In the present study, we sought to examine the neurophysiological effect of WS on the selectivity of BB activation in healthy adults using TMS. We expected that increased WS would modulate the isometric activity of AD and improve the selectivity of BB by reducing CME of BB preceding an antagonist contraction. We investigated parametric WS using a commercially available rehabilitation device that provided gravity compensation through a forearm brace. As a reference, tonic background activity was analysed from the AD and BB muscles. We then examined CME of BB preceding phasic agonist (elbow flexion) and antagonist (forearm pronation) contractions by analysing MEP amplitude. We hypothesised that an increase in WS would lead to a decrease in CME of BB preceding forearm pronation.
5.3 Methods

5.3.1 Participants
Fifteen right-handed healthy adults (mean age: 23.8 years, range: 19.9–30.3 years, nine female) without a history of upper limb injury or neurological illness participated in this study. All procedures were approved by the University of Auckland Human Participants Research Ethics Committee in accordance with the Declaration of Helsinki. Participants provided written informed consent and were screened for contraindications to TMS by a neurologist.

5.3.2 Design
Participants completed all experimental conditions in a single-session repeated measures design. Single-pulse TMS was used to elicit MEPs in BB during two rhythmic motor tasks (elbow flexion or forearm pronation) at three levels of WS (low, medium, high). The order of WS was counterbalanced across participants. Within each WS level, the elbow flexion task was always completed before the pronation task. The session lasted approximately 2.5 hours.

5.3.3 Posture and arm support
Figure 5.1 schematically illustrates the experimental setup. Participants were seated with their left arm resting on their lap. The right arm was supported by a mobile arm support system (SaeboMAS, Saebot Inc., Charlotte, NC). The SaeboMAS attaches to the forearm via a custom brace through which WS is provided and adjusted via spring tension. In the task, the brace was modified to include a vertical cylindrical handle for participants to grasp, and a cushioned support surface for the elbow and forearm. The forearm was firmly secured to the brace using elasticized fabric wrap. Motor tasks were performed in a standardised arm posture with the shoulder flexed approximately 80˚ in the sagittal plane and internally rotated 90˚. The elbow was flexed at 90˚ and the forearm supinated. The handle was grasped with the palm
facing the torso using a neutral wrist position. Joint angles were set using a goniometer. The SaeboMAS prevented rotation of the brace in the vertical plane thus ensuring the forearm was always parallel to the floor. The brace was tethered to wall-mounted anchors using two nylon cords. The tethers provided static resistance for the elbow flexion task and maintained a constant distance between the forearm and torso. The overall effect of the bracing and tethering was to enable isometric elbow flexion and forearm pronation tasks without restricting shoulder circumduction. Participants received visual feedback about their arm posture by centring a laser pointer on a circular target.

We defined three discrete levels of WS. At low support (0%), the device compensated for its weight and provided no further support. At medium and high support levels, the device provided 45 and 90% of the force required to compensate fully for the weight of the arm. These values were determined from a force-titration procedure in which we monitored activity in the AD muscle and incrementally decreased the supportive force from a high setting until root mean squared EMG (rmsEMG) was observed to deflect away from the baseline and then scaled accordingly (Runnalls et al., 2014).

![Figure 5.1](image.png) A schematic illustration of the experimental setup. The EMG electrodes and the elastic wrap used to secure the forearm to the brace have been omitted for clarity. A laser pointer attached to the brace provided visual feedback of the arm position.
5.3.4 Motor tasks
While maintaining the standardised posture using voluntary AD activity, participants performed either repetitive elbow flexion or forearm pronation tasks paced at 0.8 Hz by an audible metronome. Participants were instructed to relax the task agonist between each contraction completely. Visual feedback of rectified EMG from the agonist was presented to participants to assist timing and relaxation. Three familiarisation sets of each task were completed before collection. Data from the last familiarisation set were averaged to obtain a time value for typical EMG burst onset relative to the metronome. Following familiarisation and adjustments, 8 sets of contractions were collected for each condition. Each set consisted of 39 repeated contractions and was 49 s in duration. Adequate rest was provided between sets.

5.3.5 Electromyography and transcranial magnetic stimulation
Surface electromyography was used to record activity from the right anterior deltoid (AD), biceps brachii (BB), and pronator teres (PT) muscles. Following skin preparation, self-adhesive 10 mm diameter Ag-AgCl electrodes (BlueSensor N; Ambu, Denmark) were arranged in a bipolar montage approximately 2 cm apart over the belly of each muscle. A common ground electrode was placed over the acromion process (Red Dot: 3M Health Care, Canada). Signals were amplified (CED 1902; Cambridge Electronic Design, Cambridge, UK) with 1000× gain, band-pass filtered (5–1000 Hz), sampled at 2 kHz (CED 1401), and saved for subsequent offline analysis using CED Signal software (v5.07).

Single-pulse TMS of left M1 was delivered using a MagStim 200 magnetic stimulator (Magstim, Dyfed, UK). A figure-of-eight shaped coil (Magstim D70²) was held tangentially to the scalp and perpendicular to the central sulcus, inducing a posterior to anterior current flow in M1. The coil was positioned at the optimal site for eliciting motor-evoked potentials (MEPs) in the right BB muscle, and the location
was marked on the scalp. Active motor threshold (AMT) for the right BB was defined as the minimum stimulus intensity that elicited an MEP in four out of eight trials while performing a sustained weak muscle contraction in the standardised posture at the high support level.

TMS intensity was initially set at 130% of AMT. The MEP amplitude evoked by this intensity preceding elbow flexion at the high support level (typically around 1 mV) was used as a target for adjusting TMS intensity at other support levels. For adjustment sets, TMS was delivered 150 ms preceding the typical burst onset time every 3–5 repetitions. During the main collection sets, TMS was delivered 50, 100, 150, or 200 ms prior to the typical burst onset time every 4–6 repetitions in a pseudo-randomised order (Gerachshenko and Stinear, 2007). In total, 64 MEPs were elicited from the right BB at each of the 6 combinations of task and support level. A total of 384 stimulation trials were recorded from each participant.

5.3.6 Data analysis
EMG traces were inspected for correct task performance and the presence of an appropriate stimulus artefact. Trials that did not meet these criteria were discarded from further analysis. As the primary dependent measure, BB MEP amplitude was measured within a 20 ms window that was determined manually for each participant. Pre-trigger BB activity was measured as the rmsEMG amplitude over a 50 ms window preceding the stimulus.

A task ratio measure was used to quantify the behaviour of the task agonist (BB or PT). The ratio was calculated as the rmsEMG amplitude following burst onset, relative to baseline rmsEMG amplitude. An EMG burst onset interval was determined manually for each trace as the time between stimulation and EMG burst onset. Only trials with a burst onset interval between 100–300 ms were included in
the analysis. Raw MEP amplitudes were rescaled between 0 and 1 within each participant. Similarly, all rmsEMG values were linearly normalised relative to each participant’s maximum voluntary contraction (MVC) for a given muscle. Stimulus intensity was expressed relative to AMT.

5.3.7 Statistical analysis
Statistical analyses were carried out using R 3.1.2 (R Core Team, 2014) with the nlme: Linear and Nonlinear Mixed Effects Models (Pinheiro et al., 2015) and predict means: Calculate Predicted Means for Linear Models packages (Luo et al., 2014). Distributional assumptions were examined through inspection of q-q plots.

To examine the effect of weight support on tonic muscle activity, a linear mixed effects analysis was conducted on baseline muscle activity. We modelled SUPPORT LEVEL as a fixed effect and used an error term with random intercepts grouped by SUBJECT.

To examine the effect of weight support on corticomotor excitability, a linear mixed effects analysis was conducted on BB MEP amplitude with TASK and SUPPORT LEVEL as categorical factors, and continuous covariates for PRE-TRIGGER ACTIVITY, STIMULUS INTENSITY, TASK RATIO, and EMG BURST ONSET INTERVAL. The error term included random intercepts grouped by SUBJECT. A random slope was also included for PRE-TRIGGER ACTIVITY. Interpolated means were calculated at the median values of the four covariates.

An alpha level of 0.05 was adopted as the criterion for statistical significance. Post-hoc comparisons were evaluated using Tukey HSD adjusted p-values. Means and standard errors (SE) are reported in the text.
5.4 Results

None of the 15 participants reported adverse effects from the procedures. Data from 2 participants were not included in the final analysis because of inconsistent task performance as indicated by task ratio values. Of the 64 MEPs collected from each participant per condition, an average of 52 fell within the burst onset interval criteria and were retained for analysis. Example EMG traces are presented in Figure 5.2.

Figure 5.2 Example EMG traces from a representative participant. The TMS stimulus artefact is visible at 100 ms, followed by the biphasic MEP between approximately 115–135 ms. Task-related phasic bursting is evident at the end of the trace.
5.4.1 Effect of weight support on tonic muscle activity

As expected there was a main effect of SUPPORT LEVEL for AD ($F_{(2,4017)} = 2480.37$, $p < 0.0001$; Fig 5.3a), for BB ($F_{(2,1972)} = 73.00$, $p < 0.0001$; Fig 5.3b) and for PT ($F_{(2,2030)} = 67.70$, $p < 0.0001$; Fig 5.3c). All three muscles exhibited less tonic activity with higher levels of external support. Mean values and standard errors are presented in Table 5.1.

Table 5.1 Mean (SE) normalised baseline muscle activity expressed as a proportion of maximum voluntary contraction.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Support level</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (0%)</td>
<td>Medium (45%)</td>
<td>High (90%)</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>0.1040 (0.0012)</td>
<td>0.0743 (0.0010)</td>
<td>0.0384 (0.0008)</td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td>0.0508 (0.0010)</td>
<td>0.0448 (0.0011)</td>
<td>0.0397 (0.0011)</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>0.0368 (0.0008)</td>
<td>0.0332 (0.0008)</td>
<td>0.0302 (0.0008)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 5.3 Baseline EMG activity at low (0%), medium (45%), and high (90%) levels of WS is plotted for A: anterior deltoid, B: biceps brachii, and C: pronator teres. Each data point represents rmsEMG from a single trial normalised to maximum voluntary contraction. Each column presents all traces within the support level.
5.4.2 Effect of weight support on BB MEPs

Omnibus ANOVA results are shown in Table 5.2 and descriptive statistics in Table 5.3. There were main effects of TASK and SUPPORT LEVEL, and a TASK × SUPPORT LEVEL interaction (all \( p < 0.0001 \)). For covariates, the factors STIMULUS INTENSITY \( (p = 0.1597) \) and TASK RATIO \( (p = 0.0741) \) did not significantly affect BB MEP but were retained in the model. There were significant effects of PRE-TRIGGER ACTIVITY \( (p < 0.0001) \) and BURST ONSET INTERVAL \( (p = 0.0016) \). MEP amplitude was larger with greater pre-trigger activity and shorter burst onset interval.

*Table 5.2* Omnibus ANOVA for the linear mixed model of BB MEP amplitude.

<table>
<thead>
<tr>
<th>Model Term</th>
<th>F</th>
<th>DF&lt;sub&gt;num&lt;/sub&gt;</th>
<th>DF&lt;sub&gt;den&lt;/sub&gt;</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support Level</td>
<td>48.69</td>
<td>2</td>
<td>4005</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Task</td>
<td>331.46</td>
<td>1</td>
<td>4005</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pre-trigger Activity</td>
<td>18.53</td>
<td>1</td>
<td>4005</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Task Ratio</td>
<td>3.19</td>
<td>1</td>
<td>4005</td>
<td>0.0741</td>
</tr>
<tr>
<td>Stimulus Intensity</td>
<td>1.98</td>
<td>1</td>
<td>4005</td>
<td>0.1597</td>
</tr>
<tr>
<td>Burst Onset interval</td>
<td>9.94</td>
<td>1</td>
<td>4005</td>
<td>0.0016</td>
</tr>
<tr>
<td>Support Level × Task</td>
<td>27.33</td>
<td>2</td>
<td>4005</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Support Level × Pre-trigger Activity</td>
<td>6.03</td>
<td>2</td>
<td>4005</td>
<td>0.0024</td>
</tr>
<tr>
<td>Task × Pre-trigger Activity</td>
<td>43.11</td>
<td>1</td>
<td>4005</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Support Level × Task × Pre-trigger Activity</td>
<td>22.85</td>
<td>2</td>
<td>4005</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Figure 5.4  Predicted mean MEP amplitudes for flexion and pronation tasks plotted against WS level. Error bars represent standard error of the mean. Adjusted p-values for pairwise comparisons are indicated at right.

Table 5.3  Mean (SE) values of observed covariate factors and BB MEP amplitude. Pre-trigger activity is expressed as a proportion of maximum voluntary contraction. Burst onset interval is expressed in seconds. Stimulus intensity is expressed as a proportion of active motor threshold. Task ratio is an expression of EMG burst amplitude relative to baseline EMG amplitude. Raw MEP amplitudes were rescaled between 0 and 1 within each participant.

<table>
<thead>
<tr>
<th>Observed Variable</th>
<th>Low Support Flexion</th>
<th>Low Support Pronation</th>
<th>Medium Support Flexion</th>
<th>Medium Support Pronation</th>
<th>High Support Flexion</th>
<th>High Support Pronation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-trigger Activity</td>
<td>0.0415 (0.0010)</td>
<td>0.0303 (0.0009)</td>
<td>0.0361 (0.0010)</td>
<td>0.0254 (0.0008)</td>
<td>0.0311 (0.0010)</td>
<td>0.0169 (0.0007)</td>
</tr>
<tr>
<td>Burst Onset Interval (s)</td>
<td>0.1843 (0.0021)</td>
<td>0.1865 (0.0021)</td>
<td>0.1851 (0.0022)</td>
<td>0.1906 (0.0021)</td>
<td>0.1870 (0.0021)</td>
<td>0.1866 (0.0021)</td>
</tr>
<tr>
<td>Stimulus intensity</td>
<td>1.2557 (0.0042)</td>
<td>1.2529 (0.0043)</td>
<td>1.3154 (0.0029)</td>
<td>1.3176 (0.0032)</td>
<td>1.3242 (0.0027)</td>
<td>1.3274 (0.0027)</td>
</tr>
<tr>
<td>Task ratio</td>
<td>5.1247 (0.1510)</td>
<td>8.8021 (0.1969)</td>
<td>6.3926 (0.2197)</td>
<td>10.1044 (0.1892)</td>
<td>6.8140 (0.2430)</td>
<td>11.0445 (0.2796)</td>
</tr>
<tr>
<td>MEP amplitude</td>
<td>0.3954 (0.0086)</td>
<td>0.2775 (0.0067)</td>
<td>0.3529 (0.0070)</td>
<td>0.2804 (0.0076)</td>
<td>0.3231 (0.0075)</td>
<td>0.1713 (0.0061)</td>
</tr>
</tbody>
</table>
Because of these covariate effects, it was not possible to perform post-hoc tests on the MEP data directly. Instead, pairwise comparisons were conducted using the linear mixed model to interpolate predicted means at equivalent points along the covariate distributions. Interpolations were made using the following values specified from each covariate distribution: pre-trigger activity of 0.03 × MVC, burst onset interval of 180 ms, stimulus intensity of 1.3 × AMT, and task ratio of 8.0. Predicted means and standard errors for each experimental condition are shown in Figure 5.4, and results of pairwise tests in Table 5.4. For elbow flexion, BB MEP amplitude exhibited a negative monotonic relation with support level; MEP amplitude was greater at low support compared to medium support ($p = 0.017$), and likewise greater at medium support than at high support ($p = 0.019$). The omnibus task × support level interaction is apparent in the relation of BB MEP amplitude and support level for forearm pronation. MEP amplitude did not differ between low and medium support levels ($p = 0.554$). The hypothesised smaller MEP amplitude with greater WS was observed only at high support ($p < 0.001$).

Table 5.4 The matrix of test statistics for pairwise comparisons of predicted BB MEP amplitude. Adjusted p-values are below the diagonal, t-statistics are above the diagonal.

<table>
<thead>
<tr>
<th></th>
<th>low:pron</th>
<th>low:flex</th>
<th>med:pron</th>
<th>med:flex</th>
<th>high:pron</th>
<th>high:flex</th>
</tr>
</thead>
<tbody>
<tr>
<td>low:pron</td>
<td>-</td>
<td>-12.3345</td>
<td>-1.6661</td>
<td>-8.7408</td>
<td>8.0019</td>
<td>-5.9109</td>
</tr>
<tr>
<td>low:flex</td>
<td>0.0000</td>
<td>-</td>
<td>10.1635</td>
<td>3.2048</td>
<td>17.9571</td>
<td>5.9573</td>
</tr>
<tr>
<td>med:pron</td>
<td>0.5544</td>
<td>0.0000</td>
<td>-</td>
<td>-7.8027</td>
<td>10.5346</td>
<td>-4.8011</td>
</tr>
<tr>
<td>med:flex</td>
<td>0.0000</td>
<td>0.0171</td>
<td>0.0000</td>
<td>-</td>
<td>16.8658</td>
<td>3.1792</td>
</tr>
<tr>
<td>high:pron</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>-</td>
<td>-14.4229</td>
</tr>
<tr>
<td>high:flex</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0186</td>
<td>0.0000</td>
<td>-</td>
</tr>
</tbody>
</table>
5.5 Discussion
This study examined task dependent modulation of *biceps brachii* corticomotor excitability under systematic variation of arm weight support. In line with previous findings, baseline tonic muscle activity decreased across the upper limb as WS was increased. Consistent with our hypothesis, there was improved BB selectivity at the highest level of WS. As an agonist to elbow flexion, BB CME reduced monotonically with each increase in WS. As an antagonist to forearm pronation, BB CME was suppressed only at the highest level of WS. Overall, these results support a model of integrated upper limb control, which interacts with WS through independent excitatory and inhibitory mechanisms. These novel findings may inform applications of WS in clinical settings such as upper limb rehabilitation following stroke.

5.5.1 Weight support reduces tonic muscle activity across the upper limb
The WS manipulation provides evidence for a common neural drive to muscles of the arm. Greater WS reduced tonic muscle activity across the upper limb. As indicated by baseline EMG values (Table 5.1, Figure 5.3), AD is the principal muscle generating antigravity torque for the posture examined and exhibited the greatest difference in tonic activity between low and high levels of WS. This finding confirms the efficacy of the WS manipulation and is consistent with previous studies employing multiple gradations of WS (Coscia et al., 2014; Runnalls et al., 2014). Although BB is at least weakly synergistic for shoulder flexion during typical reaching tasks, in this case BB was not positioned to act against gravity. Instead, BB and PT were recruited primarily during the phasic movement tasks, which did not differ across levels of WS. The tendency for WS to indirectly exert an influence on tonic activity in BB and PT reflects a common drive to muscles across the upper limb.
5.5.2 Weight support affects task-dependent modulation of corticomotor excitability

_Biceps brachii_ MEP amplitude was modulated by the WS manipulation differentially for the flexion and pronation motor tasks. For the elbow flexion task, progressively greater WS resulted in a monotonic decrease in BB MEP amplitude. This observation was made after statistically controlling for variation in pre-trigger EMG activity and EMG burst onset timing and indicates that WS modulates the excitability of neurons upstream of the spinal motoneuron pool. Sensory information from cutaneous mechanoreceptors, muscle spindles, and Golgi tendon organs may have modulated spinal interneuron excitability. Differences in afferent information across levels of WS and their accordant influence on MEP amplitude were, however, minimised because posture and bracing were stable. In the context of previous evidence for cortically mediated proximal-distal integration and earlier neurophysiological studies of WS, it is probable that WS modulates CME to a significant although non-exclusive extent at a supraspinal level (Devanne et al., 2002; Runnalls et al., 2014). An up-regulation of CME preceding voluntary recruitment of BB for elbow flexion is expected and established in this paradigm as observed previously (Gerachshenko and Stinear, 2007; Gerachshenko et al., 2008). The functional significance of weaker BB CME facilitation preceding elbow flexion with WS is not known. The reciprocal ability to suppress CME before an antagonist contraction may be of greater importance to coordination.

Given the role of BB as a forearm supinator, BB CME must be selectively suppressed to pronate the forearm. As hypothesised, BB MEP amplitude was suppressed during the forearm pronation task at the high level of support. This could be indicative of a greater inhibitory network available to suppress CME. A reduction in the activity of proximal anti-gravity muscles may act through putative neural inhibitory networks within M1 to reduce excitatory input to the BB motor neurons. BB MEP amplitude
differed between low and medium support during the flexion task, indicating the WS manipulation was able to influence motor cortical excitability under these conditions. The differential pattern of BB CME modulation between flexion and pronation suggests that WS might preferentially engage inhibitory circuits to reduce excitatory activity when antagonist suppression is required. A similar observation was made by Devanne et al. who found that shoulder activity could influence short latency intracortical inhibition of M1 forearm representations (Devanne et al., 2002).

5.5.3 Neural mechanisms for integrated control and selective muscle activation
The present findings support a model of integrated neuromuscular activity along the proximal-distal axis. In this study, WS led to changes in tonic muscle activity across the upper limb and a modulation of phasic BB CME. A linked neural architecture may facilitate coordination of behaviours such as forward reaching and could incorporate cortical and subcortical mechanisms. A cortical basis for proximal-distal linkages is supported by evidence of multiple non-contiguous muscle representations in the animal M1 that exhibit extensive overlap with those of other muscles (Donoghue et al., 1992; Schneider et al., 2001; Rathelot and Strick, 2006). Furthermore, representations of proximal muscles have been reported to systematically surround those of more distal muscles (Park et al., 2001). A similar overlapping architecture has been observed in the human motor cortex (Sanes et al., 1995; Devanne et al., 2006). In the context of present findings, the direct effect of WS on the voluntary drive to the AD could propagate to linked representations and result in positively correlated changes in tonic motor neuron activity.

The linking of muscle activity across the upper limb may also be mediated via subcortical and spinal mechanisms. The extensive divergence of descending corticomotor pathways could contribute a common obligatory drive to multiple
motoneuron pools (McKiernan et al., 1998). In parallel, ipsilateral descending pathways contribute to proximal limb control and exhibit less specific patterns of innervation. Notably, suppression of the ipsilateral motor cortex by cathodal transcranial direct current stimulation mediates an improvement in BB selectivity (McCambridge et al., 2011; Uehara et al., 2015). Other motor pathways such as the C3-C4 propriospinal system link multiple spinal segments and can modulate cortical output to the forearm (Pauvert et al., 1998; Pierrot-Deseilligny, 2002). Additionally, spinal interneuron circuits can produce stable patterns of coordinated activity across multiple muscles (Bizzi et al., 1991; Bizzi and Cheung, 2013). In summary, it is likely that a combination of cortical and subcortical mechanisms contributes to a scaling of tonic activity across the upper limb with changes in WS.

A task dependent modulation of phasic CME suggests that WS interacts with excitatory linking mechanisms as well as local inhibitory circuits. The monotonic pattern of CME modulation preceding elbow flexion indicates a linear scaling of excitatory inputs, whereas the pattern preceding pronation may be indicative of a threshold or saturation effect in the inhibitory circuits. Selective recruitment of upper limb muscles like BB requires centrally mediated phasic activation commands that may be superimposed upon tonic coactivation (De Luca and Mambrito, 1987; Flanders and Herrmann, 1992). Although agonist-antagonist pairs are reciprocally inhibited at the spinal level, sophisticated activation patterns are possible because cortical representations are linked through excitatory axon collaterals (Capaday et al., 1998). The action of local inhibitory circuits normally suppresses cortical motor neurons but can be lifted either selectively or in concert, to achieve the desired pattern of motor output (Ethier et al., 2007). The differential response of phasic CME is indicative that WS interacts with local inhibitory circuits independently of excitatory linking mechanisms.
5.5.4 Potential limitations

A limitation of the present study is an absence of behavioural data beyond the EMG measures. Whether there are functional correlates of the observed CME modulation is not clear. Notably, there was no clear trend or statistically significant effect of the EMG-based task ratio measure. Furthermore, this study sampled young healthy adults, a population that other studies have reported is able to maintain invariant reaching kinematics with changes in WS (Prange et al., 2009b; Coscia et al., 2014). Future studies are warranted to examine the effects of WS on CME and arm function in neurologically impaired individuals (e.g. after stroke resulting in upper limb impairment). It is clear that reduced suppression of BB CME preceding an antagonist contraction is related to upper limb impairment in stroke patients (Gerachshenko et al., 2008; Bradnam et al., 2012).

5.5.5 Implications for the use of weight support for neurorehabilitation

Weight support of the arm may have relevance to upper limb rehabilitation after brain injuries such as stroke (Prange et al., 2006; Brewer et al., 2007; Mehrholz et al., 2012). In addition to facilitating training dosage, WS may facilitate the production of movements that are not achievable without assistance. By reducing the amount of muscle activity required to move the paretic upper limb, WS can reduce the effect of abnormal joint coupling and increase the reachable workspace area (Beer et al., 2004; 2007; Sukal et al., 2007; Housman et al., 2009; Ellis et al., 2009b; Krabben et al., 2012). This could be advantageous for practising reach and retrieval tasks that are associated with daily living activities such as feeding, grooming, dressing, or preparing meals. It remains to be determined if the extent to which WS may improve the selective activation of muscles like BB depends on structures affected, such as the extent of damage to the motor cortex, or the corticospinal tract. We previously reported that in healthy adults, WS influences CME across the upper limb.
(Runnalls et al., 2014). This study additionally demonstrates that WS modulates CME during a phasic movement task, improving BB selectivity. In the context of integrated limb control, the level of WS may interact with excitatory and inhibitory mechanisms independently. Nonlinear responses to WS highlight the importance of supportive force as a dosing variable. Independent modulation could, in turn, create unique neuromechanical control profiles and opportunities for targeted therapeutic exercises. By facilitating otherwise unachievable patterns of neuromuscular activity in addition to training dosage, WS may be a valuable tool for driving neuroplasticity. Moreover, the use of progressive loading with partial rather than full WS may in itself be an important factor driving recovery of upper limb function (Ellis et al., 2009a). Further characterising muscle coordination and control at different levels of WS (Coscia et al., 2014) will contribute to optimising the use of WS as an adjuvant to upper limb rehabilitation therapy.

5.5.6 Conclusions
A manipulation of WS led to changes in tonic muscle activity across the upper limb and a task-dependent modulation of phasic corticomotor excitability to *biceps brachii*. For elbow flexion, corticomotor excitability to *biceps brachii* was reduced with incremental increases in WS. For forearm pronation, corticomotor excitability to *biceps brachii* was reduced only with high WS. This different pattern of modulation indicates WS interacts with inhibitory circuits independently, potentially increasing the inhibitory network available to suppress unwanted muscle recruitment. Overall, these results demonstrate that the amount of WS has direct and indirect influences on neuromuscular activity across the upper limb. Tunable supportive force may be an important consideration in the design and application of WS devices. With further characterisation of parametric WS, its role in neurorehabilitation may be refined and individualised.
**Posture interacts with arm weight support to modulate corticomotor excitability to the upper limb**

This experiment has been reported in Experimental Brain Research 2017; 235: 97–107. The final publication is available at Springer via http://dx.doi.org/10.1007/s00221-016-4775-5.

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### 6.1 Abstract

The use of arm weight support (WS) to optimise movement quality may be an avenue for improved upper limb stroke rehabilitation. However, the underlying neurophysiological effects of WS are not well understood. Rehabilitation exercises may be performed when sitting or standing, but the interaction of posture with WS has not been examined until now. We explored the effect of posture with WS on corticomotor excitability (CME) in healthy adults. Thirteen participants performed static shoulder abduction in two postures (sitting and standing) at three levels of WS (0, 45, and 90% of full support). Transcranial magnetic stimulation of primary motor cortex was used to elicit motor-evoked potentials (MEPs) in eight upper limb muscles. Stimulus-response (SR) curves were fitted to the MEP data using nonlinear regression. Whole body posture interacted with WS to influence tonic activity and CME in all muscles examined. SR curve parameters revealed greater CME when standing compared to sitting for upper arm muscles but lower CME to the shoulder, forearm, and hand. Distal to the shoulder, tonic activity and CME were modulated independently of any explicit differences in task requirements. Overall, these results support a model of integrated upper limb control influenced by whole body posture and WS. These findings have implications for the application of WS in settings such as upper limb rehabilitation after stroke.
6.2 Introduction

Stroke is a leading cause of adult disability with two-thirds of stroke survivors experiencing lingering upper limb impairment (Feigin et al., 2010; Mendis, 2013). Weight support (WS) can be used to augment arm movements made during stroke rehabilitation therapy (Prange et al., 2006; Brewer et al., 2007; Kwakkel et al., 2008; Mehrholz et al., 2015) and may be applied manually, or through devices ranging from passive supports to sophisticated robotic systems (Loueiro et al., 2011). The benefits of WS for upper limb rehabilitation have been ascribed to increasing the intensity or volume of therapeutic exercises (Kwakkel and Meskers, 2014). Beyond its role in facilitating increased training dosage, WS can also improve movement quality. For example, in reaching tasks, the application of WS results in a reduction of antagonist muscle activity in both healthy older adults and chronic stroke patients (Prange et al., 2009a; 2009b). WS can also lessen abnormal coupling of joint torques between the shoulder and elbow through a reduction in antigravity torques required for shoulder abduction (Dewald and Beer, 2001; Beer et al., 2004). As a functional consequence individuals who express the stereotyped flexor synergy can achieve greater elbow extension under gravity-compensated conditions thereby increasing access to the reaching workspace (Sukal et al., 2007). To date, the neural mechanisms underlying transient changes in motor behaviour with WS have received less attention and are not well understood.

Change in whole body posture can also affect motor control of the upper limb, but its interaction with WS has not been investigated. Rehabilitation exercises may be performed when sitting or standing thus an interaction of posture with WS on upper limb control may inform its clinical application. Standing postures introduce balance requirements that alter the way arm movements are coordinated and increase the complexity of reaching and pointing tasks (Pozzo et al., 2001; 2002; Berrigan et al.,
Centrally mediated changes in the accessibility of muscles for activation may be assessed using transcranial magnetic stimulation (TMS). Compared to sitting, standing results in greater corticomotor excitability (CME) to the anterior deltoid but no change in CME to the first dorsal interosseous (Kantak et al., 2013). Posture-related modulation of CME to the shoulder, but not the hand, likely reflects a greater mechanical role played by proximal muscles in shifting the centre of mass; e.g. to maintain stability in response to a perturbation. Neuromuscular activity is modulated across the limb with WS and may involve both excitatory and inhibitory mechanisms (Devanne et al., 2002; Runnalls et al., 2014; 2015). Whether the neural mechanisms underpinning posture-related changes in upper limb control interact with the neural linkages modulated by WS is unknown.

In the present study, we sought to examine the interaction of whole body posture and WS on CME to upper limb muscles. TMS was used to elicit motor-evoked potentials (MEPs) from muscles in the shoulder, arm, forearm, and hand of healthy adults. We expected that tonic muscle activity would modulate with both WS and posture manipulations. It was hypothesised that tonic activity would be reduced with greater WS, and greater during standing compared to sitting. CME was examined by analysing MEP area and comparing stimulus-response (SR) curves fitted to group means. It was hypothesised that SR curves would reflect greater CME with a standing posture, evident by steeper slope and associated parameters. Greater CME during standing may facilitate an increased biomechanical role of the upper limb for postural stabilisation. Furthermore, less excitatory input under conditions with greater WS may permit a wider range of posture-related modulation to manifest; thus we expected the magnitude of posture-related differences would be greater with WS.
6.3 Methods

6.3.1 Participants
Thirteen neurologically healthy right-handed adults without a history of upper limb impairment participated in this study (mean age: 28 y, range: 20–50 y, 3 female). All participants gave written informed consent and were screened for contraindications to TMS by a neurologist. Study procedures were approved by the University of Auckland Human Participants Research Ethics Committee in accordance with the Declaration of Helsinki.

6.3.2 Design
All procedures were completed in a single session using a repeated measures design. Single-pulse TMS was used to elicit MEPs from muscles of the arm during 2 postures (sitting and standing) at 3 levels of WS (low, medium, high). The order of the 6 experimental conditions was randomised between participants. Within each experimental condition, a range of TMS intensities was randomised on a trial-by-trial basis. Each session lasted approximately three hours.

6.3.3 Posture and arm support
Figure 6.1 illustrates the sitting and standing experimental conditions. The right arm was supported by a SaeboMAS arm support system (Saebo Inc., Charlotte, NC). Force was provided and adjusted via spring tension. A custom brace provided a rigid and cushioned surface for the forearm and hand. Elasticized fabric wrap was used to secure the forearm to the brace in a palm-down position. For both sitting and standing conditions, TMS was performed in a standardised arm position with the shoulder flexed forward approximately 80° and abducted 45° in the horizontal plane, and the elbow flexed at 90°. Joint angles were initially set using a goniometer and subsequently maintained by aligning a laser pointer to a reference point on the wall. The brace prevented rotation in the vertical plane ensuring the forearm was
parallel to the floor. The support system provided no resistance to horizontal motion, i.e., participants could not push or pull on the brace to regulate postural sway. In the sitting condition, participants sat in a chair with their feet on the floor and left arm resting on their lap. In the standing condition, participants stood with their feet shoulder width apart and left arm resting at their side.

![Figure 6.1 Demonstration of sitting (A) and standing (B) postures.](image)

Three discrete levels of WS were defined relative to the force required to compensate for the weight of the arm fully. At low support (0 %), the device carried its own weight but provided no additional support to the arm. The force required for full support (100 %) was determined using a force titration procedure. While maintaining the standardised arm position, the supportive force was incrementally decreased from a superfluous setting requiring shoulder adduction. Full support (100 %) was defined as the last point before root mean square EMG amplitude (rmsEMG) in the anterior deltoid was observed to deflect away from the baseline activity that persists even with excessive support (Runnalls et al., 2014; 2015). Medium and high support levels were then defined as 45 and 90 % of full support.
6.3.4 Electromyography

Surface electromyography was used to record activity from eight muscles of the right arm and hand: anterior deltoid (AD), biceps brachii (BB), triceps brachii (TB), brachioradialis (BRD), extensor carpi radialis (ECR), flexor carpi radialis (FCR), first dorsal interosseous (FDI), and abductor pollicis brevis (APB). Following standard skin preparation, self-adhesive Ag-AgCl electrodes (Blue Sensor N; Ambu, Denmark) were placed approximately 2 cm apart in a bipolar montage over the belly of each muscle. The common ground electrode was placed over the acromion process (Red Dot; 3M Health Care, Canada). Signals were amplified (AMT-8; Bortec Biomedical, Calgary, Canada) with 1000× gain, band-pass filtered (10–1000 Hz), sampled at 2 kHz (CED Power 1401 mkII; Cambridge Electronic Design, Cambridge, UK), and saved for subsequent offline analysis using CED Signal software (v6.03c).

6.3.5 Transcranial magnetic stimulation

Single-pulse TMS was applied over the left motor cortex using a MagPro X100 magnetic stimulator and MC-B70 butterfly coil (MagVenture, Denmark). The coil was held tangentially to the scalp and angled approximately 45° away from the midline. A monophasic pulse was used to induce a posterior to anterior current flow in M1. The coil was positioned at the optimal site for eliciting MEPs in the right ECR muscle. A single experimenter conducted all the tests. Task motor threshold (MT) for the right ECR was defined as the minimum stimulus intensity that elicited a 50 µV MEP in four out of eight trials while seated with the arm in the standardised position at the high support level.

For each of the six experimental conditions, stimulus–response (SR) curves were collected using a single stimulation site to elicit MEPs in all muscles concurrently. Eleven stimulus intensities were set relative to task motor threshold of ECR: -10, -5, 0, +5, +10, +15, +20, +25, +30, +35, +40 % of maximum stimulator output (% MSO).
Stimulation was based on the site and threshold for ECR because it was somatotopically central and most consistently captured the stimulus-response range for the set of examined muscles. For each curve, 88 stimuli were delivered in a randomised order (8 stimuli for each of the 11 intensities). To mitigate fatigue, participants rested their arm on a table for approximately 15 seconds after every six stimuli.

6.3.6 Data analysis
Individual EMG traces were inspected for the presence of an appropriate stimulus artefact and absence of phasic muscle activity. Trials that did not meet these criteria were discarded from further analysis. Measures were obtained from individual raw EMG traces. The main dependent measure, MEP area, was calculated over a 20 ms window determined manually for each muscle for each participant. To account for systematic differences in MEP size between participants, raw MEP area values were normalised between 0 and 1 across conditions within each muscle. As a covariate, background muscle activity was measured as the rmsEMG amplitude over a 50 ms window preceding the stimulus.

6.3.7 Statistical analysis
Analyses of background muscle activity and MEP area were conducted using R 3.1.2 (R Core Team, 2014) with the nlme: Linear and Nonlinear Mixed Effects Models (Pinheiro et al., 2015) and predict means: Calculate Predicted Means for Linear Models packages (Luo et al., 2014). Outlying data points were identified by analysing background muscle activity on a within-subject basis. Observations of rmsEMG more than 1.5× the interquartile range either above the third quartile or below the first quartile, along with their associated MEP values, were excluded from further analysis. Data were log-transformed to satisfy the assumption of normally distributed residuals.
To assess the interaction of weight support and posture on background muscle activity across the upper limb, separate linear mixed effects analyses were carried out for each muscle. In each case, background muscle activity was modelled as a function of SUPPORT LEVEL and POSTURE as factors, with random intercepts for SUBJECT. The sequential sum of squares was used for Wald tests of model terms (Pinheiro and Bates, 2000). As a measure of effect size, log response ratios were calculated for differences between marginal means (Hedges et al., 1999). For support level, the response ratio was expressed as the natural logarithm of high support relative to low with negative values indicating less muscle activity with high support. For posture, the response ratio was expressed as the natural logarithm of standing relative to sitting; negative values indicate less muscle activity when standing.

For MEP area, separate linear mixed effects models were constructed for each muscle. In each case, MEP area was modelled as a function of STIMULUS INTENSITY, SUPPORT LEVEL, and POSTURE as factors. BACKGROUND MUSCLE ACTIVITY was included as a continuous covariate term. The error term included random slopes for BACKGROUND MUSCLE ACTIVITY and random intercepts for SUBJECT. Each model was subsequently used to infer predicted means and standard errors for MEP area at the median value of the BACKGROUND MUSCLE ACTIVITY distribution (Welham et al., 2004). This procedure permitted comparisons of MEP area between experimental conditions by accounting for underlying differences in background muscle activity.

Stimulus-response curves were fitted to group level data for each muscle using nonlinear regression in Prism 7 (GraphPad, San Diego, CA). For each experimental condition, a three parameter Boltzmann function was fitted to both observed and predicted mean MEP areas (Devanne et al., 1997). To improve the rate at which nonlinear regression converged on a fit, the upper plateau was constrained to its
theoretical range of normalised MEP area between 0 and 1. Similarly, the half-maximal stimulus intensity (S50) was constrained to be between 0 and 40 %MSO above task motor threshold. The slope was unconstrained. Omnibus extra sum-of-squares F tests were used to assess whether individual regression curves for each condition fit the data significantly better than a single curve for the muscle across conditions. To examine whether the posture manipulation shifted the SR curve within each support level, log response ratios were calculated as the natural logarithm of the standing value divided by the sitting value for the S50 and slope parameters that defined each curve. For each muscle, the best-fit parameters were analysed separately using one-way ANOVA. Planned tests were then conducted on the difference between postures within each support level. Multiple comparisons were corrected by controlling the false discovery rate (Q = 0.05) with a two-stage step-up method (Benjamini et al., 2006).

6.4 Results

Data from all 13 participants were included in the analysis. Of the 88 stimuli delivered to each participant per condition, an average of 79 traces (range: 64–86) were retained in the final analysis. Trials containing outlying values of background muscle activity were discarded. Example EMG traces are presented in Figure 6.2.
Figure 6.2 A) Single EMG traces recorded from a representative participant. Traces from all muscles were recorded simultaneously during the seated high support condition. The intensity of the stimulus was 35 %MSO above task motor threshold. B) Average EMG traces for TB and ECR as representative muscles from the same participant and stimulus intensity. Colour shade corresponds to WS level.
6.4.1 Effects of weight support and posture on background muscle activity

Group means for background muscle activity are presented in Figure 6.3. There were significant main effects of both the SUPPORT LEVEL and POSTURE factors, as well as a concomitant interaction between SUPPORT LEVEL and POSTURE in all muscles (Table 6.1). As expected, the magnitude of the support level effect was greatest for proximal muscles AD, BB, and TB. The direction of the effect was uniform across muscles, with less background muscle activity at high support. For the effect of posture on background muscle activity, the magnitude and direction of the response were not consistent across all muscles.

Table 6.1 Omnibus analyses for linear mixed models of background muscle activity. Negative response ratios represent smaller values at high support relative to low, and when standing relative to sitting.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Model Term</th>
<th>F</th>
<th>DF_num</th>
<th>DF_den</th>
<th>p</th>
<th>Response Ratio</th>
</tr>
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<td>AD</td>
<td>Support Level</td>
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<td></td>
<td>Posture</td>
<td>163.86</td>
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<td></td>
<td>Support Level × Posture</td>
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<tr>
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<td>6150</td>
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<td>-0.962</td>
</tr>
<tr>
<td></td>
<td>Posture</td>
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<td>1</td>
<td>6150</td>
<td>&lt; .0001</td>
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<tr>
<td></td>
<td>Support Level × Posture</td>
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<td>6150</td>
<td>&lt; .0001</td>
<td>0.001</td>
</tr>
<tr>
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<td>&lt; .0001</td>
<td>0.104</td>
</tr>
<tr>
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<td>0.104</td>
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Figure 6.3 Background muscle activity responds to changes in support level and posture. Group averages for background muscle activity are plotted at low (0 %), medium (45 %), and high (90 %) levels of weight support. Solid lines represent data from the seated condition while dashed lines are used for the standing condition. Error bars represent ±1 SEM.
6.4.2 Effects of weight support and posture on stimulus-response curves

The left column of Figure 6.4 presents SR curves fitted to group means of observed MEP area. Significant effects of the experimental manipulations on background muscle activity warranted further analysis of MEP data using values derived from the statistical models. Mean MEP area and standard error were predicted for each combination of SUPPORT LEVEL, POSTURE, and STIMULUS INTENSITY. The procedure accounted for co-varying background muscle activity. SR curves fitted to the predicted means are presented in the right column of Figure 6.4. For all muscles, extra sum-of-squares F tests indicated that SR curves for each condition fit the data significantly better than a single regression curve (AD: $F_{(15,46)} = 30.72, p < 0.0001$; BB: $F_{(15,46)} = 207.6, p < 0.0001$; TB: $F_{(15,43)} = 108.0, p < 0.0001$; BRD: $F_{(15,48)} = 18.04, p < 0.0001$; ECR: $F_{(15,48)} = 14.46, p < 0.0001$; FCR: $F_{(15,45)} = 4.64, p < 0.0001$; FDI: $F_{(15,47)} = 9.02, p < 0.0001$; APB: $F_{(15,42)} = 2.95, p = 0.0029$).

Shifts in SR curves were examined by testing for differences in the S50 and slope parameters that defined each curve. Omnibus results of the one-way ANOVAs for curve parameters are presented in Table 6.2 and represented by asterisks next to muscle labels in Figures 6.5 and 6.6. Response ratios for posture-related change in the S50 and slope parameters are presented as bars in Figures 6.5 and 6.6 respectively. For S50, the average magnitude of change across muscles was greatest at high support (5.8% MSO) followed by low (3.9% MSO) and medium support (2.0% MSO). Similarly, for slope, the average magnitude of change was also greatest at high support (0.022% MSO$^{-1}$) followed by low (0.014% MSO$^{-1}$) and medium support (0.006% MSO$^{-1}$). Specific tests for posture-related differences in the S50 and slope parameters within support levels are represented by asterisks next to individual bars in Figures 5 and 6.
Figure 6.4 SR curves shift in response to changes in support level and posture. On the left, SR curves are fitted to group means of observed MEP area. On the right, SR curves are fitted to means predicted using the linear mixed effects model for the median level of background muscle activity.
Figure 6.5 Shift in S50 parameter plotted as log response ratios between postures. Positive response ratios reflect larger S50 values for standing relative to sitting. Bar shading represents support level. Vertical lines indicate the mean across support levels for each muscle. Statistical significance is indicated next to muscle labels for omnibus tests and next to the respective bar for planned comparisons (*p < 0.05, **p < 0.01, ***p < 0.001).

Figure 6.6 Shift in slope parameter plotted as log response ratios between postures. Negative response ratios reflect smaller (less steep) slopes for standing relative to sitting. Bar shading represents support level. Vertical lines indicate the mean across support levels for each muscle. Statistical significance is indicated next to muscle labels for omnibus tests and next to the respective bar for planned comparisons (*p < 0.05, **p < 0.01).
**Table 6.2** One-way ANOVAs for SR curve parameters.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Parameter</th>
<th>F</th>
<th>DF_num</th>
<th>DF_den</th>
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<tr>
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</tr>
<tr>
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<tr>
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<tr>
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<td>ECR</td>
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<td>Slope</td>
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</table>
6.5 Discussion
In this study, we examined the interaction of change in whole body posture and systematic variation of arm weight support (WS) on corticomotor excitability (CME) to upper limb muscles. In support of our hypothesis, there was an interaction of whole body posture and WS on CME for all muscles examined. In line with previous findings, tonic activity of muscles across the upper limb was less when WS was high, compared to when WS was medium or absent (low). Tonic muscle activity was also affected by posture. However, the hypothesis that activity would be greater when standing was found for only a subset of muscles (AD, BB, APB). As expected, CME modulated with WS and posture manipulation. Consistent with our hypothesis, analyses of CME measures indicated a trend for smaller half-maximal stimulus intensity (S50) and larger slope parameters to accompany standing for BB and TB. In contrast, muscles in the shoulder, forearm, and hand exhibited the opposite pattern reflecting lower CME when standing. We also expected that the magnitude of posture-related differences would be largest with greatest levels of WS, but support for this hypothesis was equivocal. While the S50 and slope parameters both exhibited the largest average difference at high support, the smallest magnitude difference occurred with medium rather than low support. Apart from the direct effect of WS on AD activity, the observed modulation of tonic activity and CME across upper limb muscles occurred independently of any differences in the specified arm abduction task.

6.5.1 Interactions of weight support and posture on tonic muscle activity and CME
The change in tonic muscle activity in response to changes in WS provides evidence in support of a common neural drive to muscles of the upper limb. Common drive may involve distributed sensory feedback in addition to descending input. Tonic muscle activity diminished with greater WS as indicated by values of background
EMG (Table 6.1, Figure 6.3). The largest magnitude of EMG activity and the greatest
difference between high and low WS were exhibited by AD. This finding reflects the
role of AD as the principal muscle generating antigravity torque and confirms the
efficacy of the WS manipulation. The finding is consistent with results reported by
previous studies employing multiple levels of WS (Coscia et al., 2014; Runnalls et al.,
2014; 2015). Changes in WS did not alter the task requirements for forearm and
hand muscles because the forearm was fully supported and secured to the brace.
Any torques generated by the forearm or hand would be counteracted within the
braced segment and could not have an anti-gravity effect without accelerating the
arm out of position. The specified arm abduction task did not vary for BB and TB
because they were not oriented to act against gravity. Observed differences in tonic
activity were nonessential to task performance and remote to the primary action of
WS at the shoulder. This tendency for WS to influence tonic muscle activity is
indicative of a common neural drive across the upper limb.

Dissociation between muscles for the response to sitting versus standing suggests
the influence of whole body posture on tonic activity of upper limb muscles is
mediated by distinct mechanisms in addition to common neural drive. As evidenced
by response ratios (Table 6.1), AD was the most sensitive muscle to WS but the least
sensitive to posture. The relatively small response of tonic muscle activity to change
in posture may reflect a strong independent voluntary descending drive to maintain
shoulder abduction. In more distal muscles that receive mostly secondary input
derived from the primary drive to the shoulder, the absence of a strong and
potentially saturating voluntary drive could have permitted the manifestation of
larger relative responses to posture. The signals conveying postural information
appear to interact with neural linking mechanisms responsible for distributing
common drive. The factors determining whether a muscle will express greater tonic
activity in sitting or standing are not clear from the present results. A reciprocal relation between agonist and antagonist is supported for BB and TB. It is possible that mechanical restriction from the WS brace contributed to the absence of similar reciprocity in the forearm. Future studies may be warranted to investigate the impact of WS brace design on peripheral nerve conduction. A non-global influence on tonic activity across the upper limb refutes the hypothesis that standing would result in a general increase in muscle activity and suggests postural information can modulate neural drive on a muscle-specific basis.

Posture exerted an influence on upper limb CME over and above those changes evident in tonic muscle activity alone. This was borne out in statistical analyses of MEP area which accounted for differences in background EMG. A similar postural manipulation without WS was previously reported to elicit increased CME to the proximal AD but not the distal FDI (Kantak et al., 2013). The present findings indicate that whole body posture can affect CME to the arm, forearm, and hand, as evidenced by SR curve parameters (Table 6.2, Figures 5 & 6). The discrepancy between the earlier reports and present findings could be attributed to the arm postures examined. Kantak et al. tested the arm in a resting state hanging at the side whereas the present study examined a task-relevant arm posture that elicited nonessential tonic activity. The additional neural elements engaged by the reaching-related arm posture could provide a substrate for interaction with whole body postural information. Consistent with previous findings, an up-regulation of CME with less WS (Figure 6.4) appears to subserve both voluntary activity in AD and nonessential activity in more distal upper limb muscles. Whole body posture also influences CME. However, the factors determining whether changing posture has a facilitatory or inhibitory effect on a specific muscle are not clear.
6.5.2 Postural demands and mechanisms for integrated upper limb control

Integrated control of neuromuscular activity may facilitate the coordination of voluntary actions like forward reaching and ancillary actions for postural stabilisation. In the present study, changes in tonic activity and CME provide evidence for integrated control along the proximal-distal axis. Unlike previous reports of distal responses to shoulder activation (Devanne et al., 2002; Runnalls et al., 2014; 2015) and shoulder position (Dominici et al., 2005; Ginanneschi et al., 2005; 2006) the present findings do not exhibit a clear anatomical or task-related pattern. Differential modulation of CME to upper limb muscles could reflect non-universal membership within specific neural linkages or synergies, or it may be an expression of multiple synergies with complex or competing interactions. Further studies are warranted to distinguish between these possibilities.

Modulation of CME with whole-body posture could reflect the priming of a response that satisfies potential mechanical demands imposed by the specific task. Standing postures have greater stability requirements than sitting and require larger displacements of the arm for compensatory reactions to perturbations (Allum et al., 2002; Roos et al., 2008). Standing also increases the complexity of arm dynamics for goal-directed movements like reaching (Berrigan et al., 2006). One or more posture-sensitive upper limb synergies may act to prepare the arm for its altered biomechanical role. For example, standing may necessitate a general increase of CME to muscles that have a significant influence on the centre of mass. Putative posture-sensitive neural linkages may interact with those that respond to descending drive to the shoulder and are thus sensitive to WS.

It is worth considering the neural mechanisms that may mediate the proximal-distal neural linkages and shape motor output. In primary motor cortex, anatomical co-
location of muscle representations may facilitate functional interaction. Multiple non-contiguous representations overlap with those of other muscles in animals (Donoghue et al., 1992; Schneider et al., 2001; Rathelot and Strick, 2006), and humans (Sanes et al., 1995; Devanne et al., 2006). Furthermore, representations of distal forelimb muscles are systematically surrounded by those of proximal muscles (Park et al., 2001). Functionally, intracortical disinhibition has been implicated as a mechanism contributing to modulation of CME with shoulder activation and whole body posture (Devanne et al., 2002; Kantak et al., 2013). Passive shoulder position influences distal CME through intracortical facilitation (Ginanneschi et al., 2005; 2006). Subcortical and spinal mechanisms may also play a role. Anatomically, divergence of descending corticomotor pathways can provide correlated input to multiple motoneuron pools (McKiernan et al., 1998). Propriospinal neurons link multiple spinal segments and can modulate descending drive to the forearm (Pauvert et al., 1998; Pierrot-Deseilligny, 2002). Additionally, spinal interneuron circuits are a substrate for stable muscle synergies (Bizzi and Cheung, 2013). Functionally, differences in limb position can impact motoneuron excitability through multiple proprioceptive inputs (Mogk et al., 2014; Nuzzo et al., 2016). Intrinsic electrical properties of spinal motoneurons vary with Ia and Ib afferent input (Hyngstrom et al., 2007) and shape motor output through nonlinear integration of descending synaptic and neuromodulatory inputs (Binder et al., 1993; Heckman et al., 2008). For example, the intrinsic excitability of human triceps brachii motoneurons is greater than that of biceps brachii, potentially indicating an enhanced role of persistent inward currents for postural or anatomical anti-gravity muscles (Wilson et al., 2015). In summary, there are many neural elements and mechanisms that may act to link neuromuscular activity to control movement and posture of the upper limb. It is likely that multiple mechanisms are sensitive to
posture and WS, thus contributing to the complex pattern of CME modulation observed in this study.

6.5.3 Potential limitations
A limitation of the present study is the absence of a dynamic movement task. Although participants were required to maintain their static posture accurately, there was no dynamic component to challenge stability or introduce a goal-directed movement intention. It is unclear whether additional dynamic constraints would have biased CME in a more consistent pattern. The present study was conducted with healthy adults who may easily adapt reaching behaviour across levels of WS (Coscia et al., 2014). Future studies may be warranted to investigate the interaction of posture and WS in the elderly, and in those with motor impairment such as after stroke. It is possible a sensorimotor system with reduced capacity would be less adaptable at a neural level to posture and WS manipulation.

6.5.4 Conclusions
A novel combination of WS and posture manipulations led to changes in tonic muscle activity across the upper limb and some modulation of CME to muscles in the arm, forearm, and hand. Tonic activity and CME are not uniformly greater in standing compared to sitting. Whole body posture may increase or decrease CME depending on the muscle and level of WS. The results support a model of integrated upper limb control and suggest posture-sensitive neural linkages may be distinct from those responsible for modulation with WS. These findings may have relevance for upper limb rehabilitation, e.g. after stroke. With further characterisation, the combination of WS and posture manipulation may create avenues to balance CME for optimal engagement in rehabilitation exercises.
Effects of arm weight support on corticomotor excitability and reaching performance in chronic stroke

This experiment has been formatted as a manuscript in preparation for submission to a scholarly journal.

7.1 Abstract

Arm weight support (WS) may be used as an adjuvant to increase training dosage and improve movement quality during upper limb stroke rehabilitation. However, the underlying neurophysiological effects of WS are not well understood. We investigated the effects of WS on muscle activity and corticomotor excitability (CME) in 13 chronic stroke patients and 6 age-similar healthy controls. Lesion location and corticospinal tract integrity were assessed using magnetic resonance imaging. Measurements were repeated with three levels of WS (0, 50, and 100% of full support) in a single session. Surface EMG was recorded from 8 upper limb muscles. First, participants performed reaching movements to an array of 14 targets using the paretic or dominant arm. There were significant interactions of impairment severity and WS for the number of targets hit, and for muscle activity. Patients with moderate-severe impairment were able to reach more targets with greater WS whereas the effect was smaller for those with mild impairment. Higher WS resulted in less muscle activity across the upper limb although a smaller degree of modulation was noted in patients with moderate-severe compared to mild impairment. Second, transcranial magnetic stimulation of primary motor cortex was used to elicit motor-evoked potentials (MEPs) in the paretic or dominant arm during static arm abduction. Stimulus-response (SR) curves were fitted to the MEP data using nonlinear regression. Overall, greater WS tended to lessen CME, however the pattern of modulation varied between proximal versus distal muscles and was
irregular with more severe impairment. Taken together, these findings demonstrate that WS has direct and indirect effects on muscle activity and CME across the upper limb of chronic stroke patients and age-similar healthy adults. The pattern of modulation is sensitive to impairment severity and differs between dynamic tasks like reaching and static tasks like arm abduction.
7.2 Introduction

Stroke is a leading cause of acquired adult disability with two-thirds of stroke survivors experiencing lingering upper limb impairment (Feigin et al., 2010; Mendis, 2013). The likelihood of regaining functional independence following stroke is strongly influenced by the initial severity of motor deficits and subsequent recovery of motor function (Kwakkel et al., 1996; Patel et al., 2000; Meijer et al., 2003; Veerbeek et al., 2011). Physical therapy with high-intensity practice and a high number of repetitions can facilitate task-specific recovery of upper limb function (Kwakkel et al., 2004; Veerbeek et al., 2014). Providing arm weight support (WS) may augment the performance of arm movements and increase the intensity or volume of therapeutic exercises (Kwakkel and Meskers, 2014). Studies of WS as an adjuvant to neurorehabilitation have typically included WS as a component of robotic-aided therapies without separating it from other assistive or resistive forces and sensory feedback (Johnson, 2006; Loureiro et al., 2011). Less is known about the effects of separate WS on the upper limb movements of stroke patients (Prange et al., 2009a; Krabben et al., 2012). A better understanding of WS and its underlying neural mechanisms may inform a more principled and individualised application of WS in stroke rehabilitation.

In addition to facilitating greater training dosage, WS can also improve movement quality. During reaching tasks, WS reduces antagonist muscle activity in both healthy older adults and chronic stroke patients (Prange et al., 2009a; 2009b). Abnormal coupling of joint torques between the shoulder and elbow is also lessened with WS (Dewald and Beer, 2001; Beer et al., 2004). The stereotyped flexor synergy can thus be mitigated with WS, permitting greater elbow extension and access to the reaching workspace (Sukal et al., 2007). Understanding transient modulation of
motor behaviour with WS has relevance because the expressed patterns of neuromotor activity may be reinforced with repetition.

Recent experiments have shown corticomotor excitability (CME) to the upper limb of healthy adults is modulated with the amount of WS provided (Runnalls et al., 2014; 2015; 2017). The reduction of antigravity torques required for shoulder abduction has indirect effects on other upper limb muscles through putative neural linkages or muscle synergies. The effects of WS on measures of CME have not previously been examined in chronic stroke patients. In another study, the level of WS influenced the activation, but not composition, of muscle synergies in healthy adults during a reaching task (Coscia et al., 2014). To what extent muscle activity and CME are sensitive to graded WS in chronic stroke patients is unknown.

In the present study, we investigated the effects of WS in chronic stroke patients with a range of upper limb impairment. First, we examined upper limb muscle activations during a reaching task. Surface electromyography (EMG) was recorded from eight muscles while participants performed reaching movements to an array of targets with high, medium, and low levels of WS. We expected patients would be able to reach more targets with greater WS. It was hypothesised that support level would interact with impairment severity and target location to modulate integrated EMG area (iEMG). Second, we examined CME at high, medium, and low levels of WS. Transcranial magnetic stimulation (TMS) was used to elicit motor-evoked potentials (MEPs) during a static shoulder abduction task. CME was examined by comparing stimulus-response (SR) curves fitted to means derived from statistical models of MEP area. It was hypothesised that WS would modulate CME to promote a balancing of recruitment properties across the limb. It was thus expected that the pattern of modulation would depend on impairment severity.
7.3 Methods

7.3.1 Participants

Thirteen chronic stroke patients (mean age 70.8 years, range 47–88 years, four females) with upper limb impairment participated in this study. Patients were included if they reported any degree of upper limb impairment resulting from a first-ever stroke that occurred more than six months before testing. Patients were excluded if they had no active range of motion at the shoulder. Patients were excluded from the MRI or TMS component if screening revealed any contraindications. Patients were characterised as having mild impairment if upper extremity Fugl-Meyer assessment score was 50 or more. Patients with scores below 50 were characterised as moderate-severe (mod-sev). Six neurologically healthy adults (mean age 65.2 years, range 51–71 years, all right dominant, two females) participated as age-similar controls. All participants gave written informed consent. Study procedures were approved by the University of Auckland Human Participants Research Ethics Committee in accordance with the Declaration of Helsinki.

Figure 7.1 Anatomical T1-weighted images in the transverse plane for each patient. Lesions are indicated by crosshairs. Patient numbers correspond with Table 7.1.
**Table 7.1 Participant characteristics**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Chronicity (months)</th>
<th>Affected Limb</th>
<th>FM</th>
<th>ARAT</th>
<th>MAS</th>
<th>FA$_{AI}$</th>
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</table>

| Min | 47  | 13  | 9   | 0   | 0   | -0.06 |
| Max | 88  | 167 | 66  | 57  | 3   | 0.42  |
| Mean| 70.8| 9 M | 70.8| 8 R | 43.7| 36.5  |

Note: FM, upper extremity Fugl-Meyer score (maximum 66); ARAT, action research arm test (maximum 57); MAS, modified Ashworth spasticity scale for the elbow (maximum 4). FA$_{AI}$, fractional anisotropy asymmetry index for the posterior limb of the internal capsule (perfect symmetry = 0). Mild, FM > 50; Moderate-Severe (Mod-Sev), FM < 50.

**7.3.2 Design**

Participants attended an initial session to complete clinical assessments with a physical therapist. The therapist was not involved in any other aspects of the study. In a subsequent session, participants performed the repeated measures reaching task. Four blocks of reaching trials were completed for high, medium, and low levels of arm weight support. The total twelve blocks were performed in a randomised...
order. Eligible participants then completed the TMS component in the same session. Single-pulse TMS was used to obtain stimulus-response curves at high, medium, and low levels of arm weight support. Six blocks of stimulation (two for each level of weight support) were performed in a quasi-randomised order. In a separate session, MRI was used to obtain anatomical and diffusion-weighted images (DWI) of the brain. Healthy control participants did not undergo clinical assessments or MRI.

7.3.3 Posture and arm support

The reaching task and TMS measures were completed while participants sat in a chair with their feet on the floor and unsupported arm resting on their lap. Arm weight support was provided to the stroke-affected limb, or dominant limb for healthy controls, by a SaeboMAS arm support system (Saebo Inc., Charlotte, NC). Force was provided by spring tension through a brace that cradled the proximal forearm. The forearm was secured in the brace using elasticized fabric wrap. A standardised static arm position was set with the shoulder flexed forward approximately 80° and abducted 45° in the horizontal plane, the elbow flexed at 90°, and the forearm pronated palm down. The brace prevented rotation in the vertical plane ensuring the forearm was parallel to the floor. Joint angles were initially set using a goniometer and subsequently maintained by aligning the hand to a reference object.

Three levels of arm weight support were defined relative to the force required to compensate for the weight of the arm completely. At low support (0 %), the device carried its weight but provided no additional support to the arm. Individualised levels of support were determined using a force titration procedure. Participants maintained the standardised static arm position while supportive force was incrementally decreased from a superabundant magnitude. High support (100 %)
was defined as the last point before root mean square EMG amplitude (rmsEMG) in the anterior deltoid was observed to deflect away from the baseline activity that persists even with excessive support (Runnalls et al. 2014; Runnalls et al. 2015; Runnalls et al. 2016). Medium support was then defined as 50 % of high support.

7.3.4 Electromyography

Surface electromyography data were recorded from eight muscles of the supported arm and hand: anterior deltoid (AD), middle deltoid (MD), posterior deltoid (PD), clavicular head of pectoralis major (PM), biceps brachii (BB), lateral head of triceps brachii (TB), brachioradialis (BRD), and extensor carpi radialis (ECR). Self-adhesive Ag-AgCl electrodes (Blue Sensor N; Ambu, Denmark) were placed approximately 2 cm apart in a bipolar montage over the belly of each muscle. The common ground electrode was placed over the acromion process (Red Dot; 3M Health Care, Canada). Signals were amplified (Grass P511AC; Grass Instrument Division, West Warwick, RI) with 1000x gain, band-pass filtered (10–1000 Hz), sampled at 2 kHz using a 16-bit A/D acquisition system (National Instruments, Austin, TX), and saved for offline analysis.

7.3.5 Reaching task

Participants were seated facing a table-mounted robotic arm (UR5; Universal Robots, Denmark). A pushbutton assembly was mounted to the tool attachment point of the robot. The 6 cm diameter pushbutton responded to input anywhere on its surface; i.e. finger extension was not required. The robot moved the button to predefined locations to present it as the target for each reach. A trial would begin from a static start position in which the arm was adducted close to the torso with the elbow flexed at 90° and forearm orientated forward orthogonal to the coronal plane. If a participant could not reliably adopt this position, the nearest
approximation was used. The start position was indexed to a reference point on the wall with a laser pointer.

Each block of trials was comprised of the same sequence of fourteen targets (Figure 7.2). The targets were located at incrementally greater distances away from the start position along four direction vectors. The distribution was designed to probe the reachable limits of the forward workspace volume. Three targets were located along a low-wide vector, and four targets were located along a high-narrow vector. These vectors were mirrored laterally to test both lateral (ipsilateral) and medial (contralateral) directions.

Data recording started at the same time a computer-generated tone cued the participant to begin the movement. Participants were instructed to keep their back against the chair and reach to push the button at a comfortable speed. Recording terminated when the button was pressed. A trial was flagged as incomplete if the target button could not be pressed without compensatory strategies such as forward torso lean or stabilisation with the unaffected arm.
Figure 7.2  A) Demonstration of static start position with the robot presenting the pushbutton as a calibration point. B) Schematic illustration of reaching target positions. Targets were presented in numerical order. Targets were 10, 15, 20, and 25 cm anterior to the start position; 0, 10, 20, 30 and 40 cm above the start position; 5, 10, 15, 20, and 30 cm medial/lateral to the start position.
Individual EMG traces were detrended, rectified, and low-pass filtered using a fourth-order zero-lag Butterworth filter with a cut-off frequency of 6 Hz using MATLAB R2013a (MathWorks, Natick, MA). The resulting linear enveloped EMG traces from individual muscles were inspected in parallel to determine EMG onset for each trial. Data preceding the initial deviation of AD activity away from baseline were trimmed to make the EMG onset time consistent between trials. Integrated EMG area (iEMG) was calculated as the dependent measure for each trace. Statistical analyses of the reaching task were conducted using R 3.3.2 (R Core Team, 2016) with the lme4: Linear Mixed-Effects Models using 'Eigen' and S4 (Bates et al., 2015), car: Companion to Applied Regression (Fox and Weisberg, 2010) packages. For each participant, iEMG was normalised between zero and one across conditions within each muscle. Linear mixed effects models were fitted for each muscle to investigate the effects of weight support, impairment severity, and target parameters on muscle activity. In each case, iEMG was modelled as the dependent variable with fixed effects for SUPPORT LEVEL, IMPAIRMENT, TARGET DISTANCE, TARGET HEIGHT, and TARGET SIDE. Random intercepts were included for SUBJECT. Model terms were tested using type II Wald F tests with Kenward-Roger degrees of freedom.

7.3.6 Transcranial magnetic stimulation

Single-pulse TMS was delivered to M1 using a MagStim 200 magnetic stimulator (Magstim, Dyfed, UK). A figure-of-eight coil (Magstim D70²) was held tangentially to the scalp and angled to direct current posterior to anterior across the central sulcus. The coil was positioned at the optimal site for eliciting MEPs in the contralateral BB and ECR muscles and the location was marked on the scalp. Task motor threshold (MT) was defined as the minimum stimulus intensity that elicited a 100 µV MEP in four out of eight trials with the arm in the standardised static position at the high support level.
Stimulus–response (SR) curves were collected for high, medium, and low levels of weight support. A single stimulation site was used to concurrently elicit MEPs in all muscles. Five stimulus intensities were set relative to task motor threshold of BB: -5, +5, +15, +25, and +35 per cent of maximum stimulator output (% MSO). For each curve, forty stimuli were delivered over two blocks (eight stimuli for each of the five intensities). Participants were instructed to align their hand to the reference point and otherwise relax. To mitigate fatigue, participants rested their arm after every four stimuli for 15–30 seconds.

Raw EMG traces were inspected and processed using Signal 5.11 (CED, Cambridge, UK). Trials were excluded from further analysis if there was no stimulus artefact or if there was phasic muscle activity present. Dependent measures were obtained from individual EMG traces. MEP area was calculated over a 20 ms window determined manually for each muscle. Background muscle activity was calculated as the rmsEMG amplitude over a 50 ms window preceding the stimulus.

Statistical analyses of background muscle activity and MEP area were conducted using R 3.3.2 with the lme4, car, and predictmeans: Calculate Predicted Means for Linear Models packages (Luo et al., 2014). Outliers were identified for each muscle by analysing background muscle activity on a within participant basis. Observations of rmsEMG more than 1.5× the interquartile range either above the third quartile or below the first quartile, along with their associated MEP values, were removed from the dataset. For each participant, MEP area was normalised between zero and one across conditions within each muscle. Logarithmic transforms were applied to normalised MEP area within the models to better satisfy the assumption of normally distributed residuals.
To assess the effect of weight support on background muscle activity, as well as any interaction with impairment severity, linear mixed effects models were fitted for each muscle. In each case, background muscle activity was modelled as the dependent variable with fixed effects for SUPPORT LEVEL and IMPAIRMENT. Random intercepts were included for SUBJECT. Model terms were tested using type II Wald F tests with Kenward-Roger degrees of freedom.

For MEP area, independent linear mixed effects models were constructed for each muscle. In each case, MEP area was modelled as the dependent variable with fixed effects for STIMULUS INTENSITY, SUPPORT LEVEL, and IMPAIRMENT. BACKGROUND MUSCLE ACTIVITY was included as a continuous covariate term. The error term included random slopes for BACKGROUND MUSCLE ACTIVITY and random intercepts for SUBJECT. The models were then used to predict means and standard errors for MEP AREA at the median value of the BACKGROUND MUSCLE ACTIVITY distribution (Welham et al., 2004). This procedure controlled for systematic differences in background muscle activity thus permitting unbiased analysis of MEP area.

Stimulus-response curves were fitted to group level predicted means using nonlinear regression in Prism 7 (GraphPad, San Diego, CA). For each combination of support level and impairment, a three parameter Boltzmann function was fitted to predicted mean MEP area as a function of relative stimulus intensity (Devanne et al., 1997). The upper plateau was constrained to its theoretical range between zero and one to improve the rate at which regression converged on a fit. The slope and half-maximal stimulus intensity (S50) parameters were unconstrained. To test whether changes in support level shifted the stimulus-response curve, extra sum-of-squares F tests were used to assess whether individual regression curves fit the data significantly better than a single curve within each impairment group.
7.3.7 Magnetic resonance imaging

Brain images were acquired using a 3T MAGNETOM Skyra MRI scanner (Siemens, Germany). An MP-RAGE sequence was used to acquire high-resolution T1-weighted anatomical images ($T_R = 1900$ ms, $T_E = 2.07$ ms, FoV = 256 mm, voxel dimensions of 1.0×1.0×1.0 mm). Diffusion-weighted images (DWI) were acquired using a single shot echo planar imaging sequence ($T_R = 3600$ ms, $T_E = 92.4$ ms, FOV = 220 mm, voxel dimensions 2.0×2.0×2.0 mm), with thirty diffusion gradient orientations ($b = 2000$ s/mm$^2$).

Lesions were located and masked on T1-weighted images using FSLView from the FMRIB Software Library (Jenkinson et al., 2012). Diffusion-weighted images were processed using FMRIB's Diffusion Toolbox. Images were skull stripped using the Brain Extraction Tool (Smith, 2002), and corrected for motion and eddy currents (Jenkinson and Smith, 2001; Jenkinson et al., 2002; Andersson and Sotiropoulos, 2016). To quantify corticospinal tract (CST) integrity, mean fractional anisotropy (FA) was calculated within the posterior limb of the internal capsule (PLIC) for the ipsilesional (FA$_{Ipsi}$) and contralesional (FA$_{Contra}$) hemispheres. A fractional anisotropy asymmetry index (FA$_{AI}$) was calculated as $FA_{AI} = (FA_{Contra} - FA_{Ipsi}) / (FA_{Contra} + FA_{Ipsi})$, resulting in a value between -1 and 1 for each participant (Stinear et al., 2007). An asymmetry index near zero represents high CST integrity, whereas positive values correspond to reduced FA in the ipsilesional PLIC and negative values correspond to reduced FA in the contralesional PLIC.
7.4 Results

7.4.1 Reaching task

Data from all nineteen participants (six control, seven mild, six moderate-severe) were included in the analysis. Of the 14 targets attempted, mild participants hit an average of 12.8 targets (SD = 3.0) at low support and 12.9 (SD = 2.7) at medium and high support. Moderate-severe participants hit an average of 8.9 targets (SD = 4.6) at low support, 10.6 (SD = 3.3) at medium, and 11.4 (SD = 2.5) at high. Control participants successfully hit all 14 targets at all support levels. For the number of targets hit successfully, SUPPORT LEVEL had a significant interaction with IMPAIRMENT ($F_{(4,32)} = 8.63, p = 0.002$). Means for iEMG are presented in Figures 7.3, 7.4, and 7.5 for target distance, target side, and target height contrasts respectively. Muscles were analysed separately with independent statistical models. Table 7.2 presents the results of the ANOVA for each muscle.
Figure 7.3 Mean iEMG for target distance contrast. Targets 1–8 were grouped as near (10–15 cm anterior to start position), while targets 9–14 were grouped as far (20–25 cm anterior to start position). Line shading represents support level: 0 % (low), 50 % (medium), 100 % (high). Impairment groups are presented in columns and muscles are shown in rows.
Figure 7.4 Mean iEMG for target side contrast. Medial targets required reaching towards and across the midline of the body while lateral targets required reaching away from the start position. Line shading represents support level: 0 % (low), 50 % (medium), 100 % (high). Impairment groups are presented in columns and muscles are shown in rows.
Figure 7.5 Mean iEMG for target height contrast. Low targets were located at the same height as the start position while high targets required upward movement from the start position. Line shading represents support level: 0 % (low), 50 % (medium), 100 % (high). Impairment groups are presented in columns and muscles are shown in rows.
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### 7.4.2 Transcranial magnetic stimulation

Data from six control, six mildly impaired, and two moderate-severely impaired participants were included in the analysis. Of the 40 stimuli delivered to each participant per condition, an average of 38.6 traces (range: 28–40) were retained in the final analysis. Traces were discarded based on outlying values of background muscle activity. Example EMG traces are presented in Figure 7.6.
7.4.3 Effects of weight support and impairment on background muscle activity

Boxplots for background muscle activity recorded immediately before each TMS stimulus are presented in Figure 7.7. All muscles exhibited a significant main effect of SUPPORT LEVEL and a significant interaction between SUPPORT LEVEL and IMPAIRMENT (Table 7.3). With the exception of BB, which exhibited less activity in the control group (0.008 mV) compared to mild (0.026 mV) and moderate-severe (0.021 mV) groups, there were no significant main effects of IMPAIRMENT.
Figure 7.7 Background muscle activity versus support level for control, mild, and moderate-severe impairment groups during the standardised static arm abduction task. Boxplots summarise rmsEMG measured before each TMS stimulus from all individual traces. Whiskers extend to $1.5 \times$ inter-quartile range from the hinge.
Table 7.3 ANOVA for linear mixed models of background muscle activity.

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<td>Support × Impairment</td>
<td>4</td>
<td>1611</td>
<td>36.16</td>
<td>&lt; .001</td>
<td>***</td>
</tr>
<tr>
<td>TB</td>
<td>Support</td>
<td>2</td>
<td>1597</td>
<td>242.27</td>
<td>&lt; .001</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>Impairment</td>
<td>2</td>
<td>11</td>
<td>3.09</td>
<td>0.086</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Support × Impairment</td>
<td>4</td>
<td>1597</td>
<td>25.20</td>
<td>&lt; .001</td>
<td>***</td>
</tr>
<tr>
<td>BRD</td>
<td>Support</td>
<td>2</td>
<td>1581</td>
<td>89.47</td>
<td>&lt; .001</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>Impairment</td>
<td>2</td>
<td>11</td>
<td>2.42</td>
<td>0.135</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Support × Impairment</td>
<td>4</td>
<td>1581</td>
<td>17.54</td>
<td>&lt; .001</td>
<td>***</td>
</tr>
<tr>
<td>ECR</td>
<td>Support</td>
<td>2</td>
<td>1588</td>
<td>19.00</td>
<td>&lt; .001</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>Impairment</td>
<td>2</td>
<td>11</td>
<td>2.90</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Support × Impairment</td>
<td>4</td>
<td>1588</td>
<td>18.99</td>
<td>&lt; .001</td>
<td>***</td>
</tr>
</tbody>
</table>

7.4.4 Effects of weight support and impairment on MEP area and SR curves

Figure 7.8 presents stimulus-response data derived from the linear mixed effects models. Type II Wald χ² tests of model terms indicated a significant effect (p < 0.001) of SUPPORT LEVEL on MEP area in all muscles. Mean normalised MEP area was then predicted for each combination of STIMULUS INTENSITY, SUPPORT LEVEL, and IMPAIRMENT. The procedure accounted for co-varying background muscle activity by including rmsEMG as a covariate. Stimulus-response curves fitted to the predicted means were tested for differences between support levels. Results of the extra sum-of-squares F tests are presented in Table 7.4.
Table 7.4 Comparison of stimulus-response curve fits for support levels. Tests where $p < 0.05$ indicate different curves for each support level is the preferred model.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Impairment Group</th>
<th>$F(DF_{n,DF_{d}})$</th>
<th>$p$</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Control</td>
<td>100.1$_{(6,6)}$</td>
<td>0.001</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>27.13$_{(6,6)}$</td>
<td>0.001</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>Mod-Sev</td>
<td>0.99$_{(6,6)}$</td>
<td>0.507</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>Control</td>
<td>9.16$_{(6,6)}$</td>
<td>0.008</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>19.88$_{(6,6)}$</td>
<td>0.001</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>Mod-Sev</td>
<td>8.79$_{(6,6)}$</td>
<td>0.009</td>
<td>**</td>
</tr>
<tr>
<td>PD</td>
<td>Control</td>
<td>61.08$_{(6,6)}$</td>
<td>&lt;.001</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>7.68$_{(6,6)}$</td>
<td>0.013</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>Mod-Sev</td>
<td>1.14$_{(6,6)}$</td>
<td>0.438</td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>Control</td>
<td>8.26$_{(6,6)}$</td>
<td>0.011</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>13.04$_{(6,6)}$</td>
<td>0.003</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Mod-Sev</td>
<td>19.62$_{(6,6)}$</td>
<td>0.001</td>
<td>***</td>
</tr>
<tr>
<td>BB</td>
<td>Control</td>
<td>24.08$_{(6,6)}$</td>
<td>&lt;.001</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>3.81$_{(6,6)}$</td>
<td>0.064</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mod-Sev</td>
<td>1.01$_{(6,6)}$</td>
<td>0.494</td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>Control</td>
<td>58.56$_{(6,6)}$</td>
<td>&lt;.001</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>8.64$_{(6,6)}$</td>
<td>0.009</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Mod-Sev</td>
<td>1.14$_{(6,6)}$</td>
<td>0.439</td>
<td></td>
</tr>
<tr>
<td>BRD</td>
<td>Control</td>
<td>9.81$_{(6,6)}$</td>
<td>0.007</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>2.18$_{(6,6)}$</td>
<td>0.183</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mod-Sev</td>
<td>5.68$_{(6,6)}$</td>
<td>0.026</td>
<td>*</td>
</tr>
<tr>
<td>ECR</td>
<td>Control</td>
<td>1.78$_{(6,6)}$</td>
<td>0.250</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.46$_{(6,6)}$</td>
<td>0.329</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mod-Sev</td>
<td>36.66$_{(6,6)}$</td>
<td>&lt;.001</td>
<td>***</td>
</tr>
</tbody>
</table>
Figure 7.8 Predicted mean normalised MEP area is plotted as a function of stimulus intensity at low, medium, and high levels of support for control, mild, and moderate-severe impairment groups. Line shading represents support level: 0 % (low), 50 % (medium), 100 % (high).
7.5 Discussion
In this study we examined the interaction between upper limb impairment severity and WS during a reaching task. In support of our hypothesis, there was an interaction between impairment severity and WS on the number of targets hit. As expected, WS had the greatest effect for the moderate-severe impairment group who successfully reached an average of 2.5 more targets with high compared to low WS. An average difference of 0.1 targets for the mild impairment group and 0 targets for the control group is indicative that most participants in these groups could access the entire workspace without assistance. Less variance in the number of targets hit with greater WS indicates both patient groups were more consistent with higher levels of WS. We also examined the effects of impairment severity, WS, and target location on muscle activations (Table 7.2, Figures 7.3–7.5). In line with previous findings, there was a significant effect of WS on iEMG for all muscles except TB (Prange et al., 2009a; 2009b; Coscia et al., 2014). Those with more severe impairment tended to exhibit smaller magnitudes of iEMG change between support levels. In the control group, WS affected CME for all muscles, with the exception of ECR, as observed previously in younger participants (Runnalls et al., 2014; 2017). Although WS influenced CME in both impairment groups, there was not a consistent pattern across muscles (Table 7.4, Figure 7.8). Taken together, these findings provide evidence that WS can influence the upper limb at behavioural and neurophysiological levels across the spectrum of motor impairments resulting from stroke.

7.5.1 Direct and indirect effects of weight support
The direct mechanical action of WS is to reduce the magnitude of anti-gravity torques required at the shoulder. For the AD, MD, PD, and PM muscles, WS significantly lessened both iEMG during reaching (Table 7.2) and rmsEMG during
static abduction (Table 7.3). As expected, high targets required more activity than low targets, and far targets required more activity than near targets. This pattern was evident across levels of impairment (Figures 7.3 & 7.5). Impairment severity interacted with WS during the static abduction task; the moderate-severe group exhibited less modulation of rmsEMG between support levels (Figure 7.7). An analogous interaction between impairment severity, WS, and target distance during the reaching task is indicative of an overall trend for the moderate-severe group to exhibit less iEMG only with high support. In contrast, the control and mild groups tended to exhibit a more linear response between iEMG and support level similar to previous reports of healthy adults (Coscia et al., 2014). Impairment-dependent WS thresholds could result from the recruitment of different neural elements for control. Modulation of CME with WS mirrored a similar trend of linear progression for the control and mild groups (Figure 7.8). Muscle activity patterns for the moderate-severe group are not reflected in the CME data. This disconnect could be a consequence of an increased reliance on alternative motor pathways to drive the proximal upper limb in individuals with significant corticospinal tract damage (Turton et al., 1996; Bradnam et al., 2012). The modulation of muscle activity in AD, MD, PD, and PM is primarily related to the direct mechanical effect of WS on shoulder joint torques. In control and mild groups, the up-regulation of CME with less WS appears to subserve voluntary drive to the proximal upper limb. In the moderate-severe group, neural drive may be distributed through alternative descending pathways that do not necessarily reflect modulation with WS as change in CME.

Dissociation of elbow muscle activation patterns between dynamic and static tasks provides evidence to support a distinction between direct and indirect effects of WS. A direct mechanical effect of WS is evident for the dynamic reaching task, where the
elbow flexors BB and BRD acted against gravity and were sensitive to changes in WS. In contrast, TB was not orientated to act against gravity, thus compensating for gravity with WS was unlikely to have an effect on its activation. This was borne out by the absence of a WS effect on TB activity, which is consistent with previous studies of healthy adults (Prange et al., 2009b; Coscia et al., 2014), and stroke patients (Prange et al., 2009a). Although the brace restricted rotation of the forearm, active elbow extension would not contribute to shoulder flexion. Under constant external supportive force, any additional internal torque would act to change the configuration of the limb rather than translate its centre of mass. Elbow extension for reaching movements may be passively driven by the weight of distal segments, relying on modulation of antagonist elbow flexor tension to permit lengthening. An impaired ability to appropriately modulate BB iEMG for elbow extension may be reflected in the interaction of WS with impairment severity and target height. As expected, high targets required significantly greater BB activity; however, WS affected the groups differently. The application of medium support was sufficient to achieve maximum reduction of BB activity for the control group whereas the moderate-severe group required high support to achieve any change. In both cases, the application of WS through a forearm brace reduced the required force and had the expected effect of directly lessening BB activity.

In contrast to the direct effect of WS on BB activity observed during the reaching task, changes in BB and TB activity with WS during the static arm abduction task reflect an indirect effect of WS (Table 7.3, Figure 7.8). In the sense discussed here, an apparent indirect effect of WS on a particular muscle could be considered a consequence of a direct effect on an upper limb synergy as a unit. Whereas WS directly impacted the force required for shoulder abduction, BB and TB were orientated to act orthogonal to gravity and were not required to actively perform
the task. However, the observed persistence of tonic activity in both muscles and its modulation with WS suggest a distinct mechanism may be responsible. Although the direct mechanical action of WS during the static task was at the shoulder, distal elbow muscles exhibited small but significant changes in tonic activity with WS. An indirect effect of WS is further supported by changes in CME. The observed modulation of CME with WS in the BB and TB of healthy adults is consistent with previous experiments (Runnalls et al., 2014; 2017). Considering again the task did not require any activity at the elbow, the up-regulation of CME with less WS is likely an indirect effect of altered voluntary drive to proximal muscles mediated through neural linkages. In summary, an indirect effect of WS is revealed by modulation of activity in elbow muscles during a task in which they were not mechanically involved in gravity compensation.

Given that modulation of CME to distal muscles with WS depends on severity of impairment (Table 7.4), intracortical networks susceptible to disruption by stroke are implicated as a substrate for indirect WS effects. Whether the regulation of CME reflects a functional network architecture or incidental latent connectivity is unknown. In cases of less severe corticospinal system damage, ipsilesional motor cortical areas may provide a substrate well suited for neural reorganisation subserving recovery. More severe impairments are associated with the recruitment of remote or secondary motor areas (Cramer et al., 1997; Johansen-Berg et al., 2002; Frost et al., 2003; Fridman et al., 2004). The resulting networks may be less efficient at generating motor output (Ward et al., 2006; Grefkes and Fink, 2011), or involve up-regulation of latent ipsilateral motor pathways with more diverse patterns of innervation (Bradnam et al., 2012). The observed pattern of CME modulation to distal muscles likely reflects a network structure that emerged in response to lesion-specific disruption of existing motor networks.
Variation of muscle activity and CME in distal muscles that are not mechanically involved in gravity compensation provides evidence for an indirect effect of WS. In this study, the orientation and role of ECR was constant for both the reaching and static abduction tasks. However, manipulation of WS altered the amounts of iEMG during reaching and rmsEMG during static abduction (Tables 7.2 & 7.3). Similarly, greater iEMG was observed for both high targets and far targets despite requirements for wrist extension not varying between target locations. Modulation of muscle activity in ECR, which was mechanically remote to the action of WS, mirrored patterns observed in the proximal upper limb. The present findings suggest WS may influence distal muscle activity indirectly because distal muscles like ECR are subject to common neural drive carried over from proximal muscles.

The interaction of impairment severity and WS for ECR activity and CME was unexpected. During the reaching task, iEMG in the moderate-severe impairment group was lessened only with the highest level of support. Medium support was sufficient to achieve a similar reduction of iEMG for mild impairment. The stroke groups’ response may be indicative of a WS threshold phenomenon. The control group paradoxically exhibited the most ECR activity with support, and it is unclear why the group responded in this manner. It is possible the intact motor system has sufficient physiological range to permit uncontrolled variation of muscles that do not impact task outcome. A similar argument could explain why ECR CME did not respond to WS in the control and mild groups (Table 7.4). In contrast, previous experiments with healthy adults found that ECR CME was modulated by WS (Runnalls et al., 2014; 2017). Although it is unknown which factors may account for the discrepancy between studies, e.g. participant age, the present findings provide evidence in support of an indirect modulation of neural excitability distinct from changes in muscle activity.
7.5.2 Impairment severity and mechanisms for integrated upper limb control

Integrated control of the upper limb based on neural linkages or synergies may facilitate the coordination of voluntary actions like forward reaching. In the present study, indirect effects of WS and interactions with impairment severity provide evidence for integrated control along the proximal-distal axis. Previous reports of distal CME modulation with changes to shoulder activation or shoulder position have interpreted the findings as task-relevant priming for muscle activation (Devanne et al., 2002; Dominici et al., 2005; Ginanneschi et al., 2005; 2006). The present findings support a model in which voluntary drive to proximal muscles acts as a regulatory signal in a proximal-distal hierarchy. Instances of dissociation between CME modulation and muscle activity suggest multiple neural linking mechanisms may be involved. Along the same lines, different patterns of modulation between muscles could reflect the existence of multiple synergies with complex or competing behaviours. Differential responses depending on impairment severity provide a further indication that integration of control may be accomplished at many levels of the neuraxis.

Indirect responses to upper limb WS will depend on the neural structures disrupted by the stroke and whether the lesion is up- or downstream of the point where muscle activation information is bound or linked together through anatomical divergence or physiological interactions that coordinate neural output. Cortical binding of motor commands may be mediated in primary motor cortex where anatomical comingling of muscle representations may facilitate functional interaction (Sanes et al., 1995; Devanne et al., 2006), and proximal influences on distal CME may involve both intracortical disinhibition (Devanne et al., 2002; Kantak et al., 2013), and intracortical facilitation (Ginanneschi et al., 2005; 2006). Subcortical binding of motor commands may be mediated by divergence of
descending corticomotor pathways (McKiernan et al., 1998), recruitment of the cortico-reticulo-propriospinal pathway (Pauvert et al., 1998; Pierrot-Deseilligny, 2002), or activation of spinal interneuron modules (Bizzi and Cheung, 2013). Subcortical lesions at the level of the PLIC would disrupt the pattern of cortically linked neural activity and the activation amplitude of subcortically linked neural activity (McMorland et al., 2015). Any disruption of descending input could impair the regulation of spinal network states. Future studies are warranted to investigate the effect of WS on the structure of muscle synergies in stroke populations (Cheung et al., 2012; Roh et al., 2013; García-Cossio et al., 2014).

7.5.3 Potential limitations

A limitation of the present study is the absence of kinematic measures of reaching performance. A quantitative characterisation of movement quality could reveal additional effects of WS and add context to the interpretation of EMG data. The reaching task, as defined by the array of targets, was designed to accommodate individuals with a broad range of impairments. However, there was a trade off in terms of sensitivity to detect changes. Future studies may wish to incorporate more gradations in target location or additional constraints such as a retrieval component. Lastly, this study only attempted to elicit contralateral MEPs from stimulation of the ipsilesional hemisphere. MEPs could be elicited in only two of the six patients in the moderate-severe group. The pattern of CME modulation in the moderate-severe group could change with a greater sample size. Additional measures, e.g. ipsilateral MEPs, may have yielded neurophysiological data from more of the patients with severe CST damage.
7.5.4 Implications for the clinical use of weight support

WS may benefit stroke patients with upper limb impairment through both direct and indirect mechanisms. First, by directly lessening forces required to complete tasks, individuals with decreased force generating capacity can access a larger workspace and engage in practice with a wider range of tasks. Second, by indirectly influencing linked neural elements, WS may promote a rebalancing of CME in otherwise saturated networks. Potentially, individuals can then engage a neurophysiological landscape more permissive to modulation and plasticity. The threshold of WS required to achieve a desired modulation will vary between muscles and tasks, and almost certainly depend on the specifics of the motor deficit. Further investigation may clarify how WS should be incorporated into individualised stroke neurorehabilitation programmes.
8 General Discussion

This chapter summarises the main findings, discusses potential limitations, and presents directions for future research.

8.1 Summary of main findings

The aim of the research presented in this thesis was to investigate the neurophysiological effects of arm weight support in healthy adults and chronic stroke patients. Using these experiments, we examined the effects of arm weight support (WS) on muscle activation and corticomotor excitability (CME) across the upper limb using multiple gradations of supportive force. Transcranial magnetic stimulation (TMS) and electromyography (EMG) were employed during different movement tasks. Modulation of muscle activity and CME was interpreted in the context of task biomechanics to infer neural connectivity that may mediate responses to WS. There were several novel findings that contribute to our understanding of integrated upper limb control in healthy adults. The results also provide evidence that chronic stroke patients respond to changes in WS at behavioural and neurophysiological levels, and that responses vary with the severity of motor impairment. The main findings are discussed below.

The first experiment, reported in Chapter 4, established that manipulation of WS had the expected effect on the anterior deltoid (AD). In the novel experimental arrangement, isometric AD activity generated shoulder abduction (anti-gravity) torque. Consequently, AD EMG amplitude responded linearly to gradations of supportive force. Distal muscles also responded to WS, exhibiting a similar linear trend between tonic muscle activity and the degree of WS. The nonessential nature of the tonic activity in distal muscles provided evidence in support of a common
neural drive to the upper limb. Modulation of nonessential tonic activity in distal muscles that are remote to the primary action of WS at the shoulder was replicated by all subsequent experiments reported in Chapters 5–7.

The experiment reported in Chapter 4 also demonstrated that WS exerts an effect on CME to the shoulder, arm, forearm, and hand. An up-regulation of CME appears to subserve voluntary contraction in AD. In the wrist extensor ECR, CME was elevated only at the lowest level of WS. This shift was accompanied by a lifting of short latency intracortical inhibition. The intrinsic hand muscle FDI exhibited a contrasting pattern of CME modulation, being elevated only at the highest level of WS. The dissociation between modulation of tonic activity and CME is indicative of distinct underlying mechanisms. The discontinuous change of CME in response to linear gradations of WS is suggestive of a threshold in the modulatory mechanisms. Finally, the differential pattern of CME modulation in FDI provides evidence that muscle representations can be subject to intracortical modulation without being integrated into an obligatory proximal-distal linkage. This could be related to the extent a muscle influences intersegmental limb dynamics.

The second experiment, reported in Chapter 5, showed task-dependent modulation of biceps brachii (BB) CME with manipulation of WS. Because it acts as a forearm supinator, BB CME must be selectively suppressed to pronate the forearm. Preceding elbow flexion, when BB acts as an agonist, CME decreased with incrementally greater WS. Preceding forearm pronation, when BB acts as an antagonist, CME decreased only at the highest level of WS. The relative difference in CME preceding agonist and antagonist contractions is an indicator of the ability to selectively suppress the muscle. In this case, BB selectivity improved, but only at the highest level of WS. The results provide evidence that WS may interact with
excitatory linking mechanisms as well as local inhibitory circuits. The pattern of modulation preceding pronation could be indicative of a threshold for the effect of WS on inhibitory circuits, similar to that proposed in Chapter 4.

The third experiment, reported in Chapter 6, established that whole-body posture interacts with WS to modulate CME and tonic muscle activity across the upper limb. This study examined a larger set of muscles and corroborated earlier findings that nonessential tonic muscle activity decreases with a greater degree of WS. Whole-body posture (standing versus sitting) had a small but significant effect on tonic activity in the arm, although the interaction with WS did not reflect a consistent influence across muscles. In parallel, whole-body posture affected CME to the arm, forearm, and hand. The biceps brachii and triceps brachii exhibited greater CME in the standing posture whereas other muscles showed greater CME when sitting. The factors determining the pattern of modulation with posture are not clear. Postural information may act to prime or otherwise modulate upper limb synergies involved in the maintenance of stability.

The fourth study, reported in Chapter 7, examined the effects of WS in chronic stroke patients and investigated if there was an interaction with impairment severity. During a reaching task, patients with moderate-severe upper limb impairment were able to hit more targets with greater WS. In other words, WS facilitated access to the reaching workspace. WS also had significant effects on muscle activity, which tended to decrease with supportive force. The magnitude of the change with WS was smaller for patients with more severe impairment. WS had an influence on CME in control, mild, and moderate-severe impairment groups. The control group responded similarly to healthy adults in the earlier experiments.
However, the pattern of modulation was not consistent for the stroke patients. This variability likely reflects individual differences in lesion extent and location.

8.2 Potential limitations

Limitations specific to each experiment have been discussed in Chapters 4–7. This section discusses factors that apply more broadly to the experiments and the interpretation of data.

The experiments presented in this thesis utilised TMS to probe the excitability of neural elements controlling motor output to the upper limb. It should be borne in mind that TMS does not necessarily activate corticospinal neurons in the same way that they would be recruited volitionally. TMS acts on corticospinal neurons both pre-synaptically and post-synaptically. Consequently, MEPs reflect an artificial integration of pre-synaptic inputs and post-synaptic excitability (Di Lazzaro et al., 2008). Although MEPs are a useful indicator of the physiological state of the motor cortical system, the relation between MEP size and functional volitional output is not direct (Bestmann and Krakauer, 2015). Putative intracortical networks involved in synergy formation may behave differently in the milieu of natural neural activity compared to activation by TMS. The changes in MEP size observed in the present experiments are valid reflections of CME modulation. However, the relative patterns of CME modulation revealed by TMS may not replicate modulation of volitional motor output. For example, it is possible the posture-related changes reported in Chapter 6 are functionally structured for a task, but the pattern was not evident in MEP change across muscles.

The linear mixed model approach made it possible to analyse MEP data that was observed in the presence of co-varying background muscle activity. While the models are valid representations of the data, interpretation of the output is not
without caveats. Relations that may have subtle non-linearity, such as that between background muscle activity and MEP size, are modelled as linear approximations. Thus relative differences are preserved, but absolute values predicted by the models may not correspond directly with observed data. In this sense it is not unlike the limitations of interpreting MEPs discussed above, inferences should be made from relative differences rather than absolute values.

On a related note, TMS was delivered to a single site in all of the present experiments. The dynamic nature of the motor cortical system and the inherent variability of MEPs necessitated that measures from different muscles were made in close temporal proximity. Concurrently eliciting MEPs from various muscles enabled stronger inferences about correlated responses between muscles and putative linking mechanisms. However, the use of a single stimulation site may bias estimates of correlated CME modulation. The influence of intracortical linking mechanisms between muscle representations could be overestimated by preferentially stimulating corticospinal neurons in close spatial proximity. Projections to a given motoneuron pool arise from multiple loci in the motor cortex (Schneider et al., 2001; Rathelot and Strick, 2006). Corticospinal neurons distant to the site of stimulation may be differently involved in synergy formation or intracortical linking and will be under-represented in the modulation of MEPs. For example, in contrast to findings of Chapters 4 and 6, the absence of a WS effect on CME to ECR for the control group in Chapter 7 could be attributed to a slightly different stimulation site that was biased toward BB. It may be interesting for future studies to examine whether TMS stimulation site affects the modulation of MEP size with WS.
Spinal motoneuron excitability also contributes to MEP size (Taylor, 2006; Groppa et al., 2012). The experiments reported in this thesis did not directly measure excitability of the spinal motoneuron pool. Thus the observed changes in MEP size cannot be solely attributed to supraspinal mechanisms. Peripheral sensory inputs could modulate the excitability of motoneurones and interneurons through a variety of mechanisms including group Ia and Ib afferents, cutaneous afferents, or propriospinal neurons (Rossini et al., 1996; Pauvert et al., 1998; Nuzzo et al., 2016). It is unlikely that these factors alone can explain the results reported in this thesis. Constant joint angles, static postures, and consistent bracing limit differences in muscle spindle and cutaneous inputs between experimental conditions. Distribution of Ib afferent information from anti-gravity agonists like AD to multiple spinal segments could represent another mechanism for integrated upper limb control. The intrinsic electrical properties of spinal motoneurons can also vary with peripheral input, resulting in distinct functional states that differ in the way they integrate inputs (Binder et al., 1993; Hyngstrom et al., 2007; Heckman et al., 2008). The role of peripheral sensory input in upper limb control should be considered for the design and implementation of WS devices. Lastly, the methodology employed throughout this thesis defined levels of WS relative to full support; the amount of supportive force required to permit shoulder abduction without anterior deltoid activity. An alternative approach estimates arm segment mass as a percentage of body mass (Coscia et al., 2014). Both methods make assumptions about the biomechanics of WS. As an example, the shoulder abduction torque required for reaching movements is assumed to be more or less constant for the subset of tasks examined in these studies. However, the generalisability of these assumptions to a wider range of movement tasks has not been established. Going forward, the amount of supportive force should be
considered an important parameter. Future investigations may be warranted to conduct a more robust biomechanical analysis of WS as it relates to particular movement tasks.

8.3 Future directions for WS in stroke rehabilitation

The research presented in this thesis has identified several neurophysiological effects of WS that may have relevance for its use in stroke rehabilitation. Further study may elucidate the underlying mechanisms and establish their influence on real-world arm function. The relation between WS, neuroanatomical integrity and severity of motor impairment needs to be characterised in more detail to inform a more individualised application of WS in stroke rehabilitation.

WS appears to act through direct and indirect mechanisms, both of which may have benefits for stroke patients with upper limb impairment (Chapter 7). The direct mechanical effect of WS may address the muscle weakness component of hemiparesis. By reducing the anti-gravity torques required to perform movements, individuals with limited force generating capacity can access a larger workspace and engage in practice with a wider range of tasks. Thus facilitating intensity of practice and task-specific training with time-locked sensory feedback, critical factors driving motor recovery (Krakauer, 2005; Veerbeek et al., 2014). The same factors have been identified as a primary advantage of robot-assisted therapy, which frequently incorporates WS (Kwakkel and Meskers, 2014; Veerbeek et al., 2017). Comparatively few studies have examined training with WS alone (Sanchez et al., 2006; Housman et al., 2009; Krabben et al., 2012; Dipietro et al., 2007), and only one has investigated parametric supportive force as a dose variable (Ellis et al., 2009a). Future clinical trials should examine whether training with WS can augment other therapeutic techniques and work towards establishing the dosage response of this
intervention. The time-course of adaptation to WS and the persistence of learning effects after gravity is re-introduced should also be investigated.

The indirect effect of WS through linked neural elements may address the dyscoordination component of hemiparesis. By modulating excitability of intracortical neurons involved in linking muscle activity, and by lessening descending drive to spinal interneuron circuits, WS may influence the expression of synergies. Research into the effect of WS training on abnormal synergies has been inconclusive (Krabben et al., 2012). Future studies should utilise quantitative measures of synergies and focus on specific movement tasks. Furthermore, thresholds for modulation with WS (Chapters 4 & 5) indicate the amount of supportive force may be a key parameter. In healthy adults, the level of WS influenced the activation of synergies during reaching but not which synergies were recruited or their underlying structure. The effect of parametric WS on upper limb muscle synergies in stroke patients is an attractive avenue for future research.

Finally, the effects of WS appear to vary with impairment severity (Chapter 7). The differences may reflect motor networks that emerge in response to disruption of neuroanatomical structures. For example, patients with more severe damage to the ipsilesional corticospinal tract may rely on an up-regulation of latent ipsilateral motor pathways to the proximal upper limb (Bradnam et al., 2012; 2013). Characterising the effects of WS on alternate motor pathways may inform the most appropriate application of WS for different patient groups.
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Participant Information Sheet

Title of Project: A novel method for measuring cortical representations of upper limb coordination

Researchers:
Professor Winston Byblow, Dept of Sport & Exercise Science
Mr Keith Runnalls (PhD Student), Dept of Sport & Exercise Science

Dear Participant:

We are conducting research that examines how patterns of coordinated muscle activity are represented in the motor cortex area of the brain.

What does the study involve?

You will be required to attend
- One experimental session at the Movement Neuroscience Laboratory, 731.134 Tamaki Campus. The session will take 2–3 hours.

In this study you will be asked to:
- Complete a questionnaire that will be used to determine your handedness (aprx. 5 minutes).
- Complete a questionnaire that will ensure you can safely participate in the procedures (aprx. 5 minutes).
- Undergo transcranial magnetic brain stimulation with a special device that induces a very weak stimulating current in the neural tissue in the part of the brain associated with movement. This is noninvasive and painless. This technique will also be conducted in conjunction with peripheral nerve stimulation (aprx. 1–1.5 hours).
- Undergo brief electrical stimulation over nerves in your shoulder and arm using a weak current and short duration pulse that may cause some mild, short lasting discomfort but has no after effects.
- Perform repeated arm movements while your arm is partially supported by a brace.

Am I eligible to participate?

You are eligible to participate in this study if you are aged between 18 and 75 years, and have no history of neurological illness. You are not eligible to participate if you have a cardiac pacemaker, shoulder or arm injury, peripheral nerve damage or experience seizures. If you volunteer for this study, you will be asked to complete a safety checklist, to ensure that you are eligible to participate. You will also be asked to complete a handedness questionnaire, to determine how right- or left-handed you are. If you aren’t eligible to participate, then any materials relating to you, such as the safety checklist and handedness questionnaire, will be immediately destroyed.
Further details are as follows:

Electromyography recording

We will record the electrical activity of your arm and shoulder muscles. This electrical activity will be recorded by sensors positioned on the skin over the muscles of interest. The skin must first be prepared by shaving any hair and mild abrasion of a small patch of skin. This can result in a mild and transient irritation of the skin in some people that does not require treatment.

Movement Task

You will be asked to position your arm in a variety of static postures that are related to daily living activities. Depending on the experimental condition, you may also be asked to perform a series of arm movements. These movements will consist of reaching forward to a target. We will inform you of the experimental condition in advance. You will be either seated or standing in front of a table while performing the movement tasks. The weight of your arm will be partially supported by a brace attached to a spring counterbalance system. In total you may perform approximately 100 reaching movements. Frequent rest breaks will be provided.

Kinematic recording

We will record the motion of your arm using sensors called accelerometers. These are small, lightweight electronic devices that are attached to your arm using velcro straps. The accelerometers passively record motion and do not stimulate in any way.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) involves gently holding a plastic device against your scalp. This device produces a very brief magnetic field that activates some of the cells in the movement areas of the brain. This stimulus causes a brief twitch in the muscles of the forearm from which we record muscle activity using electromyography. Occasionally, some people experience mild, transient scalp discomfort, due to the activation of the scalp muscles by the magnetic field. If you feel uncomfortable at any time during the experiment, please notify the experimenter.

Peripheral nerve stimulation

Peripheral nerve stimulation (PNS) will be used to activate specific motor pathways to the arm. Two stimulating electrodes will be placed on the skin of your neck or arm through which a weak current will be delivered. The stimulation will feel like a mild pricking sensation that should not be painful. Each pulse is very brief (1 ms) and may produce a pin-prick sensation. The strength of the stimulus will be adjusted so it is comfortable for you and time will be taken for you to get used to the sensation. You will be given regular rest periods during the experiment, however if you feel uncomfortable at any time during the experiment, please notify the experimenter.

There are no risks associated with the use of TMS and PNS in the same experimental session. Effects of TMS and PNS are transient and will not affect your ability to drive home, or return to study or work after participation.

Risks and Benefits

There are no specific benefits to participants taking part in this research. As outlined above, you may experience mild, transient discomfort during skin preparation for surface electromyography. You may also experience mild, short-lasting discomfort during peripheral nerve stimulation and transcranial magnetic stimulation. These experiments will use single-pulse TMS protocols (NOT repetitive TMS). TMS is safe and non-invasive and carries minimal risk. It can cause mild, transient discomfort due the contraction of scalp musculature
underneath the stimulating coil. This can be minimized by slight alterations to the coil position and orientation. Peripheral nerve stimulation will feel like a mild pricking sensation that should not be painful. Each pulse is very brief and may produce a pin-prick sensation. There are no lasting effects.

The risk of adverse effects of TMS will be minimized by the use of the TMS safety screening checklist, which will be completed by all volunteers and screened by a neurologist (Professor PA Barber, Dept of Medicine – Neurology Research Unit) prior to their participation.

**Participation**

Your participation is voluntary and you may withdraw from participating at anytime during the experiment without stating a reason, and at your request we will stop the experiment. You have the right to withdraw your data from this study up to 3 months after you complete the study. Withdrawal or non-participation will not affect your relationship with the University. You will be assigned and identified by a code. The data obtained from this experiment will be stored to disk for a period of up to six years and will be used for publication in a scientific journal. After six years, your data will be deleted from disk and your consent form and all related paperwork put through a shredder. No material that could personally identify you will be used in any reports in this study. The information and data collected from you will be stored securely, in locked cabinets and on secure computer networks. Only the investigators will have access to this information, and your data will be made anonymous by assigning a unique code to it. You can request a summary of the study’s results, which we can send to you once the project is complete.

**Summary of Your Rights**

- Your participation is entirely voluntary.
- You may withdraw from the project at any time without stating a reason.
- You may have your data withdrawn from the study within three months of your participation.
- You may obtain results regarding the outcome of the project from the experimenters upon completion of the study.
- Your identity will be kept strictly confidential, and no identification of you or your data will be made at any time during collection of the data or in subsequent publication of the research findings.
- After six years, your data will be deleted from disk and your consent form and all related paperwork put through a shredder.
- Discomfort or incapacity have not been reported from any of the procedures that will be used in this project, however, if the procedures cause you concern, you may withdraw from the project at any time.
- You are encouraged to consult with your whanau/family, hapu or iwi regarding participation in this project.

**Compensation**

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation, and Compensation Act 2001. ACC cover is not automatic, and your case will need to be assessed by ACC according to the provisions of the Injury Prevention, Rehabilitation, and Compensation Act 2001. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors, such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses, and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.
Who should I contact if I have further questions?

Please feel free to ask any questions as we proceed.
If you have any further questions please feel free to contact either:

Professor Winston Byblow     Keith Runnalls, PhD Student
Building 731, Tamaki Campus   Building 731, Tamaki Campus
Phone 373-7599 ext 86844        Phone 373-7599 ext 84897
w.byblow@auckland.ac.nz       k.runnalls@auckland.ac.nz

You may contact the Head of Department of Sport and Exercise Science,
Associate Professor Greg Anson on 373-7599 ext 82975 or email ganson@auckland.ac.nz

For any concerns regarding ethical issues you may contact the Chair, the University of
Auckland Human Participants Ethics Committee, at the University of Auckland, Research
Office, Private Bag 92019, Auckland 1142. Telephone 09 373-7599 ext. 83711.
Email: ro-ethics@auckland.ac.nz*

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS
COMMITTEE on 15/09/2015 for a period of 3 years, Reference Number 8737.
Appendix B: Consent form for experiments with healthy young adults in Chapters 4–6

DEPARTMENT OF SPORT & EXERCISE SCIENCE

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Consent Form

THIS CONSENT FORM WILL BE HELD FOR A PERIOD OF SIX YEARS

Title of Project: A novel method for measuring cortical representations of upper limb coordination

Researchers:
Professor Winston Byblow, Dept of Sport & Exercise Science
Keith Runnalls (PhD Student), Dept of Sport & Exercise Science

I have been given and understood the explanation of this research project and my role as a participant. I have had the opportunity to consult my whanau, hapu or iwi, or a family member/friend to help me ask questions. I have had time to consider whether to take part. I am satisfied with the answers I have been given. I know who to contact if I have any further questions about the study.

I understand that:

- My participation is voluntary
- The total time required for the study is 2–3 hours, occurring in a single session
- I may withdraw myself from the experiment at any time without giving a reason
- I can withdraw any information traceable to me, from this study, up until three months after I have completed this study
- I may obtain results regarding the outcome of this experiment from the named researcher upon completion of the study
- After six years, my data will be deleted from disk and this consent form and all associated paperwork will be destroyed
- My anonymity will be maintained in any reporting of this research

I agree to take part in this research during which I may be asked to:

- Complete a questionnaire that will be used to determine the extent of my handedness.
- Complete a questionnaire that will ensure I can safely participate in the procedures.
- Undergo magnetic brain stimulation with a special device that will induce a weak stimulating current in the neural tissue in the part of the brain associated with movement.
- Undergo brief electrical stimulation over nerves in my shoulder and arm using a weak current and short duration pulse that may cause some mild, short lasting discomfort but has no after effects.
- Perform repeated arm movements while my arm is partially supported by a brace.
- Notify the experimenter if at any time I feel uncomfortable or unsure of the stimulation being applied.
I would like the researchers to send me a summary of the study results
(please circle)  YES  NO
If YES: my address is __________________________________________

Signed: ______________________________________________________
Name: __________________________________ Date: __________________
(please print in full)

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS
COMMITTEE on 15/09/2015 for a period of 3 years, Reference Number 8737.
Appendix C: Participant information sheet for experiment with stroke patients in Chapter 7

Participant Information Sheet

Title of Project: Individualised neuromodulation for motor recovery after stroke

Researchers:

Professor Winston Byblow, Dept of Sport & Exercise Science
Alana McCambridge (PhD Student), Dept of Sport & Exercise Science
Associate Professor Cathy Stinear, Dept of Medicine
Keith Runnalls (PhD Student), Dept of Sport & Exercise Science
Professor Alan Barber, Dept of Medicine
April Ren, Lab Manager, Dept of Sport & Exercise Science

Dear Participant,

We are conducting research that examines whether it is possible to improve coordination of arm muscles using non-invasive brain stimulation. Please take your time to think about the information provided below, and feel free to discuss it with your whanau, family or significant other support people. If you are Māori, and on request, we will arrange for you to discuss your role in this study with a member of the office of the Pro Vice-Chancellor (Māori), at the University of Auckland. Taking part is completely voluntary (your choice). If you decline the offer to participate, your continuing health care will not be affected in any way.

What does the study involve?

If you agree, and are eligible to participate you will be asked to attend;

- Up to four experimental sessions at the Movement Neuroscience Laboratory, 731.134 Tamaki Campus. Each session will take up to 2.5 hours.
- One session at the Centre for Advanced MRI, Grafton Campus, University of Auckland. This session will take up to 60 minutes.

In this study you will be asked to:

- Complete two questionnaires that will ensure you can safely participate in the procedures (appr. 5 minutes).
- Complete a questionnaire that will be used to determine your handedness (approx. 5 minutes).
- Undergo transcranial magnetic brain stimulation with a special device that induces a very weak stimulating current in the neural tissue in the part of the...
brain associated with movement. This is noninvasive and painless. This technique will also be conducted in conjunction with peripheral nerve stimulation (approx. 2.5 hours).

- Undergo brief electrical stimulation over nerves in your arm using a weak current and short duration pulse that may cause some mild, short lasting discomfort but has no after effects.
- Receive 20 minutes of brain polarisation from a device that delivers a weak current to the neural tissues in the motor area of the brain controlling your arm movement. This is noninvasive and painless.
- Undergo clinical assessments of arm function with a trained investigator. This will include performing various movements with your arms.
- Undergo Magnetic Resonance Imaging to obtain an anatomical scan of your brain (approx. 60 minutes).
- Perform repeated reaching movements while your arm is partially supported by a brace.

Am I eligible to participate?

You are eligible to participate in this study if you:

- have experienced one stroke more than 6 months ago
- have hand or arm weakness or impairment from your stroke
- are able to give informed consent

If you volunteer for this study, you will be asked to complete a safety checklist, to ensure that you are eligible to participate. We will also ask you to give your consent for us to obtain limited medical information from your family doctor or neurologist that will allow our consulting neurologist to make a decision regarding your suitability and your safety to be a participant in this study.

If you aren’t eligible to participate, then any materials relating to you, such as the safety checklist and handedness questionnaire, will be immediately destroyed.

You are not eligible to participate if you:

- are currently undergoing rehabilitation (i.e. part of a rehabilitation programme)
- have participated in an interventional research study less than 6 weeks prior
- have a history of neurological problems other than stroke
- have a cardiac pacemaker, or other metal implants that prevent you from having an MRI scan
- experience seizures
- take certain types of medication
- have other impairments deemed unsuitable by the investigators that may affect task protocols (e.g. hemianopia or neglect)

The study will use the following procedures:

Electromyography recording

We will record the electrical activity of your hand, arm, and shoulder muscles. This electrical activity will be recorded by sensors positioned on the skin over the muscles of interest. The skin must first be prepared by shaving any hair and mild abrasion of a small patch of skin. This can result in a mild and transient irritation of the skin in some people that does not require treatment.
Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) involves gently holding a plastic device against your scalp. This device produces a very brief magnetic field. Occasionally, some people experience mild, transient scalp discomfort, due to the activation of the scalp muscles by the magnetic field. If you feel uncomfortable at any time during the experiment, please notify the experimenter. There are no other specific risks associated with the procedures and the equipment used in the study.

Peripheral nerve stimulation (PNS)

Peripheral nerve stimulation will be used to activate specific motor pathways to the arm. Two stimulating electrodes will be placed on the skin of your elbow through which a weak current will be delivered. The stimulation will feel like a mild pricking sensation that should not be painful. Each pulse is very brief (1 ms) and may produce a pin-prick sensation. The strength of the stimulus will be adjusted so it is comfortable for you and time will be taken for you to get used to the sensation. You will be given regular rest periods during the experiment, however if you feel uncomfortable at any time during the experiment, please notify the experimenter.

Brain Polarisation using Transcranial Direct Current Stimulation (tDCS)

We will use Transcranial Direct Current Stimulation (tDCS), which is a safe, painless and non-invasive technique. It induces brain polarisation with a low-intensity direct current, delivered to the scalp using a small, battery-powered device. Brain polarization can be used to temporarily increase or decrease the activity of the motor areas of the cortex, depending on the location of electrode placement over the scalp, and the protocol used. This stimulation is usually imperceptible due to the low current involved.

TDCS involves delivering a low-intensity current with two damp sponge electrodes placed on your scalp. One electrode will be positioned over motor areas on your brain. You will experience a slight tingling sensation under the electrodes for up to 2 minutes, after which the sensation diminishes and may become imperceptible. There is no need to shave your head and the area under the electrode on your forehead will be cleaned using an alcohol wipe. The stimulation period will be up to 20 minutes. This protocol has been shown to induce after-effects that last for 30 – 60 minutes. You will be asked to sit quietly during the period of stimulation, and for 5 minutes afterwards to consolidate effects. If you feel uncomfortable at any time during the stimulation, please notify the experimenter.

There are no risks associated with the use of TMS, PNS and tDCS in the same experimental session. Effects of TMS and tDCS are transient and will not affect your ability to drive home, or return to study or work after participation.

Assessments of arm function

We will use commonly used clinical assessments to measure various aspects of your arm function. These will be performed with a trained investigator. You will be asked, if possible, to perform various movements with your arms (e.g. place a block on a target). These tests will determine how well you can control your arm muscles and whether your muscles are stiff.

We will assess arm co-ordination using a circle drawing task. You will be asked to draw large circles on a device while paced to an auditory metronome.
Movement task

You will be asked to perform a series of reaching movements with your arm. These movements will consist of reaching forward to a target. You will also be asked to position your arm in a variety of postures that are related to daily living activities. The weight of your arm will be partially supported by a brace attached to a spring counterbalance system. In total you may perform approximately 100 reaching movements per arm. Frequent rest breaks will be provided.

Kinematic recording

We will record the motion of your arm using special cameras that track reflective markers. These are small, lightweight plastic balls that are attached to your arm using velcro straps. The cameras only record the position of the plastic markers, you will not be videotaped or photographed.

Magnetic Resonance Imaging (MRI)

We will obtain a structural image of your brain, using magnetic resonance imaging (MRI). MRI is a widely used, safe, non-invasive imaging technique. Some people experience mild anxiety during magnetic resonance imaging, as the scanner is an enclosed space. You will be provided with a safety buzzer in one hand, so that if you want to stop the scanning at any time, you can use this device to alert the radiographers.

In the event that a condition which is assessed to be a clinical abnormality is detected through performing a scan on you, you will be informed of this and will be advised to consult your general practitioner or other health professional of your choice. Because the images are not routinely reviewed by a radiologist, we are unable to perform diagnostic scans for medical purposes of areas where you have known abnormalities. If you do not wish to be informed of any abnormalities detected, then you should not participate in this project.

Risks and Benefits

There are no specific benefits to participants taking part in this research. As outlined above, you may experience mild, transient discomfort during skin preparation for surface electromyography. You may also experience mild, short-lasting discomfort during direct current stimulation, peripheral nerve stimulation and transcranial magnetic stimulation. These experiments will use single-pulse TMS protocols (NOT repetitive TMS). TMS is safe and non-invasive and carry minimal risk. It can cause mild, transient discomfort due the contraction of scalp musculature underneath the stimulating coil. This can be minimized by slight alterations to the coil position and orientation. TDCS can produce a transient itching or tingling sensation. Most participants report little sensation under the electrodes once this dissipates (usually 1 – 2 minutes). Peripheral nerve stimulation will feel like a mild pricking sensation that should not be painful. Each pulse is very brief and may produce a pin-prick sensation. There are no lasting effects.

The risk of adverse effects of TMS and tDCS will be minimized by the use of the TMS safety screening checklist, which will be completed by all volunteers and screened by a neurologist (Professor PA Barber, Dept of Medicine – Neurology Research Unit) prior to their participation.
Confidentiality

No material that could personally identify you will be used in any reports in this study. The information and data collected from you will be stored securely, in locked cabinets and on secure computer networks. Only the investigators will have access to this information, and your data will be de-identified by assigning a unique code to it.

Participation

Your participation is voluntary and you may withdraw from participating at anytime during the experiment without stating a reason, and at your request we will stop the experiment. You have the right to withdraw your data from this study up to 3 months after you complete the study. Withdrawal or non-participation will not affect your relationship with the University, Centre for Brain Research (CBR) or Brain Recovery Clinic. If felt that this assurance has been breached you can contact Associate Professor Greg Anson (contact details below). You will be assigned and identified by a code. The data obtained from this experiment will be stored to disk for a period of up to six years and will be used for publication in a scientific journal. After six years, your data will be deleted from disk and your consent form and all related paperwork put through a shredder. No material that could personally identify you will be used in any reports in this study. The information and data collected from you will be stored securely, in locked cabinets and on secure computer networks. Only the investigators will have access to this information, and your data will be de-identified by assigning a unique code to it. You can request a summary of the study’s results, which we can send to you once the project is complete.

You will also be offered reimbursement for your travel expenses in the form of petrol or taxi vouchers.

The study does not include therapeutic procedures and therefore the study protocols cannot be offered to you as a treatment.

Summary of Your Rights

- Your participation is entirely voluntary.
- You may withdraw from the project at any time without stating a reason.
- You may have your data withdrawn from the study within three months of your participation.
- You may obtain results regarding the outcome of the project from the experimenters upon completion of the study.
- Your identity will be kept strictly confidential, and no identification of you or your data will be made at any time during collection of the data or in subsequent publication of the research findings.
- After six years, your data will be deleted from disk and your consent form and all related paperwork put through a shredder.
- Discomfort or incapacity have not been reported from any of the procedures that will be used in this project, however, if the procedures cause you concern, you may withdraw from the project at any time.
- You are encouraged to consult with your whanau/family, hapu or iwi regarding participation in this project.
Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation, and Compensation Act 2001. ACC cover is not automatic, and your case will need to be assessed by ACC according to the provisions of the Injury Prevention, Rehabilitation, and Compensation Act 2001. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors, such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses, and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

Who should I contact if I have further questions?

Please feel free to ask any questions as we proceed. If you have any further questions please feel free to contact either:

**Professor Winston Byblow**  
Building 731, Tamaki Campus  
Phone 373-7599 ext 86844  
w.byblow@auckland.ac.nz

**Alana McCambridge, PhD Student**  
Building 731, Tamaki Campus  
Phone 373-7599 ext 84897  
amccambridge@auckland.ac.nz

You may contact either:

Head of Department of Sport and Exercise Science,  
Associate Professor Greg Anson on 373-7599 ext 82975 or email  
g.anson@auckland.ac.nz

Associate Professor Cathy Stinear, Research Director for the Brain Research Clinic,  
on +64 9 373 7599 ext 83779 or email c.stinear@auckland.ac.nz

For any queries regarding ethical concerns please contact:

The Chair,  
University of Auckland Human Participants Ethics Committee  
University of Auckland  
Private Bag 92019, Auckland  
Tel: 373 7599 ext 87830

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE ON 15/01/2014 for a period of 3 years. Reference number UAHPEC 10457.
Appendix D: Consent form for experiment with stroke patients in Chapter 7

Consent Form

THIS CONSENT FORM WILL BE HELD FOR A PERIOD OF SIX YEARS

Title of Project: Individualised neuromodulation for motor recovery after stroke

Researchers:

Professor Winston Byblow, Dept of Sport & Exercise Science
Alana McCambridge (PhD Student), Dept of Sport & Exercise Science
Keith Runnalls (PhD Student), Dept of Sport & Exercise Science
Professor Alan Barber, Faculty of Medical & Health Science
April Ren, Lab Manager, Dept of Sport & Exercise Science

By signing this consent form, you are making the following statements:

1. I have read and I understand the information sheet dated 15/01/2014 for volunteers taking part in the study, which explores whether non-invasive brain stimulation improves arm function.
2. I have had the opportunity to discuss this study.
3. I am satisfied with the answers I have been given.
4. I have had sufficient time and the opportunity to discuss this project with Family/Whanau, or with a friend to help me ask questions and understand the study.
5. I understand that taking part in this study is voluntary (my choice).
6. I understand that the information obtained from my medical files will be used to assess eligibility (stroke participants only).
7. I understand I may withdraw from the study at any time without giving a reason.
8. I understand that I can withdraw any information traceable to me from this study, up until three months after I have completed this study.
9. I understand my participation and my medical information used in this study is confidential and no material that could identify me will be used in reports of this study.
10. I understand that the investigation will be stopped if it should appear harmful to me.
11. I understand the compensation provisions for this study.
12. I understand that after six years, my data will be deleted from disk and this consent form and all associated paperwork will be destroyed.
13. I understand that any incidental findings and an appropriate course of action will be explained to me by the researchers. If I do not wish to be informed of incidental findings I will be excluded from participating.
14. I have had time to consider whether to take part.
15. I know whom to contact if I have any side effects to the study.
16. I know whom to contact if I have any questions about the study.

I agree to take part in this research during which I will be asked to:

- Complete questionnaires that will ensure I can safely participate in the procedures.
- Complete a questionnaire that will be used to determine the extent of my handedness.
- Undergo magnetic brain stimulation with a special device that will induce a weak stimulating current in the neural tissue in the part of the brain associated with movement.
- Undergo brain polarisation using a device that delivers a weak current to the neural tissues in the brain associated with movement.
- Undergo weak peripheral nerve stimulation over nerves in my arm
- Undergo clinical assessments of my arm function/ability
- Perform a circle drawing task
- Perform repeated reaching movements while my arm is partially supported by a brace
- Have an MRI scan of my brain
- Notify the experimenter if at any time I feel uncomfortable or unsure of the stimulation being applied.

The total time required for the study is up to 10 hours, spread over five sessions. For the MRI scan, the session will last 30 - 45 minutes. The four experimental sessions at the Movement Neuroscience Lab may last up to 2.5 hours each.

I would like the researchers to send me a summary of the study results (please circle)  YES   NO

If YES: my address is ______________________________________________________________
I hereby consent to take part in this study.

Signed: ________________________________

Name: ________________________________ Date: ____________________
(please print in full)

Project explained by: ________________________________

Signature: ________________________________

Date: ____________________

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMANS PARTICIPANTS ETHICS COMMITTEE ON 15/01/2014 for a period of 3 years. Reference Number 010457.
Appendix E: TMS safety checklist

PARTICIPANT CHECKLIST FOR USING TRANSCRANIAL MAGNETIC AND TRANSCRANIAL ELECTRICAL STIMULATION

Last name ___________________________ DOB __________ dd/mm/yyyy

First names ___________________________ Sex  ☐ Male ☐ Female

Please take a moment to carefully answer all questions.

Question: Do you suffer from epilepsy, or have you ever had an epileptic seizure?  Yes ☐ No ☐

Question: Does anyone in your family suffer from epilepsy?  Yes ☐ No ☐

Question: Do you have any metal implant(s) in any part of your body or head?  Yes ☐ No ☐

Excluding tooth fillings

Question: Do you have an implanted medication pump or any other implanted electronics?  Yes ☐ No ☐

Question: Do you have a pacemaker or defibrillator?  Yes ☐ No ☐

Question: Do you suffer from any form of heart disease or had heart surgery?  Yes ☐ No ☐

Question: Do you suffer from recurring headaches?  Yes ☐ No ☐

Question: Have you ever had a skull fracture or head injury?  Yes ☐ No ☐

Question: Have you ever had any head or brain surgery?  Yes ☐ No ☐

Question: Is there any chance you could be pregnant?  Yes ☐ No ☐

Question: Do you take any medication?  Yes ☐ No ☐

Question: Do you suffer from any neurological or other medical conditions?  Yes ☐ No ☐

Interview guidelines and medication screening checklist developed by Dr. Winston Byblow (PhD), Dr. Alan Barber (PhD, MBChB, FRACP Neurology) and Dr. Cathy Simner (PhD), for use in the Movement Neuroscience Laboratory, Clinical Neuroscience Laboratory, Visual Neuroscience Laboratory and Metabolic Neuroscience Laboratory. Updated: January 2011. Pharmaceutical review: February 2009.

Page 1 of 5
<table>
<thead>
<tr>
<th>Drug</th>
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<th>No to all</th>
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<tbody>
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</tr>
<tr>
<td>Symmetrel®</td>
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<td>Baclofen</td>
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<td>Pacifen ®</td>
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<tr>
<td>Benztrpine</td>
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<td>Benztrpine (tab), Cogentin® (injection)</td>
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<td>Clonazepam</td>
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<td>Rivotril® (oral drops &amp; injection), Paxam® (oral)</td>
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<td>Levodopa + benzerazide</td>
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<td>Vigabatrin</td>
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</table>

Interview guidelines and medication screening checklist developed by Dr. Winton Byklow (PhD), Dr. Alan Barber (PhD, MBChB, FRACP Neurology) and Dr. Cathy Stinor (PhD), for use in the Movement Neuroscience Laboratory, Clinical Neuroscience Laboratory, Visual Neuroscience Laboratory and Metabolic Neuroscience Laboratory. Updated: January 2011. Pharmacist review: February 2009.
Appendix F: Interview guidelines to accompany TMS safety checklist

PARTICIPANT CHECKLIST FOR USING TRANSCRANIAL MAGNETIC AND TRANSCRANIAL ELECTRICAL STIMULATION

INTERVIEW GUIDELINES

1. Do you suffer from epilepsy, or have you ever had an epileptic seizure? Exclude.

2. Does anyone in your family suffer from epilepsy?
   Ask: Does anyone in your family (related by birth) suffer from epilepsy?
   Ask: Do you know if their epilepsy is caused by something in particular, such as a head injury or stroke?
   If they are related by marriage to someone with epilepsy, rather than genetically related, they can be included.
   If they are genetically related to someone with epilepsy, but it was caused by a specific event, such as head trauma, stroke, brain tumour or brain surgery, they can be included.
   If they are genetically related to someone with epilepsy, but they aren’t sure whether it was caused by trauma, stroke, brain tumour or brain surgery consult study physician.
   If they are genetically related to someone who experiences epilepsy, with no known cause, consult study physician.

3. Do you have any metal implant(s) in any part of your body or head? (Excluding tooth fillings)
   Ask: Where in your body?
   If the metal is implanted in the head or neck, exclude.
   If metal is implanted at the level of the shoulders or below, they can be included.

4. Do you have an implanted medication pump or any other implanted electronics? Exclude.

5. Do you have a pacemaker or defibrillator?
   Exclude.

6. Do you suffer from any form of heart disease or had heart surgery?
   Ask: What sort of heart disease or heart surgery?
   Ask: If heart surgery, did they implant anything, such as a new valve?
   If they have had a valve replacement, or any other cardiac implants consult study physician.

Interview Guidelines developed by Dr Winston Byblow (PhD), Dr Alan Barber (PhD, MBCB, FRACP Neurology) and Dr Cathy Stinear (PhD), for use in the Movement Neuroscience Laboratory. Updated: July 2009
7. **Do you suffer from recurring headaches?**
   Ask: How often do you experience a headache?
   Ask: Do you know what triggers your headaches?
   Ask: Does the headache respond to over the counter medications?
   Ask: Have you consulted your doctor about these headaches?
   If they experience headaches more than once per week, or the headaches don’t respond to over the counter medications, consult study physician.

8. **Have you ever had a skull fracture or head injury?**
   If skull fracture, exclude.
   If head injury with loss of consciousness, consult study physician.
   If head injury with no loss of consciousness, within last six months, exclude.
   If they experience ongoing symptoms as a result of their head injury, exclude.
   If the head injury did not result in a loss of consciousness, and was more than six months ago, and they don’t experience any ongoing symptoms, they can be included.

9. **Have you ever had any head or brain surgery?**
   If brain surgery, exclude.
   Ask: What type of head surgery?
   Ask: When was the surgery?
   Ask: Was any metal implanted, such as screws, plates or pins? If YES, exclude. If NO, consult study physician.

10. **Is there any chance you could be pregnant?**
    Exclude.

11. **Do you take any medication?**
    Ask them to list all medications they take on the checklist.
    Ask them to fill in the ‘TMS Medication Screening Checklist’, follow its criteria, to check for any medication contraindications.

12. **Do you suffer from any neurological or other medical conditions?**
    Ask them to fill in the ‘TMS Medication Screening Checklist’, follow its criteria, to check for any medication contraindications.
    If they take medication that is not on the ‘TMS Medication Screening Checklist’, consult study physician.

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Interview Guidelines developed by Dr Winston Byblow (PhD), Dr Alan Barber (PhD, MBChB, FRACP Neurology) and Dr Cathy Stinear (PhD), for use in the Movement Neuroscience Laboratory. Updated: July 2009

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# TMS Medication Recommendations Checklist

<table>
<thead>
<tr>
<th>Medication (generic)</th>
<th>Medication (brand or tradename)</th>
<th>Action</th>
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<tbody>
<tr>
<td>Amantadine</td>
<td>Symmetrel®</td>
<td>Consult study physician</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Xanax®</td>
<td>Consult study physician</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Pacifen®</td>
<td>Consult study physician</td>
</tr>
<tr>
<td>Benztropine</td>
<td>Benztrop® (tab) Cogentin® (injection)</td>
<td>Consult study physician</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tegretol® Tenil®</td>
<td>Exclude</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celaqram® Arrow-citalopram® Citalopram-ReX® Cipramil</td>
<td>Consult study physician</td>
</tr>
<tr>
<td>Clobazam</td>
<td>Frisium®</td>
<td>Exclude</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Rivotril® (oral drops &amp; injection) Paxam® (oral)</td>
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</tr>
<tr>
<td>Fluoxetine</td>
<td>Fluox® Prozac® (not funded)</td>
<td>Consult study physician</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Neurontin® Nupentin®</td>
<td>Exclude</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol® (injection) Serenace®</td>
<td>Exclude</td>
</tr>
<tr>
<td>Hyoscine</td>
<td>Scopaderm® (patch) Buscopan®</td>
<td>Consult study physician</td>
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<td>Ketamine</td>
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<tr>
<td>Lamotrigine</td>
<td>Lamictal® Arrow-lamotrigine® Mogine®</td>
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TMS Medication Screening Checklist developed by Dr Winston Byblow (PhD), Dr Alan Barber (PhD, MBChB, FRACP Neurology) and Dr Cathy Stinear (PhD), for use in the Movement Neuroscience Laboratory. Updated: April July 2009. Pharmacist review: February 2009

V#3 17/07/2009
<table>
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<th>Medication (generic)</th>
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<td>Sabril®</td>
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</table>

TMS Medication Screening Checklist developed by Dr Winston Byblow (PhD), Dr Alan Barber (PhD, MBChB, FRACP Neurology) and Dr Cathy Stinear (PhD), for use in the Movement Neuroscience Laboratory. Updated: July 2009. Pharmacist review: February 2009

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Appendix G: MRI safety and consent form

MRI SAFETY AND CONSENT FORM

Name ______________________________________  ____________________
Date of Birth ___/___/____ NHI ______________
Weight _________ kg  Height _________ cm

Magnetic Resonance Imaging involves the use of an extremely powerful magnet. 
For your safety please answer the following questions

Have you had a previous MRI scan?  □ yes  □ no
Do you have or have you ever had a cardiac pacemaker?  □ yes  □ no
Do you have a brain aneurysm clip?  □ yes  □ no
Have you ever had an injury to the eye with a metallic object or fragment?  □ yes  □ no
Have you had any previous surgery?  □ yes  □ no
Please list ____________________________________________
Do you have any allergies to medications?  □ yes  □ no
Please list ____________________________________________
Do you have any of the following:
Anaemia, blood disorders, kidney disease or seizures?  □ yes  □ no

FEMALE PATIENTS
Is there any chance that you could be pregnant?  □ yes  □ no
Are you currently breastfeeding?  □ yes  □ no

PLEASE ANSWER THE QUESTIONS ON THE BACK OF THIS SHEET
DO YOU HAVE ANY OF THE FOLLOWING?

- Implanted cardiac defibrillator
- Implanted electronic or magnetic device
- Metallic stent, filter or coil
- Cochlear implant or other ear implant
- Heart valve prosthesis
- Any type of prosthesis (eye, limb etc)
- Joint replacement
- Screws, plates or wires in bones or joints
- Shunt (spinal, intraventricular, or heart)
- Vascular or drug access port or catheter
- Radiation seeds or implants
- Medication patches (Nicotine or hormone)
- Tattoo or permanent makeup
- Dentures or partial plate
- Hearing aid
- Shrapnel, bullets or other metal

**BEFORE ENTERING THE MR SCAN ROOM**

You must remove all metallic objects, including jewellery, watches, keys, coins, credit cards, pens, cell phones, hearing aids, clothing with metallic zips and fasteners, metallic threads, or glitter finishes. You may be asked to change into a gown.

Owing to the loud noises emitted by the MR system, you will be given headphones or ear plugs to protect your hearing.

If you answer YES or are uncertain regarding any of the above, please contact us on (09) 303 5966 prior to your appointment.

**USE OF YOUR IMAGES**

As a University it may be useful to use your images (without your name or other identifying details) for all or some of the following purposes -

- education and training by Centre for Advanced MRI staff
- scientific publications, reports and presentations
- University teaching
- publicity material for the Centre for Advanced MRI
- the Centre for Advanced MRI website and websites of organisations we collaborate with (e.g. Siemens the manufacturer of the machine)
- publicity materials for non-profit organisations
- television documentaries or other public interest media
- databases that may be published on the internet

I give consent for my images to be used for the above purposes provided that all details that could allow me to be identified have been removed

**I confirm that the above information is correct to the best of my knowledge.**

Signature ___________________________ Date __/__/____

Screening form checked by ___________________
Appendix H: Action Research Arm Test

ACTION RESEARCH ARM TEST

Set up
- Remove items from box, put it upright, with handle up and align board
- Position patient in chair, with back against the back of the chair
- Fingertips of patient’s hand passively extended, palm down
- Unaffected arm should reach the top of the box when upright (handle up)

Script
- Always start and finish each task with your AFFECTED hand palm down, on the table
- I’ll count you down by saying “3, 2, 1, Go”
- Wait until I say GO to start each task, and put your hand back down when you finish
- Try to move at your normal speed
- Try to keep your back against the chair

Timing
- Start the stopwatch as you say GO
- Stop the stopwatch when their hand returns and touches table

Scale
- 0 = no movement possible
- 1 = movement partially performed, task goal not achieved
- 2 = movement performed, but abnormally
- task goal achieved, BUT
- time limit exceeded, and/or
- patient loses contact with back of chair
- 3 = movement performed normally
- task goal achieved
- within time limit
- contacted maintained with back of chair
<table>
<thead>
<tr>
<th>Task Materials and Details</th>
<th>Hand Movement Components</th>
<th>Arm Movement Components</th>
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</thead>
<tbody>
<tr>
<td>Blocks: displace vertically to shelf</td>
<td>Hand voluntarily opens to the size of the block. Any type of grasp involving the thumb and fingers in opposition is acceptable.</td>
<td>a. Forearm is between midposition and pronation. b. Elbow flexed when first grasping object and then extends to reach top of shelf.</td>
</tr>
<tr>
<td>Cricket ball: displace vertically to shelf</td>
<td>Spherical grasp; fingers and thumb slightly flexed and abducted to the size of the ball.</td>
<td>c. Shoulder flexion to reach top of the shelf, and shoulder stabilization to maintain position as object is released onto shelf.</td>
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<tr>
<td>Sharpening stone: displace vertically to shelf</td>
<td>Lateral grip; sharpening stone is between the pad of thumb and the radial side of the index finger at or near interphalangeal joints.</td>
<td>d. Thumb and finger extension to release the object.</td>
</tr>
<tr>
<td>2 cups: pour water from one cup to another</td>
<td>Cylindrical grasp around cup</td>
<td>a. Forearm pronation to pour, then forearm supination to return cup to table. b. Thumb and finger extension to release the cup.</td>
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<tr>
<td>Alloy tubes: displace from starting plank to target plank</td>
<td>Any type of grasp, such as 3 jaw-chuck pinch, involving the pads of the thumb opposed with pads of any number of fingers in order to grasp the alloy tube.</td>
<td>a. Forearm is between midposition and pronation. b. Elbow is sufficiently extended to reach the distal target plank.</td>
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<tr>
<td>Washer: displace distally from tin to target plank</td>
<td>Pincer or 3 jaw-chuck grasp, with pads of the thumb and fingers in opposition, in order to grasp the washer</td>
<td>c. Shoulder movement and stabilization to maintain position as object is released. d. Thumb and finger extension to release tube/washer.</td>
</tr>
<tr>
<td>Ball bearing, from tin on table, vertically displaced to tin on shelf</td>
<td>Opposition of pads of ring finger and thumb, middle finger and thumb, and index finger and thumb, respectively</td>
<td>a. Forearm is between midposition and pronation. b. Elbow flexed when first grasping object, then extends to reach top of shelf.</td>
</tr>
<tr>
<td>Marble, from tin on table, displace vertically to tin on shelf</td>
<td>Opposition of pads of index finger and thumb, ring finger and thumb and middle finger and thumb, respectively</td>
<td>c. Shoulder flexion to reach top of shelf and shoulder stabilization to maintain position as object is released.</td>
</tr>
<tr>
<td>Hand from lap to various pericranial positions</td>
<td>Palmer side of hand (hand does not need to be open) reaches to back side of head, to top of head, and to mouth, respectively</td>
<td>a. Forearm pronation and supination. b. Full elbow flexion c. Shoulder abduction, flexion, and external rotation.</td>
</tr>
</tbody>
</table>

**ACTION RESEARCH ARM TEST**
<table>
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<th>Grasp</th>
<th>Time limit (sec)</th>
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</tr>
<tr>
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<tr>
<td>2.5 cm block</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 cm block</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5 cm block</td>
<td>3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ball</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stone</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each item must be picked up and placed on the coaster on the shelf
Hand must start and finish palm down on the table

<table>
<thead>
<tr>
<th>Grip</th>
<th>Time limit (sec)</th>
<th>Actual time (x.xx sec)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pour water cup to cup</td>
<td>7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.25 cm tube</td>
<td>4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 cm tube</td>
<td>4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place washer over bolt</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
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</table>

Fill one cup with water to the lower indent to be poured into the other cup
Each tube and the washer must be picked up and placed on the target peg
Hand must start and finish palm down on the table
Each bead must be picked up with the specified finger and thumb
The bead is dropped or placed into the lid on the coaster
Hand must start and finish palm down on the table

<table>
<thead>
<tr>
<th></th>
<th>Time limit (sec)</th>
<th>Actual time (x.xx sec)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small, ring and thumb</td>
<td>4.4</td>
<td></td>
<td>If 3, total = 18, go to grip</td>
</tr>
<tr>
<td>Large, index and thumb</td>
<td>3.8</td>
<td></td>
<td>If 0, total = 0, go to grip</td>
</tr>
<tr>
<td>Small, middle and thumb</td>
<td>4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small, index and thumb</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large, middle and thumb</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large, ring and thumb</td>
<td>4.1</td>
<td></td>
<td></td>
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</tbody>
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Hand must start and finish palm down on their lap

<table>
<thead>
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<th>Time limit (sec)</th>
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<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Hand behind head</td>
<td>2.7</td>
<td></td>
<td>If 3, total = 9, go to grip</td>
</tr>
<tr>
<td>Hand on top of head</td>
<td>2.7</td>
<td></td>
<td>If 0, total = 0, go to grip</td>
</tr>
<tr>
<td>Hand to mouth</td>
<td>2.4</td>
<td></td>
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**TOTAL**

out of 57
Appendix I: Upper Extremity Fugl-Meyer Assessment

**FUGL-MEVER UPPER LIMB SCALE**

Section A. Shoulder/Elbow/Forearm

<table>
<thead>
<tr>
<th>SECTION SCORE</th>
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</thead>
</table>

1. Normal reflex activity, biceps/triceps.
   0 = no reflex activity, 1 = some reflex activity, 2 = reflex activity present

   0 = two or three reflexes are markedly hyperactive
   1 = one reflex markedly hyperactive or at least 2 reflexes lively
   2 = no more than one reflex lively and no reflexes markedly hyperactive

3. Flexion synergy. With the elbow fully flexed and forearm fully supinated, ask the patient to raise their elbow out to the side.
   For each component of synergy:
   0 = no movement, 1 = movement partially performed, 2 = movement performed normally
   - elbow flexion
   - forearm supination
   - scapular elevation
   - scapular retraction
   - shoulder abduction to 90
   - shoulder lateral rotation

4. Extension Synergy. With elbow extension and pronation, ask the patient to cross their arm in front of their body toward the opposite hip.
   Score each component of synergy as for flexion synergy above.
   - elbow extension
   - forearm pronation
   - shoulder adduction
   - shoulder internal rotation

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5. Hand to lumbar spine.
   0 = no movement, 1 = movement partially performed, 2 = full range of movement

6. Shoulder flexion 0 to 90 with elbow extension
   0 = at rest arm is immediately abducted or elbow flexed
   1 = in later movement arm abducts or elbow flexes
   2 = movement performed normally

7. Shoulder flexion 90 – 180 with elbow extension
   Score as above for item 6

8. Shoulder abduction 0 to 90 with elbow extension & forearm pronation
   0 = any attempt at abduction is preceded by elbow flexion and/or forearm supination
   1 = abduction partially performed or elbow flexes/forearm supinates during movement
   2 = movement performed normally

9. Forearm pronation-supination with shoulder 0 & elbow 90
   0 = shoulder and elbow position not maintained and/or no pronation/supination
   1 = with shoulder & elbow correctly positioned, active pronation/supination even in limited ROM
   2 = movement performed normally

10. Forearm pronation/supination with shoulder flexed 30 - 90 & elbow extended
    Score as above for item 9

Section B. Wrist

Wrist can be lightly supported to maintain shoulder/elbow position if required

1. Wrist stability
   Shoulder at 0, elbow at 90, forearm fully pronated. Wrist raised to 15 dorsiflexion.
   0 = the patient cannot dorsiflex; 1 = dorsiflexion without resistance; 2 = dorsiflexion with slight resistance.

2. Wrist stability
   Shoulder flexed, elbow at 0. Wrist dorsiflexed to 15.
   Score as for item 1.

3. Rhythmic wrist movement
   Repeated smooth alternating dorsiflexion-palmarflexion, with fingers partly flexed.
   Arm in position as for item 1.
   0 = no movements; 1 = movement is not smooth and full; 2 = movement is smooth and full.

4. Rhythmic wrist movement
   Arm in position as for item 2. Movement and scoring as in item 3.

5. Wrist circumduction
   0 = no circumduction; 1 = jerky or incomplete circumduction; 2 = good circumduction.
Section C. Hand

1. Finger flexion (mass)
   0 = no flexion; 1 = some but not full flexion; 2 = full active flexion.

2. Finger extension (mass). Score as in item 1.

   Flex fingers maintaining metacarpophalangeal extension and thumb extension.
   0 = position cannot be acquired; 1 = weak grasp; 2 = grasp maintained against resistance.

4. Grasp B (“paper”). Adduct thumb to index metacarpophalangeal which is held at 0 deg.
   0 = adduction not performed; 1 = paper between thumb and index finger can be held but not when tugged; 2 = paper held against a moderate tug.

5. Grasp C. Patient holds pencil between pad of thumb opposed to index finger
   Scores: as for 4.

6. Grasp D. Patient grasps a drink can
   Scores: as for 4.

7. Grasp E. Patient grasps a tennis ball (overhand grasp)
   Scores: as for 4.
Section D. Coordination/speed  SECTION SCORE

Finger-to-nose test. Eyes shut. Ask the patient to touch their own nose then point out to the side and back to nose (extend elbow as much as possible and touch chest if nose cannot be reached). Assess quality and measure time to complete five rapid movements, out and back. Complete the non-aptic side and then paretic side.

Tremor
0 – marked tremor; 1 – slight tremor; 2 – no tremor.

Dysmetria
0 – unsystematic dysmetria; 1 – slight dysmetria; 2 – no dysmetria.

Speed
0 = affected side 6 seconds or more slower than unaffected side
1 = between 2 and 6 seconds slower
2 = less than 2 seconds slower

Full elbow extension, touch nose, repeat five times.

If more impaired, can touch chest and extend as far as possible.

FUGL-MEYER TOTAL SCORE
Out of 66

<table>
<thead>
<tr>
<th>Shoulder</th>
<th>Wrist</th>
<th>Hand</th>
<th>Coordination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aff. (s)</td>
<td>Unaff. (s)</td>
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Appendix J: Modified Ashworth Scale

Modified Ashworth Scale Instructions General information (derived Bohannon and Smith, 1987):

Place the patient in a supine position
If testing a muscle that primarily flexes a joint, place the joint in a maximally flexed position and move to a position of maximal extension over one second (count “one thousand one”)
If testing a muscle that primarily extends a joint, place the joint in a maximally extended position and move to a position of maximal flexion over one second (count “one thousand one”)
The test is done a maximum of three times for each joint.

Elbow. Start position: Elbow fully flexed, forearm neutral. Movement: Extend elbow from maximum possible flexion to maximum possible extension.

Wrist. Start position: Elbow as straight as possible, forearm pronated. Movement: Extend the patient's wrist from maximum possible flexion to maximum possible extension.

Patient Instructions:
The patient should be instructed to relax.

Score based on the classification below:

0  No increase in muscle tone
1  Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+ Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2  More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3  Considerable increase in muscle tone, passive movement difficult
4  Affected part(s) rigid in flexion or extension

Elbow extension score __________
Wrist flexion score __________
Appendix K: Permission to use published work in Chapter 6

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