Novel Assessment of the Paretic Upper Limb and Bimanual Coordination after Stroke

Harry T. Jordan

A thesis submitted in fulfilment of the requirements for degree of
Doctor of Philosophy in Medicine, the University of Auckland, 2022.

I. Abstract

Unimanual and bimanual upper limb impairments are often present after stroke and the neurophysiological mechanisms underlying bimanual coordination are not completely understood. This thesis had three separate aims. The first aim was to develop and provide preliminary evidence for an assessment that could categorise unimanual upper limb outcome after stroke quickly and remotely. The second aim was to use transcranial magnetic stimulation (TMS) to study the neurophysiological mechanisms mediating different forms of bimanual coordination in healthy adults. The final aim was to develop and use a novel behavioural assessment of coordination during bimanual task performance to evaluate bimanual coordination impairments and recovery after stroke.

Action Research Arm Test scores obtained in-person from 333 participants at three months post-stroke were retrospectively analysed to produce three assessments for quickly categorising upper limb outcome after stroke, called the Fast Outcome Categorisation after Stroke (FOCUS) assessments. The overall accuracy of one FOCUS assessment for categorising upper limb outcome when performed remotely during a videocall was 88.5% at three months after stroke (n = 26), 96.3% at six months after stroke (n = 27), and 78.4% at the chronic stage after stroke (n = 37).

One neurophysiological study used TMS and motor evoked potentials to assess corticomotor excitability (CME) and two measures of interhemispheric inhibition (IHI) in 20 healthy adults while they performed tasks with different bimanual coordination requirements. IHI was similar between tasks, but CME was higher during asymmetric movements than symmetric movements. This was the first study to measure CME and IHI during bimanually-active dynamic tasks requiring different forms of bimanual coordination.

The Bimanual Coordination After Stroke Scale (BCASS) is a novel behavioural assessment of coordination during bimanual task performance after stroke. In one study, preliminary evidence from 30 participants with chronic stroke found the BCASS was sensitive, valid, and reliable. In another study, the BCASS was used to measure initial impairments and recovery of bimanual coordination in 56 participants from one week after stroke to six months after stroke. Bimanual coordination plateaued at three months after stroke alongside unimanual upper limb motor recovery. The initial impairments and time course of bimanual coordination recovery depended on movement symmetry and goal conceptualisation of the BCASS tasks.

This thesis developed the novel BCASS and FOCUS assessments for evaluating function of the upper limbs after stroke, while also furthering our understanding of the neurophysiological mechanisms underlying bimanual coordination. These original contributions can facilitate future upper limb research after stroke.

II. Acknowledgements

I would like to acknowledge my colleagues, friends, and family who have supported me throughout this PhD:

- My primary supervisor Professor Cathy Stinear for her guidance and constant patience over the years, as well as my co-supervisors Professor Winston Byblow and Professor Alan Barber for their expert advice.
- My advisors Dr Marie-Claire Smith and Dr Shailesh Kantak for their advice and support.
- My colleagues in the Clinical Neuroscience Lab and Movement Neuroscience Lab who help me every day, in particular Olivia Norrie, Ben Scrivener, Phoebe Ross, Ben Chong, and Miriam Schrafl-Altermatt for their assistance with the experiments of this thesis.
- All my participants who generously gave up their time to take part in the experiments, in particular the participants with stroke and their families who continue to motivate me and my work.
- My friends who have encouraged me throughout this PhD and helped me take much-needed breaks from the grind.
- The Toronto Raptors for winning an NBA championship in 2019.
- Finally, I'd like to thank my parents Elizabeth and Gary, as well as my brothers Michael and Steven, for their continued love and support throughout this journey.

III. Preface

This thesis had three separate aims. The first aim was to develop and provide preliminary evidence for an assessment that could categorise unimanual upper limb outcome after stroke quickly and remotely. The second aim was to use transcranial magnetic stimulation (TMS) to study the neurophysiological mechanisms mediating different forms of bimanual coordination in healthy adults. The final aim was to develop and use a novel behavioural assessment of coordination during bimanual task performance to evaluate bimanual coordination impairments and recovery after stroke.

The above aims highlight the broad scope of this thesis as it investigated unimanual and bimanual upper limb function after stroke, as well as including both clinical and neurophysiological assessments. Moreover, the experimental studies of this thesis included healthy younger and older adults as well as people at the acute, subacute, and chronic stages after stroke.

This thesis contains seven introduction chapters, five experiments, and a final discussion chapter. These are compiled into three parts that address the study aims in order and each contain four chapters. Chapters 1 and 2 provide an overview of stroke and its effects on the upper limbs. Chapter 3 details the introduction of several assessments for quickly categorising upper limb outcome after stroke, and Chapter 4 provides preliminary prospective evidence using one of these assessments remotely during a videocall with people after stroke. The second part of this thesis begins with Chapter 5 which provides an overview of bimanual coordination. Chapter 6 briefly describes several theories of motor control before discussing different forms of bimanual coordination in healthy adults. Chapter 7 provides an overview of

TMS. Chapter 8 details a study using TMS to investigate interhemispheric inhibition in healthy adults performing tasks with different bimanual coordination requirements. The final component of this thesis starts with Chapter 9 describing how stroke affects bimanual coordination. Chapter 10 provides an overview of bimanual upper limb assessments that are currently used after stroke. Chapters 11 and 12 detail separate studies using a novel behavioural assessment of coordination during bimanual task performance with people at the subacute and chronic stages after stroke, respectively.

IV. Table of Contents

V. List of Tables

VI. List of Figures

1 Stroke

Stroke is clinically defined as an abrupt impairment in neuronal function due to an interruption of blood supply (1). Worldwide there are over 15 million new strokes each year and it is the third leading cause of death and disability (2). The burden of stroke has intensified over the past few decades with the incidence of stroke and the total number of disability-adjusted life years lost due to stroke increasing 70% and 36% respectively between 1990 to 2019 (3). Currently one in four people is expected to experience a stroke in their lifetime (3).

Approximately 9000 people in New Zealand experience a stroke every year, and there are approximately 50,000 New Zealanders currently living with the effects of a stroke (4). The age-adjusted stroke incidence in New Zealand has been decreasing the past few decades but the total number of people living with the effects of a stroke is expected to increase in the upcoming decades (5, 6). Much of the economic burden of stroke comes from the chronic disability experienced by people with stroke, with annual healthcare costs of approximately $NZ 700 million (4). This cost is projected to rise to $NZ 1.7 billion by 2038 as the total number of people living with the effects of a stroke is expected to increase by 60% between 2020 and 2038 due to a growing and aging population (5).

1.1 Types of Stroke

A stroke is broadly classified as ischaemic or haemorrhagic depending on the underlying pathophysiology. Ischaemic stroke accounts for 82% of all strokes in New Zealand and 62% of strokes globally (3, 7). Ischaemic stroke is defined as brain cell death due to a lack of oxygen (8). Ischaemia is initially caused by the obstruction of a blood vessel that leads to a reduction in blood flow. This results in inadequate oxygen and nutrients reaching brain tissue supplied by the blocked blood vessel, and cellular energy stores begin to deplete as a consequence (9). This cascade of events culminates in the death of brain tissue via several pathways such as glutamate excitotoxicity, inflammation, and apoptosis. The extent and consequences of damage to brain tissues depends on the duration, severity, and location of the ischaemia.

Ischaemic stroke can be subdivided using several classification systems. The Oxfordshire Community Stroke Project differentiates ischaemic stroke into four categories based on the presenting symptoms (Table 1.1) (10). The Oxfordshire Community Stroke Project correctly predicts the site of brain infarction in approximately 75% of people when established using magnetic resonance imaging or computed tomography (11, 12).

One condition worth briefly mentioning is a transient ischaemic attack (TIA). A TIA is defined as a transient episode of neurological dysfunction caused by ischaemia without acute infarction (8). TIAs were historically defined as an ischaemic event lasting less than 24 hours, however this definition has been expanded because 25 – 50% of people who have a TIA have evidence of cerebral infarction (1). Understanding and treating TIAs is important as 8% of people who have a TIA also experience a stroke in the following three months (13, 14). Increased awareness to urgently recognise and treat TIAs in the past decade though has led to a reduction in the risk of recurrent stroke (15).

Table 1.1. Presenting symptoms for categories of ischaemic stroke defined by the Oxfordshire Community Stroke Project classification system (10).

Ischaemic Stroke Categories	**Presenting Symptoms**
Total anterior circulation infarct (TACI)	All three of the following: • Unilateral motor weakness, for example in the upper or lower limb • Homonymous hemianopia • Higher cerebral dysfunction, for example dysphasia or visuospatial disorder.
Partial anterior circulation infarct	Two of the three presenting symptoms for a TACI diagnosis
Lacunar infarct	One of the following: • Pure motor symptoms • Pure sensory symptoms • Sensorimotor symptoms • Ataxic hemiparesis
Posterior circulation infarct	At least one of the following: • Bilateral motor deficits • Bilateral sensory deficits • Cranial nerve palsy with contralateral motor and/or sensory deficits • Cerebellar dysfunction without ipsilateral long-tract deficit • Disorder of conjugate eye movement • Isolated homonymous hemianopia

Haemorrhagic stroke accounts for 12% of all strokes in New Zealand and 38% of strokes globally (3, 7). A haemorrhagic stroke is caused by the rupture of a cerebral blood vessel, resulting in a collection of blood within brain tissue (16). This accumulation of blood increases swelling and intracranial pressure, leading to brain tissue damage. Secondary ischaemic damage can also occur following a haemorrhagic stroke due to compression of local blood vessels, failed autoregulation, elevated intracranial pressure, and lowered blood pressure (17). Prognosis from a haemorrhagic stroke is generally worse than ischaemic stroke and depends on the volume and location of the blood within brain tissue, as well as the extent of its expansion in the first day post-stroke (18).

1.2 Stroke Risk Factors

Stroke risk factors can be divided into those which are modifiable and those which are non-modifiable. The leading modifiable risk factor for both ischaemic and haemorrhagic stroke is hypertension which can lead to atherosclerotic plaques that can encroach into or block the lumen of arteries, or which can weaken the artery walls and increase the likelihood of rupture (19). Lowering blood pressure is the most important intervention for both primary and secondary stroke prevention. For example, reducing systolic blood pressure by 10 mmHg lowers the risk of a first-time stroke by 27% in hypertensive patients (20). One issue is that 20 – 70% of people with hypertension are unaware of it, depending on the country of origin (20-23). Hyperlipidaemia is another modifiable risk factor. Higher levels of total cholesterol are associated with an increased risk of ischaemic stroke because of atherosclerotic plaque deposits in arterial walls (24). These plaques contribute to hypertension by stiffening the artery walls but can also rupture, resulting in clots that travel to the brain and cause an ischaemic stroke (25). Diabetes mellitus type 2 also increases the risk of stroke by accelerating atherosclerotic damage to blood vessels and is projected to become a more significant problem in the future (26). For example, the prevalence of diabetes mellitus type 2 in the United States of America is projected to increase by 54% between 2015 and 2030 (27). Hypertension, hyperlipidaemia, and diabetes mellitus are all modifiable risk factors that interact to further increase the likelihood of stroke (28).

Three main lifestyle choices are also modifiable stroke risk factors. The first is cigarette smoking with a dose-response relationship between smoking and stroke (29). Smoking is also a risk factor for dyslipidaemia and diabetes mellitus type 2 (30, 31). The prevalence of smoking has decreased in most countries over the last decade but is still a significant issue in New Zealand (32). Obesity is a second important lifestyle factor. The risk of ischaemic stroke is three times higher in obese people and obesity itself is a significant risk factor for hypertension, dyslipidaemia, and diabetes mellitus type 2 (30, 31, 33, 34). Finally, heavy alcohol consumption is associated with an increased risk of stroke (35, 36).

The second type of risk factors are non-modifiable, the most important of which is age. Stroke incidence increases with age, and older people have higher stroke mortality rates (37-40). Sex is another non-modifiable risk factor. Stroke incidence is greater for males than females among young adults, but females overall have a greater risk of stroke and worse outcomes at older ages due to a higher life expectancy in women (41). Ethnicity is a third non-modifiable risk factor as Māori and Pacific people as well as African Americans and Hispanics have higher rates of stroke compared to Caucasians, while Asians have lower rates compared to Caucasians (42-44). A final non-modifiable risk factor that has seen increasing interest is genetics. Several genetic disorders have been associated with ischaemic stroke. For example, 11% of people with sickle cell anaemia experience a stroke by the age of 20, while hereditary cerebral amyloid angiopathy increases the likelihood of a haemorrhagic stroke (45, 46).

1.3 Ethnic Inequities in Stroke in New Zealand

Stroke inequities are present in New Zealand for Māori and Pacific peoples, who make up 17% and 8% of the total population respectively (7). Māori and Pacific peoples have experienced a slower decline in stroke incidence compared to other ethnicities, and the mean age of first stroke in Māori and Pacific peoples is 15 years younger than in New Zealand Europeans (6, 7). There is a complex interaction of factors that leads to increased stroke incidence in Māori and Pacific peoples. Māori and Pacific peoples have higher rates of modifiable risk factors such as heart disease, hypertension, diabetes, and smoking compared to New Zealand Europeans, and are more disadvantaged on numerous socioeconomic indicators that have been associated with higher rates of stroke (7, 47, 48).

Māori and Pacific peoples in New Zealand also experience worse outcomes from stroke compared to other ethnicities. Māori have a higher mortality rate in the first-year post-stroke compared to New Zealand Europeans (7, 49). Māori and Pacific peoples are more likely to be functionally dependent at three and twelve months after stroke and have more self-reported problems with mobility and self-care tasks compared to New Zealand Europeans (7). Ethnicities other than New Zealand Europeans are also more likely to have cognitive impairments five years after stroke (50). One cause of these ethnic inequities is that Māori are more likely to live rurally and are less likely to be financially self-sufficient after stroke (7, 51). Living rurally and lower socioeconomic status in general have been associated with poorer stroke outcomes (47, 52). Reducing these inequities in stroke occurrence and outcome should be a high priority for stroke care in New Zealand. Factors such as increasing cultural support offered to Māori and Pacific peoples and ensuring they receive appropriate acute stroke care interventions, as well as improvements with larger issues such as institutional racism and intergenerational trauma, will help reduce these inequities (7).

1.4 Outcomes from Stroke

Overall outcomes after stroke can vary greatly. Approximately 54% of strokes lead to death but the global mortality rate has decreased from 142 per 100,000 people in 1990 to 85 per 100,000 people in 2019 (3, 53). The mortality rate in New Zealand has similarly declined from 56 per 100,000 people in 1990 to 26 per 100,000 people in 2015 (49). The decline in mortality rate results from improvements in medical care both prior to and immediately after stroke (54). Developed and developing countries have experienced different trends for the total number of deaths by stroke. There has been a 20% decline in total stroke deaths in younger adults between 1990 and 2013 in developed countries, but a 37% increase in developing countries (53). The global annual number of deaths from stroke is projected to increase from 6.5 million in 2015 to 7.8 million in 2030 (55).

The decrease in stroke mortality rate over the past few decades has caused an increase in the number of people living with the effects of stroke. As a result, the number of people with lasting impairments after stroke has risen over the past few decades (3). These impairments often do not resolve as approximately 20 – 50% of people who survive a stroke are still functionally dependent on others for activities of daily living (ADLs) years later (56-58). In New Zealand, 32% of people who survive a stroke are functionally dependent five years later (50).

One of the most common issues after stroke is upper limb impairment, which has a strong influence on a person's functional independence and quality of life. The next chapter will discuss the effects of stroke on the contralesional and ipsilesional upper limb.

2 Upper Limb Motor Deficits after Stroke

Stroke has numerous debilitating effects on the upper limb. It is important to distinguish between function and impairment when discussing post-stroke upper limb disabilities because many studies use these terms interchangeably. The International Classification of Functioning, Disability and Health defines body function as physiological functions of the body system, whereas impairments are a loss of body function (59). Studies more commonly refer to function as the ability to complete a task with movements relating to everyday life, and motor impairment as a loss of motor control or strength. We will refer to function and impairment using these latter and more practical definitions. It should be noted that although function and impairment are related, it is possible to improve in one aspect but not the other. For instance, a patient may recover from impairment through increased range of movement in their upper limb, but it may not translate to better functional task performance.

Another clarification to be made is between recovery and compensation. Recovery is defined as a return of pre-stroke movement patterns to successfully complete a task (60). In contrast, compensation involves the use of alternative movement patterns for task completion. An example of upper limb compensation is the use of shoulder protraction and trunk movements during reaching. Compensation can be necessary and help in the short term after stroke but can cause long-term problems such as pain and reduced joint range of motion in the upper limb (61). Ideally all patients with stroke would experience full upper limb recovery and not rely on compensation, but this is not possible for many patients.

2.1 Contralesional Upper Limb Deficits and Recovery

The terms contralesional and ipsilesional refer to the opposite and same side of the body as the stroke hemisphere, respectively. For example, in someone with left-hemisphere stroke, the contralesional and ipsilesional upper limb refer to the right and left upper limb, respectively. Upper limb motor impairments after stroke predominantly occur in the contralesional limb because limbs are primarily controlled by the contralateral hemisphere (62). Impairment severity can range from very mild weakness to complete upper limb paralysis and can include a decrease in muscle tone, muscle power, and manual dexterity (63). These upper limb impairments can negatively impact a person's functional independence as they find it more difficult to complete everyday activities with their contralesional upper limb (64, 65).

It is difficult to estimate the prevalence of upper limb weakness early after stroke because of the wide range of assessments used to measure it (66). One of the most frequently cited studies reported approximately 70% of 421 patients had upper limb weakness in the first 24 hours after stroke using the Scandinavian Stroke Scale (67). Two more recent studies with samples of 642 and 845 patients reported upper limb weakness in just under 50% of patients when assessed within three days after stroke using the arm component of the National Institutes of Health Stroke Scale (NIHSS) and the Modified Motor Assessment Scale (68, 69). One study explored whether the assessment used to measure upper limb weakness, and the timing of the assessment, contribute to the range of reported prevalence (66). Using the arm component of the NIHSS, 57% of 546 patients had weakness on initial presentation to hospital, and this decreased to 49% by 24 hours post-admission. Upper limb weakness was present in 40% of 621 patients at two days post-stroke using the Shoulder Abduction and

Finger Extension (SAFE) score, which is the sum of the Medical Research Council strength gradings for shoulder abduction and finger extension. There are also differences in the extent of reported upper limb weakness with 48% and 38% of patients at admission and 24 hours post-admission, respectively, having severe upper limb weakness defined as a score of 3 or 4 on the arm component of the NIHSS (66). When using the SAFE score at two days post-stroke though 65% of patients had severe upper limb weakness, which was defined as a score of 0 – 4 out of 10. Together these studies indicate that contralesional upper limb weakness occurs in approximately 40 – 70% of patients with stroke.

Some degree of motor recovery occurs for most patients who experience upper limb weakness. Several time periods are often referred to when discussing recovery. The acute stage refers to between one to seven days after stroke, the early subacute stage refers to between one week and three months after stroke, the late subacute stage refers to between three and six months after stroke, and the chronic stage refers to six months and later after stroke (70). Most recovery of contralesional upper limb weakness and function occurs during the acute and early subacute stages after stroke, with lesser gains at the late subacute and chronic stages (71-73). Small spontaneous improvements in upper limb capacity have been reported for some people up to two years after stroke (72, 74). Most recovery is thought to occur early after stroke because there is a time-sensitive window of neuroplasticity after stroke which allows greater improvements to be made compared to later times after stroke (75).

Most patients with a functioning corticospinal tract (CST) recover approximately 70% of the upper limb movement they lost soon after stroke, as measured using the Fugl-Meyer Upper Extremity assessment (71, 76). Patients without an intact CST are expected to make minimal upper limb improvements and are unlikely to regain functional use of the contralesional upper limb (71, 76, 77). An important measure of upper limb recovery is daily limb use because it captures the extent to which people with stroke use their contralesional upper limb in everyday life. Daily limb use is determined by having participants wear accelerometers all day that can detect when each upper limb is being moved as they go about their normal lives. Studies agree that everyday contralesional upper limb use recovers over a similar period as impairment and function, but there are conflicting results regarding when recovery of contralesional upper limb use plateaus. One study found the amount of contralesional limb use in daily life increased between two weeks and three months after stroke but did not comment whether increases occurred at each of four, six, and eight weeks after stroke when assessments were made (78). Contralesional upper limb use increases between three weeks and three months after stroke, but not between three and six months (79). One study that only performed assessments at three weeks and twelve months after stroke found no increase in contralesional upper limb use (80). The most comprehensive study included 67 participants and performed assessments at eight time points between two and 24 weeks after stroke, and contralesional upper limb use plateaued between three and six weeks after stroke (81). Together these studies indicate that recovery of everyday contralesional upper limb use plateaus in the first three months post-stroke. It is difficult to conclusively determine the time course of recovery though due to differences between studies in the timing of assessments.

Upper limb motor deficits persist at the chronic stage after stroke. Most people with a functioning CST recover 70% of the upper limb movement they lost due to the stroke, which means residual upper limb impairment is still present once recovery has plateaued (71, 76). Another study reported 50% of patients at six months after stroke had moderate or severe weakness (82). Patients without a functioning CST early after stroke experience very limited upper limb recovery and still have severe upper limb weakness at the chronic stage after stroke (71, 77). More specific tests have shown that deficits persist in numerous domains of upper limb movement at the chronic stage such as grip strength, finger control, abnormal motor synergies, spasticity, and unimanual reaching (83-88).

Functional upper limb deficits are also common at the chronic stage after stroke. A study of 460 participants at six months post-stroke reported 70% had some degree of functional impairment (82). Of the total sample, 16% of participants had notable upper limb function, 12% had limited function, 4% had poor function, and 38% had no function. These outcome definitions were arbitrarily chosen by the authors but do highlight that the full range of functional impairments can be present at the chronic stage after stroke. Assessments were not performed at the subacute stage and so the participants' initial deficits and recovery are not known. In a study of 131 participants, 64% had some degree of impaired upper limb function at six months after stroke (89). In a separate study, only 38% of 102 participants with severe initial upper limb impairment demonstrated function in the contralesional hand at the chronic stage after stroke, defined as a score of at least 10 on the Action Research Arm Test (ARAT) (90). Moreover, only 12% of patients with function in the contralesional hand scored full marks on the ARAT, indicating a full return of contralesional hand function. Together these studies demonstrate that functional upper limb deficits are common at the chronic stage after stroke and can range from mild to severe.

People with stroke often use their ipsilesional arm to complete daily activities due to contralesional upper limb impairment. Accelerometery studies have found that people with chronic stroke use their ipsilesional upper limb more than their contralesional upper limb in daily life (91-95). For example, one study found that participants used their contralesional upper limb only 35% as much as the ipsilesional upper limb during daily life at one year after stroke (80). Similarly, people with stroke often prefer to use their ipsilesional upper limb for simple reaching tasks when given the choice of which upper limb to use (96, 97). This phenomenon has been termed ‘learned non-use’ and occurs for numerous reasons such as pain, fatigue, ease of use, and potentially negative consequences resulting from the patient using their contralesional limb (63). Apraxia, neglect, attention, and self-efficacy also influence contralesional upper limb non-use (98). Learned non-use is a problem as it can lead to people not using their contralesional upper limb during everyday life at the early subacute stage after stroke, and may hinder recovery (99). It has been found that people with stroke who use their contralesional upper limb often in everyday life perform better on measures of arm function (93, 95, 100, 101). It is therefore critical that the contralesional upper limb is actively used at the early subacute stage after stroke to increase the likelihood it can be used effectively once upper limb recovery has plateaued.

2.2 Ipsilesional Upper Limb Deficits and Recovery

Deficits can also be present in the ipsilesional upper limb after stroke. Reduced ipsilesional hand dexterity has been reported as early as one day post-stroke (102). However, ipsilesional upper limb deficits in the first few weeks post-stroke are less prevalent than contralesional deficits (103-105). Many studies use kinematics and video recording to determine the prevalence of ipsilesional upper limb deficits because clinical assessments are not always sensitive enough to detect mild deficits. For example, only seven of 106 participants with contralesional upper limb deficits scored less than perfect on the ARAT using their ipsilesional upper limb a few weeks after stroke (104). A study of 227 participants with stroke reported 37% had ipsilesional deficits compared to healthy controls within two weeks post-stroke when using a robotic device to measure movement kinematics (103). Two behavioural assessments, the Chedoke-McMaster Stroke Assessment and Purdue Pegboard Test, identified only 19% and 29% of the same 227 participants as having ipsilesional deficits, respectively (103). Another study reported no ipsilesional deficits at nine weeks after stroke based on the Box and Block Test (BBT) and the Nine-Hole Peg Test (9HPT), however a motion recording system showed their ipsilesional reaching movements were still less smooth compared to controls (105). Collectively these studies demonstrate that ipsilesional upper limb deficits can be present soon after stroke but are less common and severe than contralesional deficits.

Ipsilesional upper limb recovery occurs over the same period as contralesional recovery. A longitudinal study with 19 participants found performance on the BBT and 9HPT reached the level of aged-matched controls at nine weeks after stroke (105). A larger study including 87 participants with stroke measured recovery of hand dexterity using two assessments as well as the recovery of grip strength (106). Hand dexterity measured using the BBT improved between rehabilitation admission and six weeks after stroke, and between six weeks and six months after stroke. Conversely, hand dexterity measured using the functional dexterity test plateaued by six weeks after stroke. Grip strength improved between six weeks and six months post-stroke but not earlier. Another study with 72 participants reported recovery of proximal and distal ipsilesional upper limb weakness plateaued by one month post-stroke when measured using the Manual Function Test (107). Improvements in the speed and accuracy of ipsilesional reaching movements typically plateau by three months after stroke

(105, 108). Ipsilesional upper limb recovery therefore plateaus within the first few months after stroke, but the exact time course can depend on the assessment used.

Ipsilesional upper limb deficits can still be present at the chronic stage after stroke. Participants with stroke using their ipsilesional upper limb have performed worse than age-matched controls across a variety of clinical assessments measuring dexterity and grip strength (106, 109-111). Impaired planning, preparation, and execution of ipsilesional upper limb reaching have also been reported in participants with stroke compared to healthy controls (87, 112). One study found only four of 68 participants with stroke rated their ipsilesional upper limb recovery as incomplete at one year after stroke (106). In the same study, 49% and 32% of participants did not reach normative data levels for hand dexterity and gip strength, respectively. A dissonance between self-reported and clinically assessed ipsilesional impairments may be present at the chronic stage after stroke.

Two factors have been found to influence the severity of ipsilesional impairments at the chronic stage after stroke. The first is whether the stroke affects the left or right hemisphere. Behavioural assessments of dexterity and muscle strength have found people with left-hemisphere stroke have worse ipsilesional deficits compared to those with right-hemisphere stroke (109, 110). These deficits can be particularly challenging because ipsilesional upper limb impairments correlate strongly with functional independence in participants with severe contralesional impairment and left-hemisphere stroke but not right-hemisphere stroke (113). Since approximately 90% of adults are right-handed, most people with left-hemisphere stroke need to learn to use their non-dominant hand to perform many tasks (114). However, people with right-hemisphere stroke experience greater impairments than those with left-hemisphere stroke on measures such as final position accuracy and position variability during ipsilesional reaching (112, 113). The more severe deficits with positional accuracy in people with right-hemisphere stroke support the hypothesis that the right hemisphere is specialised for control of final steady-state position (115). The hypothesis of hemispheric specialisations is discussed in more detail in Chapter 6.

The second factor influencing ipsilesional upper limb impairment is the degree of contralesional impairment. Several studies have reported that more severe contralesional upper limb impairments correlate with more severe ipsilesional impairments (109, 116), although another study using different clinical assessments reported no such correlation (110). One of these studies reported the correlation between contralesional and ipsilesional upper limb impairments is stronger in people with left-hemisphere stroke (116). Together these studies illustrate that the hemisphere affected by stroke and the extent of contralesional impairment partially determine the degree of ipsilesional impairment at the chronic stage after stroke.

Upper limb impairments and recovery are evaluated clinically using standardised behavioural assessments that are repeated at several time points after stroke. Most common behavioural assessments are performed in-person and involve the assessor observing and scoring the participant in real-time. The COVID-19 pandemic and the increased affordability of smartphones over the past decade has increased the desire for assessments that can be performed remotely during a videocall. Several remote upper limb assessments have been proposed that are based on common in-person behavioural assessments or are novel and designed to be performed remotely (117-120). However, the use of remote upper limb assessments has yet to become widespread in stroke rehabilitation studies. The following chapter describes the development of an assessment that can be performed remotely during a videocall for categorising upper limb outcome after stroke.

3 Fast Outcome Categorisation of the Upper Limb after Stroke – FOCUS

This chapter was published as an original article in Stroke (2021).

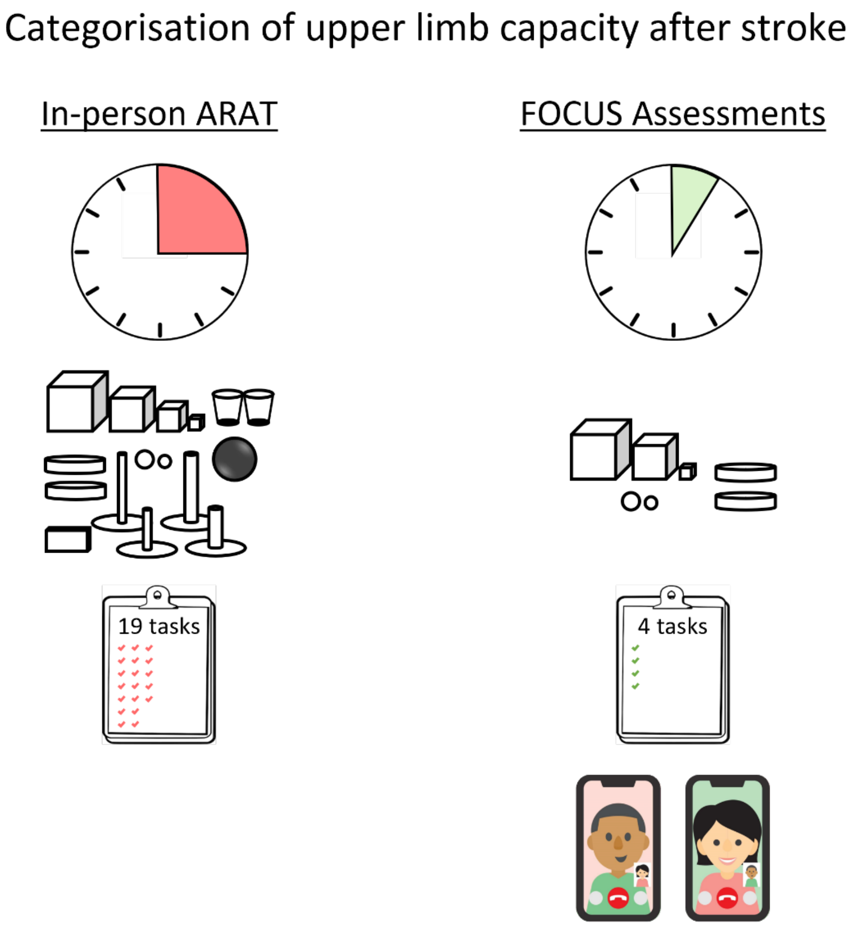
Jordan HT, Che J, Byblow WD, Stinear CM. Fast Outcome Categorization of the Upper Limb After Stroke. *Stroke*, DOI: 10.1161/STROKEAHA.121.035170.

3.1 Abstract

The Action Research Arm Test (ARAT) has been used to classify upper limb motor outcome after stroke in one of three, four, or five categories. The COVID-19 pandemic has encouraged the development of assessments that can be performed quickly and remotely. The aim of this study was to derive and internally validate decision trees for categorising upper limb motor outcome at the late subacute and chronic stages of stroke using a subset of ARAT tasks. This study retrospectively analysed ARAT scores obtained in-person at three months post-stroke from 333 patients. In-person ARAT scores were used to categorise patients' three-month upper limb outcome using classification systems with three, four, and five outcome categories. Individual task scores from in-person assessments were then used in classification and regression tree (CART) analyses to determine subsets of tasks that could accurately categorise upper limb outcome for each of the three classification systems. The decision trees developed using three-month ARAT data were also applied to in-person ARAT data obtained from 157 patients at three months post-stroke. The CART analyses produced decision trees requiring two to four ARAT tasks. The overall accuracy of the cross-validated decision trees ranged from 87.7% (SE 1.0%) to 96.7% (SE 2.0%). Accuracy was highest

when classifying patients into one of three outcome categories, and lowest for five categories. The decision trees are referred to as Fast Outcome Categorisation of the Upper Limb after Stroke (FOCUS) assessments and they remained accurate for six-month post-stroke ARAT scores (overall accuracy range 83.4% – 91.7%). A subset of ARAT tasks can accurately categorise upper limb motor outcomes after stroke. Future studies could investigate the feasibility and accuracy of categorising outcomes using the FOCUS assessments remotely via videocall.

Graphic Abstract



Fast Outcome Categorisation of the Upper Limb after Stroke (FOCUS) assessments can accurately categorise upper limb capacity at 3-months post-stroke using a subset of tasks from the Action Research Arm Test (ARAT) and can be performed by videocall.

3.2 Introduction

The recovery of upper limb motor function is critical for patients with stroke to regain independence (64, 121). The Action Research Arm Test (ARAT) is an in-person assessment of upper limb capacity often used in stroke rehabilitation research. It is the only assessment of upper limb activity limitation recommended by international consensus for stroke rehabilitation trials (122).

The ARAT score has been used to classify upper limb outcomes after stroke in one of three, four, or five categories (Table 3.1) (77, 82, 89). Nijland et al. defined ARAT cut-off scores for three categories of upper limb outcome at six months post-stroke in a sample of 131 patients (89). These authors later defined cut-off scores for five categories of upper limb outcome at six months post-stroke in a sample of 460 patients, which included the 131 patients from the original three-category classification system (82). These five categories were used by a separate research group to characterise 38 patients who were at least one year post-stroke, but ARAT scores were binarized as < 16 or ≥ 16 for analysis (123). Stinear et al. identified four categories of ARAT score using a hypothesis-free cluster analysis of scores obtained from 40 patients at three months post-stroke (124). This group later used a cluster analysis to confirm the cut-off scores for these categories in a sample of 207 patients assessed three months post-stroke (77). These four categories have also been used by a separate research group to characterise upper limb outcome for 91 patients at three months post-stroke (125). These classification systems with three, four, and five outcome categories will be referred to as the 3-CAT, 4-CAT, and 5-CAT systems respectively.

The COVID-19 pandemic has encouraged the development of assessments that can be performed quickly and remotely because the risk of infection has made in-person clinical assessments difficult, or impossible in some circumstances. To our knowledge no attempts have been made to use a subset of ARAT tasks to rapidly categorise current motor outcome either in-person or remotely. The aim of this study was to derive and internally validate decision trees for categorising upper limb motor outcome at the late subacute (3 – 6 months post-stroke) and chronic (> 6 months post-stroke) stages of stroke using a subset of ARAT tasks. This retrospective analysis only included ARAT tasks feasible to perform and score during a videocall because we wanted to ensure the resulting Fast Outcome Categorisation of the Upper Limb after Stroke (FOCUS) assessments have the potential to be performed remotely. Rapid and potentially remote FOCUS assessments could be useful for evaluating outcomes in clinical practice, and screening potential participants for trials.

Table 3.1. Upper limb motor outcome classification systems.

Classification system	Outcome category rationale	Post-stroke data used for development	Number of outcome categories	Upper limb outcome categories (ARAT score ranges)
3-CAT	Clinical reasoning	6 months	Three	Full recovery (57) Some dexterity (10 – 56) No dexterity (0 – 9)
4-CAT	Hypothesis-free cluster analysis	3 months	Four	Excellent (50 – 57) Good (34 – 49) Limited (13 – 33) Poor (0 – 12)
5-CAT	Not stated	6 months	Five	Full (55 – 57) Notable (43 – 54) Limited (22 – 42) Poor (11 – 21) No (0 – 10)

ARAT, Action Research Arm Test

3.3 Methods

3.3.1 Participants

This is a retrospective analysis of 333 in-person ARAT assessments completed at three months post-stroke. These data are drawn from a total of five studies, three of which have been published (126-128) and two are ongoing. The data utilised in this study are available from the corresponding author upon reasonable request, and this report was prepared using the STARD guidelines (129). Consecutive patients admitted to two hospitals in Auckland, New Zealand, were identified and screened for potential participation during their acute inpatient admission. All participants provided written informed consent within 3-weeks post-stroke and all studies were approved by the regional ethics committee. The 2014 study provided data from 46 patients recruited between October 2009 and March 2012, with a first-ever ischaemic stroke and upper limb weakness, half of whom completed a one-month upper limb intervention that started within one-month post-stroke (126). The 2017 study provided data from 150 patients recruited between March 2012 and October 2015 who experienced a stroke with new upper limb weakness (127). The 2020 study provided data from 21 patients recruited between November 2015 and August 2017 with a first-ever ischaemic stroke and upper limb weakness (128). Data from 84 patients were obtained from an ongoing study that began recruitment in February 2018 and is investigating the recovery of walking in the first six months post-stroke. Data were also included from 21 patients in an ongoing study that began recruitment in May 2019 and is validating the PREP2 prediction tool in patients with subacute stroke and upper limb weakness (77). Each study had independent participant cohorts, except for 11 patients who participated in both unpublished studies and completed a single three-month ARAT assessment that is included in the present study. Data from the 2014 and 2017 studies were used to develop the outcome categories for the 4-CAT system (77). All studies had the common exclusion criteria of cerebellar stroke, residing out of area precluding follow-up assessments, and cognitive or communication impairments precluding informed consent. Patient baseline demographic and clinical characteristics are summarised in Table 3.2 and were obtained 4 days post-stroke (median, IQR 3 – 5 days).

Table 3.2. Patient characteristics at baseline.

	3-month cohort (N = 333)	**6-month cohort (N = 157)**
Age (years)		
Median age (range)	72 (18 – 98)	71 (30 – 97)
< 80 years	233 (70%)	112 (71%)
Sex		
Male	180 (54%)	78 (50%)
Ethnicity		
European	213 (64%)	108 (69%)
Māori	18 (5%)	10 (6%)
Pacific	48 (14%)	19 (12%)
Asian	52 (16%)	19 (12%)
Other	2 (1%)	1 (1%)
Stroke risk factors		
Hypertension	205 (62%)	96 (61%)
Dyslipidaemia	112 (34%)	62 (40%)
Previous cardiac history	97 (29%)	38 (24%)
Atrial fibrillation	74 (22%)	30 (19%)
Diabetes mellitus	69 (21%)	32 (20%)
Ex-smoker	70 (21%)	38 (24%)
Current smoker	35 (11%)	19 (12%)
Previous stroke		
Yes	45 (14%)	18 (12%)
Stroke type		
Total anterior circulation infarct	35 (11%)	19 (12%)
Partial anterior circulation infarct	90 (27%)	26 (17%)
Lacunar infarct	128 (38%)	79 (50%)
Posterior circulation infarct	40 (12%)	25 (16%)
Intracerebral haemorrhage	40 (12%)	8 (5%)
Hemisphere		
Right	168 (51%)	90 (57%)

Hand		
Dominant	163 (49%)	65 (41%)
Intravenous thrombolysis		
Yes	36 (11%)	13 (8%)
Endovascular thrombectomy		
Yes	12 (4%)	4 (3%)
Stroke Severity		
Mild (NIHSS score 0 – 4)	143 (43%)	56 (36%)
Moderate (NIHSS score 5 – 15)	172 (52%)	93 (59%)
Severe (NIHSS score > 15)	18 (5%)	8 (5%)
Baseline FM-UE score		
Median (range)	48 (4 – 66, n = 329)	42 (6 – 66, n = 153)
3-month FM-UE score		
Median (range)	59 (4 – 66)	58 (8 – 66, n = 145)
6-month FM-UE score		
Median (range)	N/A	60 (8 – 66, n = 156)

NIHSS, National Institutes of Health Stroke Scale; FM-UE, Fugl-Meyer upper extremity; N/A, not applicable. Stroke type classified according to the Oxfordshire Community Stroke Project classification system (10).

3.3.2 Action Research Arm Test

All ARAT assessments were performed within two weeks of the three-month due date (mean = 87 d post-stroke, SD = 6 d, range 76 – 104 d). ARAT assessments were performed in-person by trained clinical assessors. The ARAT consists of 19 tasks grouped into four subscales: grasp (six tasks), grip (four tasks), pinch (six tasks), and gross (three tasks). Each task is scored on an ordinal scale from 0 – 3 (130). A score of 3 indicates the task is completed with normal movement. A score of 2 indicates the task is completed but takes abnormally long or the patient used compensatory movements. A score of 1 indicates movement is partially performed but the task is not completed. A score of 0 indicates the participant cannot perform any part of the task. Published time limits were used to determine whether task completion was slow (131). The most difficult task in each subscale is performed first and if participants score full marks then they automatically score full marks for all other tasks in that subscale (132). The easiest task in each subscale is performed second, and if a participant scores 0 for the first two tasks then they automatically score 0 for all other tasks in that subscale. In the present study, each participant's three-month in-person ARAT score was used to categorise their upper limb outcome using each of three classification systems (Table 3.1).

3.3.3 Analysis

Classification and regression tree (CART) analyses were performed using IBM SPSS (version 26). These identified subsets of ARAT tasks that accurately classified participants into the same outcome categories as a full in-person ARAT assessment for each of the three classification systems. There were no *a priori* assumptions as CART analysis produces a decision tree without the user determining which independent variables to include, or their order in the tree.

The demographic variables included in the CART analyses were age, sex, affected hemisphere (left, right), and hand affected (dominant, non-dominant). The CART analyses included scores from 13 ARAT tasks deemed feasible with respect to mailing equipment to participants and the ease of being assessed remotely with a videocall. The tasks excluded from the CART analyses were the "ball" and "stone" tasks from the grasp subscale and all grip subscale tasks because these tasks require uncommon items that are not readily available or practical to mail to participants. Separate CART analyses including scores from all 19 ARAT tasks were also performed (Tables I - IV of Appendix 1).

All CART analyses had a minimum node size of 10 cases and the maximum tree depth was set at 4 with no pruning. “Gini” was used to minimise impurity of terminal nodes. Internal validation was performed using cross-validation with 10 sample folds (133). The decision trees produced by CART analyses were used to create a FOCUS assessment for each categorisation system. The FOCUS assessments are called FOCUS-3, FOCUS-4, and FOCUS-5 for the 3-CAT, 4-CAT, and 5-CAT systems respectively.

FOCUS assessment accuracy at the chronic stage was evaluated by applying them to in-person ARAT scores obtained from a subset of 157 patients assessed six months post-stroke (Table 3.2). All ARAT assessments were performed within two weeks of the six-month due date (mean = 183 d post-stroke, SD = 4.9 d, range = 170 to 194 d).

Overall accuracy of each FOCUS assessment at 3 and 6 months was calculated as the number of correctly predicted cases divided by the total number of cases. The positive and negative predictive values (PPV and NPV, respectively) were also calculated for each outcome category. Numbers in text represent values ± standard error.

3.4 Results

3.4.1 Three-Month In-person ARAT Categorisation

The mean three-month in-person ARAT score was 41 ± 1 (range 0 – 57). Fifty-four patients (16%) had an ARAT score < 10 and 133 patients (40%) had an ARAT score > 54. The numbers of patients in each outcome category are provided in Table 3.3.

3.4.2 CART Analysis

The CART analyses produced a decision tree for each of the 3-CAT, 4-CAT, and 5-CAT systems (Figures I - III of Appendix 1). When applied to the three-month dataset from which they were derived, the trees had an overall accuracy of 96.7 ± 1.0% for the 3-CAT system, 95.2 ± 1.2% for the 4-CAT system, and 87.7 ± 1.8% for the 5-CAT system. The decision trees were used to create the FOCUS assessments presented in Figure 3.1. The overall accuracy of the decision trees produced when all ARAT tasks were available to the CART analyses was marginally higher (range 0.3 – 0.6%) (Tables I - IV of Appendix 1).

All FOCUS assessments include 2 – 4 ARAT tasks and begin with a pinch subscale task. The "grasp 7.5 cm cube" task is present in all assessments to identify the worst functioning patients. No FOCUS assessments include tasks from the gross subscale. Individual category statistics for each classification system are provided in Table 3.3.

The FOCUS-3 assessment was the most accurate overall at derivation (96.7 ± 1.0%), and in 10-fold cross-validation (95.8 ± 1.1%) (Table V of Appendix 1). This assessment included one task from each of the grasp and pinch subscales (Figure 3.1A). The PPV was greater than 90% for each category, with 100% of people correctly categorised in the Some category.

The FOCUS-4 assessment had an overall accuracy of 95.2 ± 1.2% at derivation, and 91.0 ± 1.6% in 10-fold cross-validation (Table VI of Appendix 1). This assessment included two tasks from the grasp subscale and one from the pinch subscale, with the "pinch marble with third digit" task included twice in the assessment (Figure 3.1B). The PPV ranged from 88.8% in the Good category to 97.7% in the Excellent category.

The FOCUS-5 assessment was the least accurate overall at 87.7 ± 1.8% at derivation, and 83.5 ± 2% in 10-fold cross-validation (Table VII of Appendix 1). This assessment included three tasks from the grasp subscale and one from the pinch subscale. No patients can be categorised using a single task and participants perform one or two tasks based on their score in the first task (Figure 3.1C). The FOCUS-5 assessment had a PPV of 0% for the Poor category as it did not classify anyone into this category, and the highest PPV was 96.9% for the Full category.

Table 3.3. Individual outcome category accuracies for each FOCUS assessment at derivation.

	Accuracy (95% CI)	**PPV (95% CI)**	**NPV (95% CI)**
FOCUS-3			
Full (n = 100)	97.3% (94.9 – 98.8%)	91.7% (85.4 – 95.5%)	100% (100.0 – 100.0%)
Some (n = 179)	96.7% (94.2 – 98.3%)	100% (100.0 – 100.0%)	93.3% (88.8 – 96.1%)
None (n = 54)	99.4% (97.9 – 99.9%)	96.4% (87.2 – 99.1%)	100% (100.0 – 100.0%)
FOCUS-4			
Excellent (n = 174)	97.3% (94.9 – 98.8%)	97.7% (94.1 – 99.1%)	96.9% (92.9 – 98.7%)
Good (n = 76)	95.8% (93.1 – 97.7%)	88.8% (80.6 – 93.8%)	98.0% (95.5 – 99.1%)
Limited (n = 29)	97.9% (95.7 – 99.2%)	95.8% (76.3 – 99.4%)	98.1% (96.1 – 99.0%)
Poor (n = 54)	99.4% (97.9 – 99.9%)	96.4% (87.2 – 99.1%)	100.0% (100.0 – 100.0%)
FOCUS-5			
Full (n = 133)	97.0% (94.6 – 98.6%)	97.0% (92.3 – 98.8%)	97.0% (93.7 – 98.6%)
Notable (n = 74)	91.0% (87.4 – 93.8%)	83.3% (73.4 – 90.1%)	92.9% (89.9 – 95.1%)
Limited (n = 61)	91.3% (87.7 – 94.1%)	70.0% (61.3 – 77.5%)	98.0% (95.5 – 99.1%)
Poor (n = 11)	96.7% (94.2 – 98.3%)	0% (0 – 0%)	96.7% (96.7 – 96.7%)
None (n = 54)	99.4% (97.9 – 99.9%)	96.4% (87.2 – 99.1%)	100.0% (100.0 – 100.0%)

n = number of patients in category using in-person ARAT categorisation. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

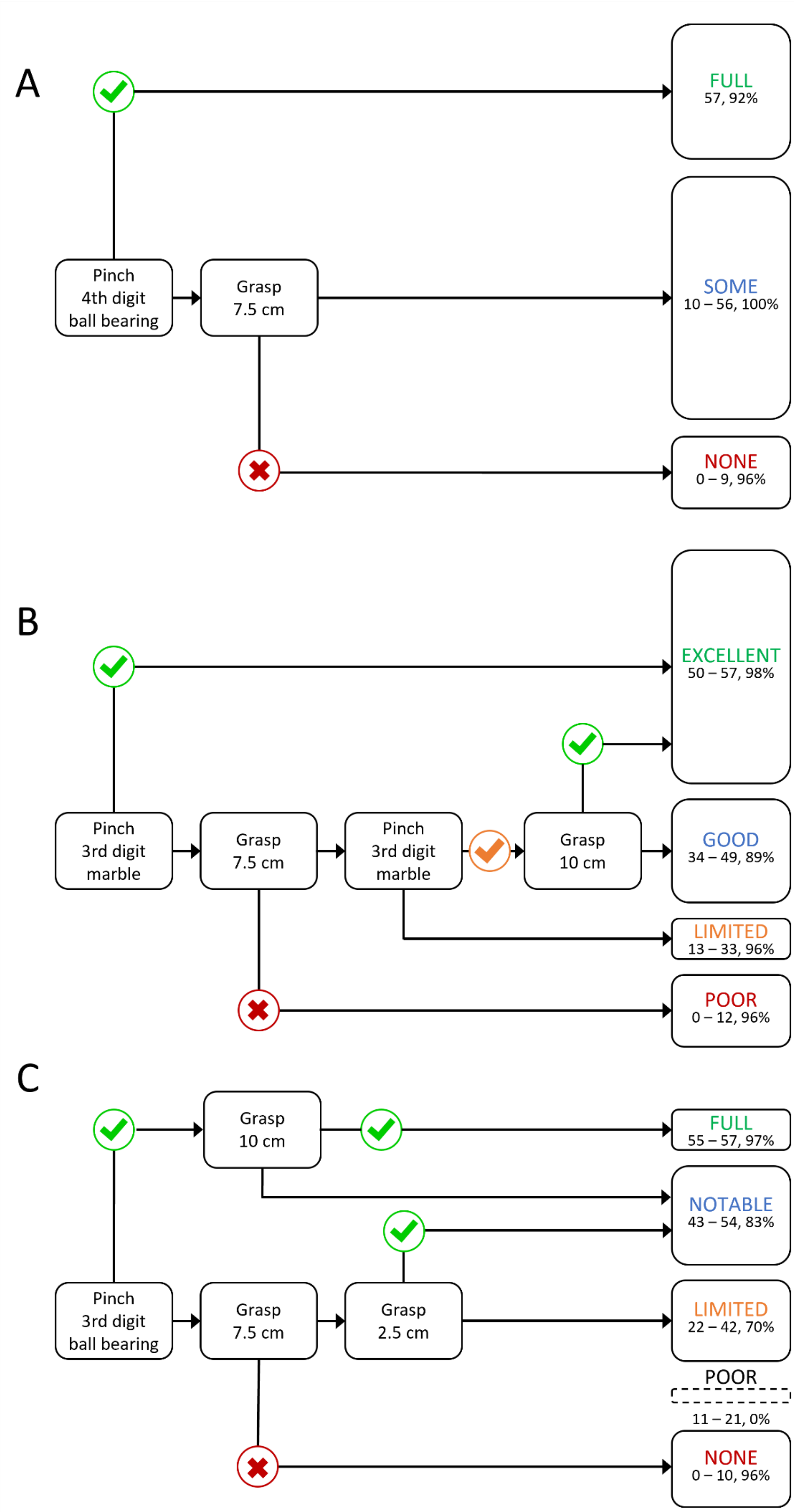

A
FULL
57, 92%
Pinch
4th digit
ball bearing
Grasp
7.5 cm
SOME
10 – 56, 100%
NONE
0 – 9, 96%
B
EXCELLENT
50 – 57, 98%
Pinch
3rd digit
marble
Grasp
7.5 cm
Pinch
3rd digit
marble
Grasp
10 cm
GOOD
34 – 49, 89%
LIMITED
13 – 33, 96%
POOR
0 – 12, 96%
C
Grasp
10 cm
FULL
55 – 57, 97%
NOTABLE
43 – 54, 83%
Pinch
3rd digit
ball bearing
Grasp
7.5 cm
Grasp
2.5 cm
LIMITED
22 – 42, 70%
POOR
11 – 21, 0%
NONE
0 – 10, 96%

Figure 3.1. The FOCUS-3 (A), FOCUS-4 (B) and FOCUS-5 (C) assessments. Each FOCUS assessment is used to categorise upper limb motor outcome for a specific classification system (3-CAT, 4-CAT, or 5-CAT). If the patient cannot ‘leave’ a box by the arrow with a tick or cross, they ‘leave’ by the alternative arrow. Green ticks indicate a score of 3 (i.e. normal task performance) for the specified task, orange ticks indicate a score of 2 or 3 (i.e. can complete the task normally or abnormally) and red crosses indicate a score of 0 (i.e. cannot perform any part of the task). The outcome boxes on the right provide ARAT score ranges and the positive predictive value for each outcome category. The outcome box size is scaled to the number of patients in each category. The dashed box in C indicates the CART analysis did not assign any person to this category.

3.4.3 Six-Month ARAT Analysis

The mean six-month in-person ARAT score was 40 ± 2 (range 0 – 57). Twenty-seven patients (17%) had an ARAT score < 10 and 67 (43%) had an ARAT score > 54. The number of patients in each outcome category are provided in Table VIII of Appendix 1.

FOCUS assessments remained accurate when applied to six-month post-stroke ARAT scores but overall accuracy was lower than for the three-month data. The overall accuracies were 91.1% for FOCUS-3, 91.7% for FOCUS-4, and 83.4% for FOCUS-5 (Tables IX - XI of Appendix 1). Each category’s PPV at six months was within 5% of the PPV at three months, with the exception of the Full category in the 3-CAT system (92% to 81%), the Limited category in the 4-CAT system (96% to 86%), and the Notable category in the 5-CAT system (83% to 66%) (Table VIII of Appendix 1).

3.5 Discussion

This retrospective analysis of ARAT scores from 333 patients collected in-person at three months post-stroke found that subsets of ARAT tasks could accurately categorise upper limb motor outcome using three classification systems. The CART analyses produced FOCUS assessments containing 2 – 4 ARAT tasks that were able to accurately categorise upper limb motor outcome at both three months and six months post-stroke. FOCUS assessments could be used to categorise upper limb outcomes rapidly and possibly remotely in clinical practice, and screen potential participants for upper limb rehabilitation trials. Further investigation will be needed to prospectively validate outcome categorisation using remote FOCUS assessments.

3.5.1 Accuracy of FOCUS Assessments

CART analyses with 13 ARAT tasks that are feasible for remote performance produced three FOCUS assessments, each with a high overall accuracy for categorising upper limb outcome. We also conducted CART analyses including all 19 ARAT tasks to see whether accuracy improved. Doing so led to one additional person being correctly classified for the 3-CAT and 4-CAT systems, and two additional people for the 5-CAT system. These results indicate that performing a subset of ARAT tasks using simple and inexpensive materials may be sufficient for accurately categorising upper limb outcome, but it remains to be determined whether accuracy is maintained when these tasks are performed remotely.

Overall accuracies for the FOCUS assessments were high, however predictive values for individual categories varied. The PPV for each category in the 3-CAT system was above 90% and this is likely helped by the fact this classification system only includes three outcome categories. The 3-CAT Full category only includes perfect ARAT scores of 57, which means it was not possible for these patients to be misclassified by the CART analysis. This is reflected in the 100% NPV for the Full category. The highest PPV in the 3-CAT system was for the Some category at 100%, and this category had by far the widest range of ARAT scores (score 10 – 56). This range means that patients with scores of 10 and 56 are in the same outcome category, despite large and meaningful differences in their upper limb capabilities. Overall, the FOCUS-3 assessment is highly accurate, but the clinical usefulness of the 3-CAT system itself is questionable.

The PPV for each 4-CAT category was above 95%, with the exception of the Good category at 89%. This is similar to findings from the study that developed the 4-CAT outcome categories, in which the Good category also had the lowest PPV (77). In the present analysis, patients in the Good category were misclassified too positively and too negatively with similar likelihood by the CART analysis. Patients in these four categories report significantly different amounts of paretic upper limb use at three months post-stroke, indicating the categories are clinically meaningful (127). The high overall accuracy and PPV for individual categories indicates the FOCUS-4 assessment has potential to be clinically useful.

The FOCUS-5 assessment had a high PPV for the top and bottom categories of the 5-CAT system, however the PPV was lower for the middle three categories than any categories in the other systems. One reason for this is the 5-CAT system has three categories for ARAT scores of 10 – 50, and patients within this range are the most difficult to predict or categorise (77, 89). Moreover, no patients were classified in the Poor outcome category (score 11 – 21). This is probably because only 11 of the 333 patients had full-ARAT scores in this range, indicating that it might not be a clinically useful category. Unfortunately there was no rationale provided for the number of categories or the ARAT ranges for each category in the 5-CAT system (82). A larger dataset containing more moderate-severely affected patients will be needed to produce a FOCUS-5 assessment that makes predictions for all 5-CAT system categories.

FOCUS assessments remained accurate when applied to in-person ARAT scores collected at six months post-stroke. Each FOCUS assessment had an overall accuracy of at least 83% when applied to the six-month data, indicating these assessments could be used with patients at later time points of stroke. However, many of the individual categories contained fewer than 30 participants and so validation is needed with a larger independent sample of patients at the chronic stage of stroke.

3.5.2 FOCUS Assessment Tasks

The only task required for every FOCUS assessment was the “grasp 7.5 cm cube” task. A score of 0 on this task was used to classify the worst outcome category in each system, indicating only patients with very low upper limb capacity were unable to complete any part of the task. This task requires more finger extension than the other grasp tasks, with the exception of “grasp 10 cm cube” which may be too difficult for even moderately affected patients to partially complete. Finger extension is important for completing tasks in the grip and pinch subscales, and so patients unable to partially complete the “grasp 7.5 cm cube” task are unlikely to able to partially complete many of the other ARAT tasks.

The first task selected for each FOCUS assessment was from the pinch subscale and a perfect score of 3 was required to categorise patients with the greatest motor capacity. This is likely because the pinch tasks are the hardest ARAT tasks as they require a high degree of individuated finger movement and control to perform (134). As a result, participants able to achieve a perfect score on the required pinch task are likely to have a high level of upper limb capacity.

The only subscale not required for any of the FOCUS assessments was the gross subscale. A Rasch analysis determined the gross tasks to be the easiest of all the ARAT tasks (134). These tasks predominantly involve active proximal movements compared to the other subscales that require some active finger and hand movement to even partially complete. Moreover, a separate Rasch analysis that collapsed tasks with scores of 0 and 1 together found two of the three gross tasks did not meet Rasch model expectations (135). Together, these findings indicate the gross subscale may not be as useful as the other subscales for categorising upper limb capacity.

3.5.3 FOCUS Assessment Applications

FOCUS assessments could have a range of applications if externally validated. These include rapid remote or in-person assessment to categorise upper limb outcome, checking the accuracy of outcome predictions made at baseline, and patient selection in future trials.

The COVID-19 pandemic has made in-person clinical assessments difficult and being able to accurately assess upper limb motor outcome remotely would provide a safe alternative. In addition to their potential for remote use, FOCUS assessments could also be used in-person to categorise motor outcome faster than the full ARAT. The FOCUS-3 assessment requires participants to perform a maximum of two tasks while the FOCUS-4 and FOCUS-5 require a maximum of three tasks. Additionally, the FOCUS-3 and FOCUS-4 assessments can categorise 33% and 48% of patients using a single task, respectively. Using FOCUS assessments could decrease assessment time when an outcome category rather than an exact ARAT score is sufficient, particularly for moderately impaired patients.

The option of remote assessments could also increase research participation because the requirement for in-person assessments may make people hesitant to participate in research. Additionally, patients are often excluded from research or lost to follow-up if they live too far away for researchers to assess in-person. Remote FOCUS assessments could help mitigate these issues and provide other benefits such as saving significant travel and assessment time and costs, even once the COVID-19 pandemic stops affecting in-person availability.

Another potential use for the FOCUS assessments is patient selection for studies. ARAT score cut-offs are often used as inclusion (136-138) or stratification (139-141) criteria for chronic stroke studies. Being able to exclude patients quickly and remotely would save significant research costs and time for both researchers and potential participants, by obviating the need for a full in-person assessment to determine eligibility. Although FOCUS assessments are not used to determine exact ARAT scores, patients may still be included or stratified depending on their outcome category. Rehabilitation trials often recruit moderately impaired patients with stroke because severely impaired patients may not be able to actively participate in the intervention while mildly impaired patients may have limited capacity for improvement. Combining the middle two and three outcome categories for the 4-CAT and 5-CAT systems, respectively, demonstrates that very few patients would be wrongly excluded as being too high or low functioning for studies selecting moderately impaired patients. A total of six patients would be incorrectly excluded using the FOCUS-4 (2.6%) and FOCUS-5 assessments (3.2%), while 11 patients (6.7%) would be incorrectly excluded using the FOCUS-3 assessment to select for the Some category. Conversely, zero (0%), five (2.2%), and four (2.9%) patients who are at the extreme functional ends would be incorrectly categorised as moderately impaired using the FOCUS-3, -4 and -5 assessments, respectively.

Together, these findings demonstrate remote FOCUS assessments have potential to quickly and accurately screen patients for study eligibility.

There are patients for whom a remote FOCUS assessment may not be appropriate. A friend or family member would likely need to be present to hold the camera so the participant can perform the tasks, and this could limit the use of FOCUS assessments with socially isolated people. Moreover, FOCUS assessments require a videocall device and some patients and their families may not know how to participate in a videocall. Cognitively impaired patients may also struggle to understand the tasks without the researcher present in-person to set up the items and demonstrate the tasks if needed. Further work is needed to validate remote use of FOCUS assessments and consider the potential effects of remote assessments on equitable access to healthcare services and research participation.

3.5.4 Strengths and Limitations

The CART analyses used a large dataset of 333 in-person ARAT scores collected three months post-stroke that included patients with the full range of motor impairment. However, median baseline FM-UE score was 48 out of 66 and 95% of patients had mild-to-moderate stroke severity based on the NIHSS. This meant that the proportion of patients with moderate-severe impairment at three and six months post-stroke was relatively low. At 3 months only 11 patients were in the Poor outcome category for the 5-CAT system, which may have prevented the CART analysis from being able to classify these patients. Another limitation is that the 3-CAT and 5-CAT systems were developed using six-month post-stroke ARAT data, and so the use of three-month data for the CART analyses may have affected the accuracies of the resulting FOCUS assessments. A strength is that the decision trees were developed using hypothesis-free machine learning methods and so no potential bias is present, other than the inclusion of 13 feasible ARAT tasks in the main analyses.

3.5.5 Future Directions

This study has developed and internally validated highly accurate tools for rapidly classifying upper limb motor outcome using three categorisation systems. However, these tools require prospective, external validation (142). This will involve performing full in-person ARAT assessments with a new cohort of stoke patients and applying the decision trees to validate and possibly recalibrate the FOCUS assessments.

The feasibility of remote FOCUS assessments remains to be determined. There are several practical aspects that need to be considered, such as which items to use and how to deliver them to participants. Cardboard cubes filled with bags of sand or uncooked rice could be used for the grasp tasks. The pinch tasks could be performed using ball bearings and marbles with shallow jar lids as the start and end targets. These items could be mailed to a participant using a large postage box, which could itself be used as the shelf for the grasp and pinch tasks. All these items are inexpensive and similar to the standardised ARAT objects (130). Other practical considerations include the camera angle and ensuring correct object and participant starting positions. In addition to feasibility, the accuracy of FOCUS assessments performed remotely needs to be determined by comparing outcome categories obtained remotely with those from a full in-person ARAT.

3.5.6 Conclusion

This retrospective analysis found that upper limb motor outcome can be accurately categorised using 2 – 4 ARAT tasks at the late subacute and chronic stages post-stroke. FOCUS assessments have potential to be performed remotely and provide an alternative to in-person ARAT assessments. Future work will be needed to prospectively validate the FOCUS assessments and determine feasibility and accuracy when performed remotely with patients with stroke.

4 Accuracy and Reliability of Remote Categorisation of Upper Limb Outcome after Stroke

4.1 Abstract

The Action Research Arm Test (ARAT) is an assessment that can be performed in-person to classify upper limb motor outcome after stroke into one of four categories. There is a growing need for assessments that can be performed quickly and remotely. The Fast Outcome Categorisation of the Upper Limb after Stroke-4 (FOCUS-4) assessment was developed via retrospective analysis but has yet to be prospectively validated for remote use. The aim of this study was to test the accuracy and reliability of the FOCUS-4 assessment for categorising upper limb outcome after stroke when administered remotely compared to an in-person ARAT. Data were collected from 26 participants at three months post-stroke (3M), 27 participants at six months post-stroke (6M), and 37 participants at the chronic stage of stroke. Participants performed an in-person ARAT and a remote FOCUS-4 assessment administered during a videocall on separate days. Participants with chronic stroke also performed a second remote FOCUS-4 assessment on a separate day. Accuracy was evaluated by comparing upper limb outcomes determined using the ARAT and FOCUS-4 assessments. Reliability was evaluated by comparing upper limb outcomes determined using the two FOCUS-4 assessments. Overall accuracy of the FOCUS-4 assessment was 88.5% at 3M and 96.3% at 6M. The overall accuracies of the first and second FOCUS-4 assessments for the chronic

stroke cohort were 78.4% and 79.4%, respectively. Both FOCUS-4 assessments classified 85.3% of participants with chronic stroke into the same outcome category. The FOCUS-4 assessment was most accurate and reliable for participants with mild or severe upper limb functional impairment, and least accurate and reliable for participants with moderate deficits. The remote FOCUS-4 assessment shows potential to be accurate and reliable for categorising upper limb outcome after stroke for participants with mild or severe upper limb functional impairment. External validation and a larger sample size including more participants with moderate upper limb functional impairments is needed to confirm the present study's findings.

4.2 Introduction

The recovery of upper limb motor function is critical for people to regain independence after stroke (64). The Action Research Arm Test (ARAT) is a 19-item in-person assessment of upper limb capacity that is often used in stroke rehabilitation research. The ARAT is the only assessment of upper limb activity limitation recommended by international consensus for stroke rehabilitation trials (122).

The ARAT has been used to categorise upper limb outcome after stroke into one of four categories: Excellent, Good, Limited, and Poor. The ARAT cut-off scores for the four categories were determined using a hypothesis-free cluster analysis (77). The same four categories have been used by two other research groups to characterise upper limb outcome for people at three months post-stroke (125, 143).

The COVID-19 pandemic has encouraged the development of assessments that can be performed quickly and remotely (144). In the previous chapter we introduced the Fast Outcome Categorisation after Stroke-4 (FOCUS-4) assessment for classifying upper limb outcome into Excellent, Good, Limited, and Poor categories. The FOCUS-4 assessment was developed with the intention to be administered and scored remotely during a videocall. However, the accuracy and reliability of the remote FOCUS-4 assessment for categorising upper limb outcome after stroke has yet to be investigated.

The current study had two aims. The first aim was to test the accuracy of the remote FOCUS-4 assessment for categorising upper limb outcome after stroke compared to the ARAT performed in-person. The accuracy of the FOCUS-4 assessment was investigated at three- and six months post-stroke as well as the chronic stage after stroke. The second study aim was to investigate the reliability of the remote FOCUS-4 assessment when used at the chronic stage after stroke. This was done by comparing the upper limb outcome determined from two remote FOCUS-4 assessments. The current study was exploratory and without *a priori* hypotheses.

4.3 Methods

4.3.1 Participants

Data came from participants in two studies. Assessments were made at three and six months after stroke (3M and 6M, respectively) in one study and at the chronic stage after stroke in a separate study. Some participants took part in both studies and so the data at each time point come from overlapping but not identical samples. Participants assessed at 3M and 6M were recruited within one week post-stroke as part of a larger prospective observational longitudinal study investigating the accuracy of PREP2 predictions made in clinical practice (77). Eligible patients admitted to Auckland City Hospital with a date of stroke between 1st May 2019 and 1st May 2021 were screened within 7 days of stroke onset. Patients were eligible for the study if they were at least 18 years old, had upper limb weakness from the stroke, and received a PREP2 prediction for upper limb motor outcome as part of routine clinical care. Patients were excluded if they lived outside the Auckland region, or if they had pre-existing conditions or cognitive impairments precluding informed consent and compliance with study assessments. This study was approved by the regional ethics committee and all participants gave their written informed consent.

Participants with chronic stroke were recruited for a prospective study comparing in-person and remote upper limb outcomes. People were eligible if they were aged 18 years or older, were at least 6 months since their most recent stroke, were still experiencing upper limb weakness resulting from stroke, and could participate in a videocall with help from a friend or family member. People were excluded if their stroke occurred in the cerebellum or if they had cognitive impairments precluding informed consent or the ability to follow study instructions. Five participants with chronic stroke and no upper limb weakness who met the other inclusion criteria were also included. This study was approved by the institutional ethics committee and all participants gave their written informed consent.

4.3.2 Procedure

Participants recruited within one week after stroke performed the ARAT in-person and the FOCUS-4 assessment remotely at three and six months after their stroke. The in-person and remote assessments were separated by at least 48 hours but for practical reasons this gap was shorter for 19 participants, including 11 participants who performed both assessments on the same day. The order of the two assessments was randomised where possible but 69% of participants who performed the ARAT and FOCUS-4 assessments on different days ended up performing the ARAT first for practical reasons. Participants with chronic stroke performed the ARAT in-person once and the FOCUS-4 assessment remotely twice. The in-person assessment was performed between the two remote assessments with at least 48 hours between assessments. The same in-person ARAT score was used as a comparison for both remote FOCUS-4 assessments. Participants at each time point also completed the Fugl-Meyer Upper Extremity (FM-UE) with their paretic upper limb during the in-person assessment to characterise the extent of upper limb impairment (145).

All assessments were performed by trained assessors. A single assessor administered all the in-person and remote assessments except for five and 11 in-person assessments at 3M and 6M, respectively. In-person assessments were completed at the University of Auckland or a location of the participant's choosing. The remote assessments were performed over a video calling application of the participant's choosing. All remote assessments were performed using mobile phones except for approximately five assessments where a tablet or laptop was used because a mobile phone was not available. Participants performed the remote assessments from a location of their choosing and the videocalls were not recorded. Participants were seated upright at a table when performing the ARAT and FOCUS-4 assessments.

Pre-stroke handedness was self-reported by participants recruited within one week after stroke. Pre-stroke handedness for participants with chronic stroke was determined using the short-form of the Edinburgh Handedness Inventory (146). Right- and left-handedness were determined by scores greater and lesser than zero, respectively.

4.3.3 ARAT

The in-person ARAT was performed using a Neuroquip ARAT test kit (Neuroquip, Cambridge, UK). The ARAT consists of 19 tasks grouped into grasp, grip, pinch, and gross subscales (130). Each task is scored ordinally from 0 – 3 and higher scores indicate better upper limb function. A score of 3 indicates the task is completed normally. A score of 2 indicates the task is completed but the patient uses compensatory movements or takes abnormally long. A score of 1 indicates movement is partially performed but the task is not completed. A score of 0 indicates the participant cannot perform any part of the task. Hierarchical scoring was used and published time limits from healthy older adults were used to determine whether task completion was abnormally long (131, 132). Participants with ARAT scores of 0 – 12 were categorised as Poor, scores of 13 – 33 as Limited, scores of 34 – 49 as Good, and scores of 50 – 57 as Excellent (147). The data collection sheet used to perform the in-person ARAT is provided in Appendix 2.

4.3.4 FOCUS-4 Assessment

A detailed description of the development of the FOCUS-4 assessment is provided in Chapter 3 and the FOCUS-4 assessment is shown in Figure 4.1. Briefly, the FOCUS-4 assessment consists of three tasks derived from the ARAT. Tasks are ordered in a decision tree and participants progress through the tree starting with the “pinch marble with third digit” task until an upper limb outcome is reached. Progress through the decision tree depends on the participant’s score on the previous task. The “pinch marble with third digit” task is present twice in the FOCUS-4 assessment but was only performed once for a single score that was used in both circumstances. The same scoring rules for the ARAT are used for the FOCUS-4 assessment and the assessor scored each task during the videocall.

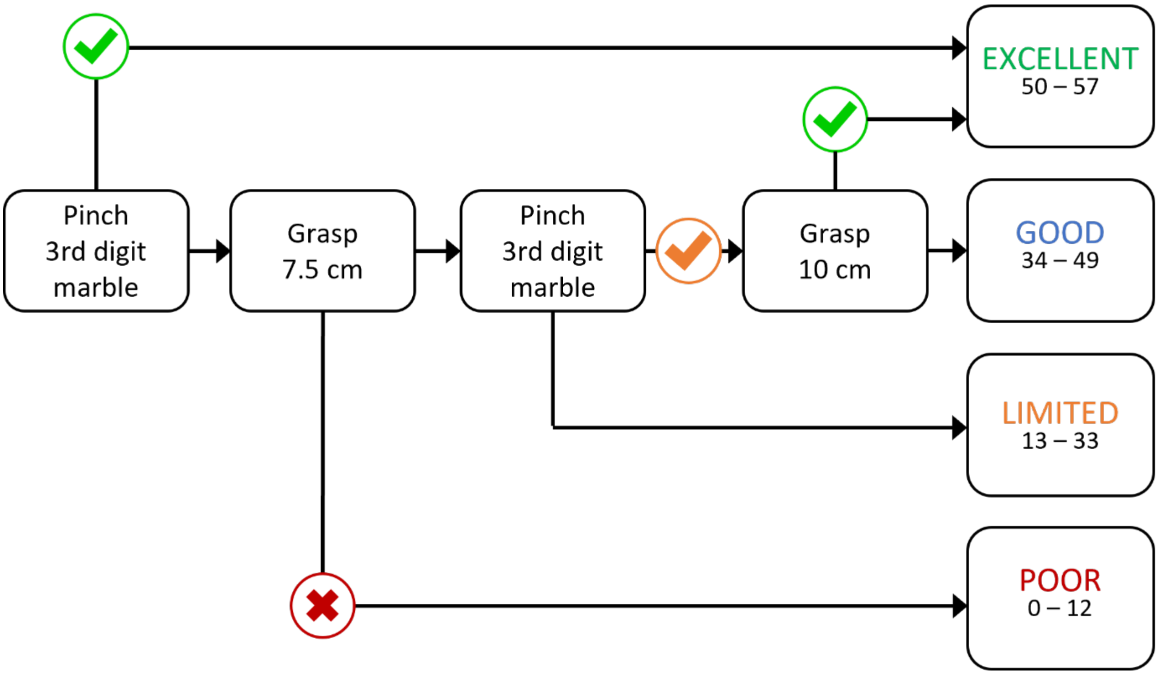


Figure 4.1. The FOCUS-4 assessment used to categorise upper limb outcome (147). If the patient cannot ‘leave’ a box by the arrow with a tick or cross then they ‘leave’ by the alternative arrow. Green ticks indicate a score of 3 for the specified task, orange ticks indicate a score of 2 or 3, and red crosses indicate a score of 0. The outcome boxes on the right provide ARAT score ranges.

The items required to perform the FOCUS-4 assessment were delivered in-person or posted to participants, and these items are displayed in Figure 4.2. Items for the FOCUS-4 assessment replicated ARAT item specifications as closely as possible (130). Cardboard boxes with edge lengths of 10 cm and 7.5 cm were filled with bags of sand and used to replicate the 10 cm and 7.5 cm wooden blocks from the ARAT, respectively. A marble and two jar lids were used for the pinch task. A marble and two jar lids were used for the pinch task. A postage box was used to replicate the ARAT table-shelf. All items were identical between cohorts except for the postage box which had a maximum height of 25 cm for the 3M and 6M assessments and 35 cm for the chronic stroke assessments.

Figure 4.2. Items provided to participants to perform the remote FOCUS-4 assessment.

A friend or family member needed to be present with the participant during the remote FOCUS-4 assessment to hold the video calling device so the participant was free to perform the tasks. A short instruction sheet was given to the participant with the delivered items to provide details about the videocall including how it would be organised, how the participant should be seated, and what camera angle should be used. A copy of this instruction sheet is provided in Appendix 3. Participants were instructed how to setup the items for each task and how to perform them during the videocall assessment. The same task-specific object positions and instructions used for the ARAT were also used for the FOCUS-4 assessment (130). A comparison of the set up for the same task performed as part of the ARAT and remote FOCUS-4 assessments is shown in Figure 4.3.

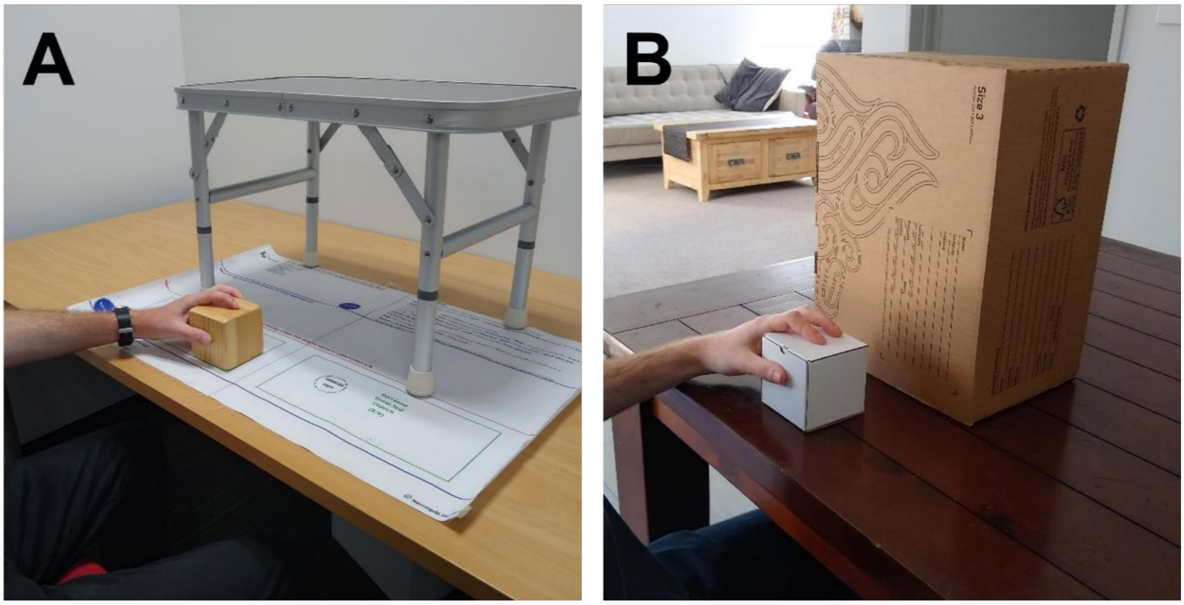


Figure 4.3. Comparison of set-up and items used for the "grasp 7.5 cm cube" task in the in-person ARAT (A) and remote FOCUS-4 assessment (B). Participants must grip the cube with their paretic hand, lift it on top of the table-shelf or postage box, then place their hand back on the table.

The tasks performed during the videocall did not follow the order of the FOCUS-4 decision tree. Rather, participants performed the 10 cm, 7.5 cm, and 2.5 cm grasp tasks in order followed by all the pinch tasks. This was done because the FOCUS-3 and FOCUS-5 assessments were also being evaluated during the videocall, but the results for these assessments are not presented here (147). The data collection sheet for the remote assessment showing the order of tasks performed is included in Appendix 4. Participants' upper limb outcome was then categorised as Excellent, Good, Limited, or Poor by applying the FOCUS-4 assessment decision tree to their individual task scores.

4.3.5 Data Analysis

Upper limb outcomes using the ARAT and FOCUS-4 assessment were only determined once both the in-person and remote assessments had been completed to minimise potential assessor bias. Overall accuracy of the FOCUS-4 assessment at 3M, 6M, and the chronic stage after stroke was calculated as the number of participants with the same outcome from the ARAT and FOCUS-4 assessments divided by the total number of participants. The positive and negative predictive values (PPV and NPV, respectively) were calculated for each outcome category. The reliability of the FOCUS-4 assessment at the chronic stage was calculated as the number of participants with the same outcome category from both FOCUS-4 assessments divided by the total number of participants. All analyses were exploratory and so no pre-specified thresholds for interpretation were used. Numbers in text represent mean values ± standard error (SE).

4.4 Results

There were 26 participants assessed at 3M, 27 participants at 6M, and 37 participants with chronic stroke. Seven people were assessed at all three time points, twenty people were assessed at both 3M and 6M, and one person was assessed at both 6M and the chronic stage after stroke. Three participants with chronic stroke were unable to complete the second FOCUS-4 assessment but were included in the comparison between the ARAT and first FOCUS-4 assessment. Participant characteristics at each time point are provided in Table 4.1.

Table 4.1. Participant characteristics in each cohort.

	Three months post-stroke (N = 26)	**Six months post-stroke (N = 27)**	**Chronic stroke participants (N = 37)**
Age			
Median (range)	73 (41 – 99)	66 (41 – 91)	65 (41 – 89)
Sex			
Male	17 (65%)	18 (67%)	25 (68%)
Female	9 (35%)	9 (33%)	12 (32%)
Handedness			
Right	22 (85%)	24 (89%)	34 (92%)
Paretic upper limb			
Dominant	14 (54%)	9 (33%)	18 (49%)
Months since stroke			
Median (range)	2.9 (2.7 – 3.4)	6.2 (5.9 – 6.9)	23.0 (7.0 – 235.0)
Days between assessments			
Median (range)	4 (0 – 14)	3 (0 – 24)	7 (2 – 65)
FM-UE score			
Median (range)	58 (8 – 66)	53 (8 – 66)	58 (12 – 66)
ARAT score			
Median (range)	48 (0 – 57)	48 (0 – 57)	50 (0 – 57)

SE, standard error; FM-UE, Fugl-Meyer Upper Extremity; ARAT, Action Research Arm Test.

4.4.1 FOCUS-4 Assessment Accuracy

The overall accuracy of the remote FOCUS-4 assessment at 3M was 88.5% (Table 4.2). The remote FOCUS-4 assessment only misclassified three out of 26 participants, and each of these three participants was misclassified into an outcome category one better than their actual outcome. Accuracy was 100% for Limited and Poor outcome categories, however there was only one participant in the Limited category.

The overall accuracy of the FOCUS-4 assessment at 6M was 96.3% (Table 4.3). All participants except one were correctly categorised by the FOCUS-4 assessment. No participants at 6M were categorised as Limited using the ARAT or FOCUS-4 assessment.

For participants with chronic stroke the overall accuracy of the first and second FOCUS-4 assessments was 78.4% and 79.4%, respectively (Tables 4.4 and 4.5). One person was misclassified by both FOCUS-4 assessments as Excellent when they were categorised as Good by the ARAT. Similarly, two people were misclassified by both FOCUS-4 assessments as Poor when they were categorised as Limited by the ARAT. The results for individual outcome categories for each cohort are shown in Tables I - IV of Appendix 5.

Table 4.2. Accuracy of the remote FOCUS-4 assessment for determining upper limb outcome compared to the in-person ARAT at three months after stroke.

		Remote FOCUS-4 assessment			
		Excellent	Good	Limited	Poor
In-person ARAT	Excellent	13	0	0	0
	Good	2	2	0	0
	Limited	0	1	1	0
	Poor	0	0	0	7
	Correct %	86.7%	66.7%	100%	100%

Table 4.3. Accuracy of the remote FOCUS-4 assessment for determining upper limb outcome compared to the in-person ARAT at six months after stroke.

		Remote FOCUS-4 assessment			
		Excellent	Good	Limited	Poor
In-person ARAT	Excellent	13	0	0	0
	Good	1	3	0	0
	Limited	0	0	0	0
	Poor	0	0	0	10
	Overall	92.9%	100%	--	100%

Table 4.4. Accuracy of the first remote FOCUS-4 assessment for determining upper limb outcome compared to the in-person ARAT at the chronic stage after stroke.

		Remote FOCUS-4 assessment			
		Excellent	Good	Limited	Poor
In-person ARAT	Excellent	18	1	0	0
	Good	1	3	2	0
	Limited	0	2	3	2
	Poor	0	0	0	5
	Overall	94.7%	50%	60%	71.4%

Table 4.5. Accuracy of the second remote FOCUS-4 assessment for determining upper limb outcome compared to the in-person ARAT at the chronic stage after stroke.

		Remote FOCUS-4 assessment			
		Excellent	Good	Limited	Poor
In-person ARAT	Excellent	19	0	0	0
	Good	1	3	0	0
	Limited	0	4	1	2
	Poor	0	0	0	4
	Overall	95%	42.9%	100%	66.7%

4.4.2 FOCUS-4 Assessment Reliability

The outcome categories determined using both remote FOCUS-4 assessments are shown in Table 4.6. Both FOCUS-4 assessments classified 85.3% of participants with chronic stroke into the same outcome category. Reliability was highest for the Excellent and Poor categories. Four of the five participants who were categorised differently between the two FOCUS-4 assessments were categorised as Limited using the first FOCUS-4 assessment and as Good using the second FOCUS-4 assessment. Five participants were classified into the same category using both FOCUS-4 assessments but into a different category using the ARAT.

Table 4.6. Comparison of upper limb outcomes determined using the first and second remote FOCUS-4 assessments with participants with chronic stroke.

		Second remote FOCUS-4 assessment			
		Excellent	Good	Limited	Poor
First remote FOCUS-4 assessment	Excellent	19	0	0	0
	Good	1	3	0	0
	Limited	0	4	1	0
	Poor	0	0	0	6

4.5 Discussion

This study investigated the accuracy of the FOCUS-4 assessment for categorising upper limb motor outcome after stroke when administered remotely. Overall, the FOCUS-4 assessment was accurate at categorising upper limb outcome at three and six months after stroke and at the chronic stage after stroke. The FOCUS-4 assessment was most accurate at categorising participants with mild or severe upper limb functional deficits but was less accurate for participants with moderate deficits. These findings provide preliminary evidence the remote FOCUS-4 assessment may be accurate at categorising upper limb outcome when used with patients with mild or severe upper limb weakness at the late subacute and chronic stages after stroke.

4.5.1 Accuracy of Remote FOCUS-4 Assessment

The remote FOCUS-4 assessment demonstrated high overall accuracy at three and six months after stroke but was less accurate at the chronic stage. The overall accuracy of the first and second FOCUS-4 assessments at the chronic stage was similar. It is possible that the lower accuracy at the chronic stage compared to three and six months after stroke was due to the extent of upper limb functional impairment in each cohort. The FOCUS-4 assessment was least accurate at classifying people into the Good and Limited categories, and 33% of participants with chronic stroke were categorised as Good and Limited using the ARAT compared to 23% and 15% of participants at three and six months after stroke, respectively. Larger sample sizes will be needed to determine whether the lower accuracy of the FOCUS-4 assessment at the chronic stage relative to earlier stages after stroke was at least partially due to the distribution of upper limb severity in the sample populations.

At each time point the FOCUS-4 assessment was most accurate for participants at the extreme ends of upper limb functional impairment. The same finding was reported during the development of the FOCUS-4 assessment using retrospective data (147). One or two participants at each time point who were categorised as Excellent with the FOCUS-4 assessment were categorised as Good with the ARAT. The misclassified participants were likely due to chance as they had no obvious shared characteristics and their total ARAT scores were spread throughout the range for the Good category.

At the other end of the impairment spectrum, the remote FOCUS-4 assessment was 100% accurate classifying participants into the Poor category at three and six months after stroke. This high accuracy is likely because participants in the Poor category have little to no voluntary movement in their upper limb and so cannot even partially complete tasks as part of either the ARAT or FOCUS-4 assessment. The remote aspect of the FOCUS-4 assessment, in addition to other slight differences between the ARAT and FOCUS-4 assessment such as the items used, were therefore unlikely to have affected task performance by participants with severe functional impairments. Two participants with chronic stroke were categorised as Poor using both the first and second FOCUS-4 assessments and were categorised as Limited using the ARAT. Both participants were categorised as Poor using the FOCUS-4 assessment because they scored 0 on the "grasp 7.5 cm cube." However, they also scored 0 for the same task using the ARAT which indicates the misclassification was not due to a problem with performing or scoring the FOCUS-4 assessment remotely. Rather, both participants scored well enough on other easier ARAT tasks, such as grasping 2.5 cm and 5 cm cubes, to exceed the ARAT score range of 0 – 12 for the Poor category. Thus, the misclassification for these patients is likely because they didn't have enough finger extension to grasp the 7.5 cm cube in the FOCUS-4 assessment but had enough movement to complete or partially complete easier ARAT tasks. Overall, the current findings indicate that upper limb outcome can be reliably determined using the FOCUS-4 assessment for participants with mild or severe upper limb motor impairment. Being able to categorise people at the extreme ends of functional impairment using a short five-minute videocall could be useful for screening potential participants for stroke studies designed to either include or exclude participants with moderate upper limb impairments.

The remote FOCUS-4 assessment was less accurate at categorising participants in the Good and Limited categories than in the Excellent and Poor categories. One potential reason is that participants in these middle categories can be misclassified into the above and below categories whereas participants in the Excellent and Poor categories can only be misclassified in one direction. Indeed, participants categorised as Good and Limited using the ARAT were misclassified into both the above and below categories with the FOCUS-4 assessment which suggests the remote FOCUS-4 assessment was not misclassifying participants in a systematic manner. The retrospective analysis for developing the FOCUS-4 assessment also found the Good category was the least accurate category to classify participants into (147). Across the three time points only five and eight participants were categorised as Limited using the FOCUS-4 and ARAT assessments, respectively. The low number of participants in the Limited category at each time point is not surprising because two other studies combined found only 20 of 140 participants had an ARAT score in the Limited category range at three months after stroke (125, 143). Similarly, among a separate sample of 3,738 ARAT scores, only 22% had a score from 11 – 42 (148). Of the seven participants with chronic stroke categorised as Limited using the ARAT in this study, only three were categorised as Limited using the first FOCUS-4 assessment. The fact only 29 of the 333 of ARAT scores used to develop the FOCUS-4 assessment were in the Limited category range may explain its low accuracy for classifying people into this category (147). Thus, a greater number of ARAT scores within the Limited range may be needed to find a more accurate task as part of the FOCUS-4 assessment for categorising participants into the Limited category. The current findings indicate the remote FOCUS-4 assessment may not be accurate for determining upper limb outcome for participants with moderate upper limb weakness and a larger sample needs to be evaluated.

4.5.2 Reliability of Remote FOCUS-4 Assessment

Reliability was determined for participants with chronic stroke by comparing the outcome categories determined using the two remote FOCUS-4 assessments. Overall, 29 of 34 participants were classified into the same category by both FOCUS-4 assessments. Four of the other five participants were categorised as Limited with the first FOCUS-4 assessment and Good with the second FOCUS-4 assessment. This could indicate participants perform better during the second FOCUS-4 assessment due to increased task familiarity. An alternative but not mutually exclusive explanation is day-to-day fluctuations in paretic upper limb capacity.

All 24 participants with chronic stroke who were categorised as Excellent or Poor with the first FOCUS-4 assessment were also categorised the same with the second FOCUS-4 assessment, although two of these participants were misclassified as Poor using both FOCUS-4 assessments. The reliability results align with the accuracy results and indicate that participants with mild and severe upper limb impairment are the easiest to categorise using the FOCUS-4 assessment while participants with moderate upper limb functional impairment are the most difficult.

4.5.3 Limitations, Strengths, and Future Directions

This study had several limitations, one being the relatively small sample sizes at each time point. Additionally, the distribution of functional impairment was skewed towards the extremes as most participants had mild or severe upper limb deficits. A third limitation is that the FOCUS-4 assessment tasks were not performed in the exact order as intended using the decision tree structure, and it is uncertain whether there are any effects of task order on the present results. One final limitation is the potential for bias because most participants were assessed by the same person for the in-person and remote assessments.

This study also had strengths. One strength is that the remote FOCUS-4 assessment demonstrated high overall accuracy at three separate time points after stroke. This includes three months after stroke, which is when upper limb outcome is often categorised using the ARAT because it is recommended that all stroke intervention trials include an assessment at three months after stroke regardless of the intervention or primary outcome (122, 124, 125, 143). Another strength is that participants with chronic stroke had at least 48 hours between assessments to reduce any practice effects, although this was not always feasible with participants at three and six months after stroke. Lastly, interrater variance was minimised by having the same assessor perform almost all the remote and in-person assessments.

The results from the current study reveal several future directions. Most importantly, the accuracy of the remote FOCUS-4 assessment for determining upper limb outcome needs to be tested with a larger number of participants and particularly those with moderate upper limb functional impairment. FOCUS-4 assessment reliability remains to be determined at three and six months after stroke. External validation of the FOCUS-4 assessment is also still required to assess its reproducibility and generalizability in other environments (149). The feasibility of using remote upper limb assessments with people with stroke could also be investigated further to identify which people with stroke are most suitable for FOCUS-4 assessment and how remote assessments could be made more accessible. Finally, it remains to be determined whether performing tasks in the intended order using the decision tree structure affects accuracy of the remote FOCUS-4 assessment.

4.5.4 Conclusion

This study demonstrated the remote FOCUS-4 assessment could be used to accurately categorise upper limb outcome for people after stroke with mild or severe upper limb motor impairments. Future research is needed to confirm the current findings in a larger group of participants, particularly those with moderate upper limb motor impairments.

The remaining two components of this thesis will move on from unimanual stroke assessments to discuss bimanual coordination, first in healthy adults and then after stroke. The next thesis component describes bimanual coordination in healthy adults and includes an experimental chapter studying interhemispheric mechanisms mediating bimanual coordination in healthy adults.

5 Bimanual Coordination

Bimanual coordination is when movements of the two upper limbs are executed simultaneously with a fine spatiotemporal arrangement. Many activities of daily living (ADLs) require bimanual coordination, such as chopping vegetables and tying shoelaces. Furthermore, completing tasks bimanually rather than unimanually is often the spontaneous preference because it is often faster and more energy efficient (150). An intuitive example is that typing on a keyboard with two hands simultaneously is much faster than with one hand. It is critical for people with conditions such as stroke to regain the ability to coordinate both upper limbs so they can be safe and functionally independent (91).

Different forms of bimanual coordination can be identified when taking into consideration the variety of bimanual ADLs and the degrees of freedom of each upper limb. Organising these forms of bimanual coordination into a systematic taxonomy has several benefits. A taxonomy can help with planning future behavioural and neurophysiological studies of specific types of bimanual coordination. A taxonomy can also be useful when comparing results between studies that use different tasks but with similar forms of bimanual coordination. Another reason is that stroke appears to impair only certain types of bimanual coordination, which is discussed in Chapter 9. A taxonomy can help identify which forms of bimanual coordination that post-stroke therapy could specifically target, and this may be applicable to other neurological conditions affecting upper limb function. Two bimanual coordination taxonomies were introduced in the middle of the 2010s by Kantak et al. and Woytowicz et al, each with a different focus (151, 152).

5.1 Taxonomies of Bimanual Coordination

Kantak et al. reviewed bimanual coordination after stroke and proposed a taxonomy defining six forms of bimanual coordination that will be referred to here as the Kantak taxonomy (151). The Kantak taxonomy is shown in Figure 5.1 and a description of each form of bimanual coordination is included in Table 5.1. Kantak et al. introduced their taxonomy so bimanual tasks used in stroke research could be categorised in a standardised way for discussing bimanual coordination. The first distinguishing feature of the Kantak taxonomy is whether the upper limbs move symmetrically or asymmetrically during the task. Homologous muscles activate simultaneously during symmetric bimanual movements whereas asymmetric movements activate non-homologous muscles simultaneously or homologous muscles at different times.

The second feature of the Kantak taxonomy is how the goal to be achieved is conceptualised. Goal conceptualisation has previously been defined in terms of spatial or symbolic cues or having internal or external guidance during the task (Oliveira and Ivry 2008). The Kantak taxonomy however defines goal conceptualisation in terms of the movements of the two hands having either the same goal or different goals, and these are termed common-goal and independent-goal respectively. This definition of goal conceptualisation used by the Kantak taxonomy has also been used elsewhere (153-156).

The Kantak taxonomy further subdivides common-goal tasks into parallel and cooperative tasks depending on whether bimanual coordination is necessary to achieve the task. These will simply be referred to as parallel and cooperative tasks. Parallel tasks do not require bimanual coordination to be successful, but coordination is desired for efficiency. As a result, parallel tasks can be completed sequentially with one hand although it is more efficient to coordinate both hands together to complete the task. An example is making a cup of coffee. Stirring a cup of coffee with one hand while pouring the water from a kettle with the other hand is more efficient than using the same hand sequentially to pour the water and then stir it. In contrast, bimanual coordination is necessary to perform cooperative tasks such as opening a jar. Cooperative tasks have been defined elsewhere as requiring the forces of one hand to counteract the opposite hand's forces, such as when opening a bottle of water, but this is not specified as a requirement in the Kantak taxonomy (157).

Most bimanual tasks performed during everyday life are asymmetric common-goal tasks. Each hand has a separate role during these tasks as either the manipulator or stabiliser. The manipulator role requires greater hand dexterity and precision and so is usually performed spontaneously by healthy adults using their dominant arm (150, 158). The stabiliser role typically requires greater force control to hold an object steady. For some tasks the manipulator and stabiliser roles are clearly defined. When opening a jar, the manipulator opens the lid while the stabiliser grasps the jar and holds it steady. In other tasks the distinction is less clear such as tying shoelaces because, depending on the technique used, both hands move asymmetrically but perform similar roles.

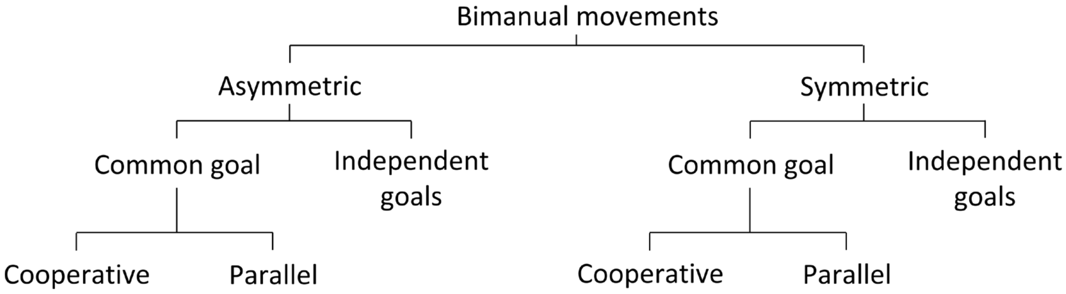


Figure 5.1. Categorisation of bimanual tasks based on the Kantak taxonomy (151). Tasks are categorised depending on movement symmetry and conceptualisation of the task goal(s).

Table 5.1. Descriptions and examples of each category of bimanual tasks based on the Kantak taxonomy (151).

Category	**Description**	**Example**
Asymmetric Cooperative	Non-homologous muscles achieve a single goal. BC is necessary.	Tying shoelaces.
Asymmetric Parallel	Non-homologous muscles achieve a single goal. BC is advantageous but not necessary.	Opening a drawer with one hand and retrieving cutlery with the other hand.
Asymmetric Independent	Non-homologous muscles achieve two separate goals.	Turning a book page with one hand while drinking from a cup with the other hand.
Symmetric Cooperative	Homologous muscles achieve a single goal. BC is necessary.	Carrying a large tray with both hands.
Symmetric Parallel	Homologous muscles achieve a single goal. BC is advantageous but not necessary	Reaching to grasp a large box with both hands.
Symmetric Independent	Homologous muscles achieve two separate goals.	Carrying a cup of water in each hand.

BC, bimanual coordination.

The Kantak taxonomy has several strengths. The distinguishing features of movement symmetry and goal conceptualisation were selected based on previous studies demonstrating behavioural and neurophysiological differences between the bimanual coordination categories (153, 155, 159-161). Another strength is that it only has a few key distinguishing features. In addition, the Kantak taxonomy was designed to be used with real-world tasks and so is relevant when discussing people with stroke regaining bimanual coordination for functional independence. Finally, since its introduction the definitions of task categories in the Kantak taxonomy have been used by other groups investigating bimanual coordination in people with stroke (156, 162).

One limitation of the Kantak taxonomy is that some bimanual tasks can be difficult to categorise. One differentiation that can be challenging is between parallel and cooperative tasks. An example is pegging a towel to a washing line. If the towel is pegged by its corner then it is a cooperative task because one hand must hold the towel to the washing line while the other hand pegs it. Conversely, if the towel is folded over the washing line before pegging then it is a parallel task because bimanual coordination is not necessary with this strategy as it could be completed with one hand. The same distinction can be difficult for novel laboratory tasks. Numerous studies have used a task where participants reach with both hands towards a single target and a virtual cursor is shown at the average distance between the hands (163-167). This is technically a parallel task although participants are instructed to move both hands as quickly as possible which changes the intent of the task to cooperative. Despite these examples, distinguishing between parallel and cooperative categories is straightforward for most common-goal tasks and it is only certain tasks where this distinction can be challenging.

Some tasks can also be difficult to assign to a single category because they contain a few sub-tasks that require different forms of bimanual coordination. An example is pouring a glass of water from a jug when one object is closer to you than the other. Reaching to grasp the glass and jug requires asymmetric independent coordination as each hand is reaching for a separate object at different distances. Once the objects have been grasped then asymmetric cooperative coordination is required as one hand stabilises the cup while the other hand pours water from the jug. It could also be argued that stabilising the glass is not necessary as it could be left on the table, and so the whole task could be categorised as a parallel task. This example highlights that each part of a task should be carefully examined if bimanual coordination is going to be compared between studies.

A separate taxonomy with five categories was proposed by Woytowicz et al. in their review on age-related changes in bimanual coordination, and will be referred to as the Woytowicz taxonomy (152). A diagram of the Woytowicz taxonomy is shown in Figure 5.2. It should be noted that Woytowicz et al. did not specifically advocate for their taxonomy to be used in future studies but rather used it to aid their review of how aging affects bimanual coordination. The first differentiating feature is whether the upper limbs are performing different movements or the same movements, and these are termed asymmetric and symmetric respectively. Asymmetric movements are subdivided into independent and complementary movements. Independent movements are defined in the same way as the Kantak taxonomy whereas complementary movements involve both hands using interacting opposing forces to achieve a singular goal. Symmetric movements are subdivided into in-phase, anti-phase, and complex phasing patterns. In-phase movements require simultaneous spatial and temporal movement from both arms in a mirror-symmetric manner. Anti-phase movements are spatially symmetric but both arms have a consistent temporal offset such as arm swing during walking. Complex phasing movements are the same as anti-phase movements except with irregular temporal alterations, for example playing the drums.

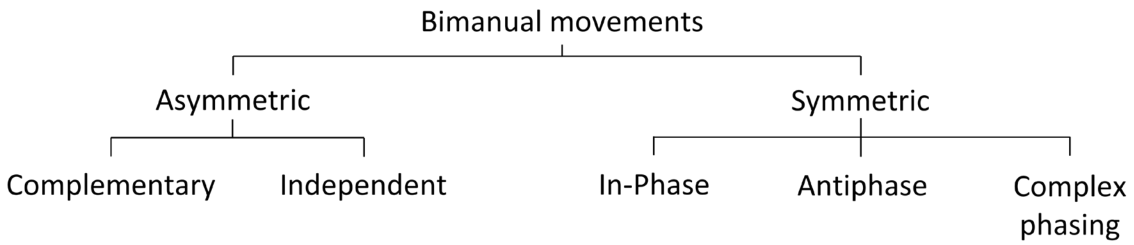


Figure 5.2. Categorisation of bimanual tasks based on the Woytowicz taxonomy (152). Tasks are initially categorised depending on movement symmetry. Asymmetric tasks are further categorised based on the task goal(s) while symmetric tasks are further categorised depending on the task's spatial and temporal characteristics.

There are several similarities between the Kantak and Woytowicz taxonomies. Both acknowledge the significance of movement symmetry and include it as a differentiating feature. Both taxonomies include an asymmetric independent-goal category while the symmetric in-phase category in the Woytowicz taxonomy is equivalent to the general definition of a symmetric task in the Kantak taxonomy. The asymmetric complementary category in the Woytowicz taxonomy is also a narrower version of the asymmetric cooperative category in the Kantak taxonomy because the former requires interacting and opposing forces between the hands during the task. Thus, the two taxonomies include several identical or similar categories of bimanual coordination.

The most significant difference between the two taxonomies is the second differentiating feature. The Woytowicz taxonomy sub-divides symmetric tasks using different criteria than is used to sub-divide asymmetric tasks. In contrast, the Kantak taxonomy uses the same criteria to sub-divide symmetric and asymmetric tasks. The Woytowicz taxonomy for symmetric tasks focuses on biomechanical properties, such as the timing and forces of the movements, whereas the Kantak taxonomy places a greater emphasis on goal conceptualisation. In addition, both anti-phase and complex phasing symmetric tasks would be classified as asymmetric movements in the Kantak taxonomy because neither are temporally symmetric. These differences between taxonomies likely reflect their purposes because the Kantak taxonomy was developed for use after stroke whereas the Woytowicz taxonomy was introduced to discuss the effects of aging on bimanual coordination.

Although the Kantak and Woytowicz taxonomies share several similarities, we will focus on the former for several reasons. Most importantly, the Kantak taxonomy was introduced to facilitate research of bimanual coordination after stroke which is the focus of the third component of this thesis. Secondly, the emphasis on goal conceptualisation in the Kantak taxonomy means it is more suitable for use with real-world tasks. The focus on the tasks' biomechanical properties in the Woytowicz taxonomy makes it more appropriate for simple laboratory-based tasks. Thirdly, the Woytowicz taxonomy does not differentiate between parallel and cooperative tasks. This distinction is important because there is some evidence that patients with chronic stroke have impaired bimanual coordination during cooperative tasks but not parallel tasks (168). Although the Kantak taxonomy does not distinguish between in-phase, anti-phase, and complex phasing symmetric tasks, these categories only differ in the timing or force of the movement which may be less important distinctions for real-world tasks. Overall, we chose to concentrate on the Kantak taxonomy because of its emphasis on bimanual coordination after stroke and its relevance for real-world tasks. The next chapter will discuss some theories relating to bimanual coordination and how bimanual coordination has been studied in healthy adults.

6 Bimanual Coordination in Healthy Adults

Bimanual coordination has been studied extensively in healthy adults to understand how humans coordinate both hands when performing a wide variety of tasks. Studying bimanual coordination in healthy adults also helps understand how it can be impaired by stroke. Additionally, understanding the neural mechanisms underlying bimanual coordination can inform the development and improvement of rehabilitation services and interventions to assist unimanual and bimanual upper limb motor recovery after stroke.

This chapter will first provide an overview of the motor system and theoretical frameworks of bimanual coordination. Following this, the influence of movement symmetry and goal conceptualisation on bimanual coordination and bimanual task performance in healthy adults will be discussed along with the underlying neural mechanisms. Finally, the effects of healthy aging on bimanual coordination will be briefly outlined.

6.1 Anatomy of the Motor System

Bimanual movements are controlled by a network of brain regions in each hemisphere (169). This network is not a rigid set of brain regions but depends on numerous factors such as task difficulty, the participant's experience with the task, and the age of the participant. Only a few regions have demonstrated consistent involvement with bimanual coordination and they will be described here.

6.1.1 Brain Regions Mediating Bimanual Coordination

The primary motor cortex (M1) plays a crucial role in the execution of unimanual and bimanual voluntary movement. Subsets of neurons within the M1 of non-human primates show greater activity during bimanual movements than unimanual movements, which provides evidence that M1 has specialised functions for bimanual coordination (170, 171). M1 is located in the grey matter of the dorsal portion of the frontal lobe and consists of six layers. Motor representations are organised here in an ordered but inverted manner, with representations of the feet located superiorly and those of the face located inferiorly (172). The main role of M1 is to integrate information from motor and non-motor regions to prepare and execute voluntary movements by encoding parameters such as speed, amplitude, and force.

The two secondary motor regions most associated with bimanual coordination are the supplementary motor area (SMA) and dorsal premotor cortex (PMd). Over half the neurons within SMA demonstrate bimanual-related activity which supports its role in bimanual coordination (170, 171). The SMA is located in the medial aspect of the superior frontal gyrus and consists of two subareas called the pre-SMA and the SMA-proper (173). The pre-SMA is located anterior to the SMA-proper and both have distinct functions. Broadly, the pre-SMA plays a more prominent role with the cognitive aspects of movement whereas the SMA-proper is more important during movement execution. This is reflected in their anatomy as only the pre-SMA connects to the prefrontal cortex whereas only the SMA-proper connects directly to M1 (173). The SMA is thought to help with several aspects of bimanual coordination including spatial and temporal processing, bimanual task learning, and sequence processing during both motor planning and execution (174). The SMA is particularly important when performing asymmetric bimanual movements by helping both hemispheres plan different motor actions for each upper limb (175-178).

The premotor cortex is located in the posterior portion of the middle frontal gyrus, with the PMd located in the dorsal area near M1. The PMd is divided into the pre-PMd in the anterior portion and the PMd-proper in the posterior portion (179, 180). The pre-PMd is thought to integrate visual information from the posterior parietal cortex and sensory information from prefrontal areas such as the dorsolateral prefrontal cortex and cingulate areas. The pre-PMd uses this information to help with planning goal-directed movements and error monitoring during movement. The PMd-proper receives few afferent connections from prefrontal regions but does have strong reciprocal connections with M1 and so is thought to be more involved with movement execution. PMd function is thought to be lateralised during bimanual tasks. The PMd contralateral to the dominant upper limb is more important during motor planning of goal-directed bimanual tasks whereas the PMd contralateral to the non-dominant upper limb plays a larger role with maintaining asymmetric patterns during movement execution (181-183).

The subcortical region with arguably the most importance for bimanual coordination is the cerebellum. The cerebellum is in the posterior region of the brain inferior to the occipital and temporal lobes of the cerebral cortex. The cerebellum’s most significant roles in motor control are helping with the online assessment of movement errors and the planning of sequential movements (184). The former role is particularly important during difficult asymmetric bimanual tasks where movement errors are more common. To detect online movement errors the cerebellum receives what is termed the efference copy during preparation of planned movement (185). The efference copy predicts the sensory outcome of the upcoming movement. The cerebellum compares the efference copy with actual sensory feedback generated by the movement that is relayed to the cerebellum via the spinal cord. If the efference copy and sensory feedback are misaligned then error signals can be sent from the cerebellum to the parietal and frontal lobes of the cerebrum to produce the necessary motor adjustments. Efferent connections from the cerebellum connect to regions such as M1, SMA, and PMd via the cerebello-thalamo-cortical pathway, and in return the cerebellum receives connections from motor regions via the cortico-ponto-cerebellar pathway (186, 187).

The transfer of temporal and spatial information between hemispheres is critical for bimanual coordination. This transfer occurs predominantly via the corpus callosum which is the primary white matter tract connecting the two hemispheres (188). It consists of approximately 200 million axons and its primary function is to transfer information between homologous and heterologous regions. Damage to the corpus callosum severely impairs performance of rhythmic bimanual tasks (189-191). There is also evidence that maturation of the corpus callosum during adolescence is necessary to reduce involuntary mirror symmetric movements and enable accurate and smooth asymmetric movements (192-194).

Homologous interhemispheric connections are present for the M1, SMA, and PMd but it is the connections between M1s via the corpus callosum that have received the most attention (195). Interhemispheric interactions between M1s have largely been thought of as inhibitory when discussing motor control, however the reality is likely more nuanced with a balance of facilitation and inhibition necessary to produce fine motor control (195, 196). The SMA and PMd are also able to influence the contralateral M1 likely via the corpus callosum (197, 198). Thus, the corpus callosum is critical for performing bimanual movements by aiding interhemispheric communication to ensure both upper limbs are coordinated correctly.

6.1.2 Descending Motor Pathways

Voluntary movement is primarily generated through motor signals that descend via the corticospinal tract (CST) to the grey matter of the spinal cord. Approximately 37% of CST fibres originate from M1, 32% from the primary sensory cortex, 21% from the SMA, and 10% from the PMd (199). The CST is separated into two tracts: the lateral CST and anterior CST. The lateral CST includes 75 – 90% of all CST fibres (200). The lateral CST is most known for its role as the primary motor pathway mediating voluntary distal movement but it has other roles including descending control of afferent inputs and the selection and gating of spinal reflexes (201).

Corticospinal neurons are the primary output cells of the CST and are predominantly located in layer five of the grey matter (62). Interneurons located in layers two and three of the grey matter synapse onto corticospinal neurons to influence their excitability via neurotransmitters such as gamma-aminobutyric acid (GABA) and glutamate. The axons of corticospinal neurons descend through the posterior limb of the internal capsule and decussate if they are part of the lateral CST once they reach the medulla before reaching the spinal cord. Corticospinal neurons of the lateral CST terminate in the dorsolateral intermediate zone, ventromedial intermediate zone, and the lateral motor nuclei where they synapse with α-motoneurons either directly or indirectly (62). From here, α-motoneuron axons project peripherally to innervate skeletal muscles and initiate their contraction. The importance of the lateral CST for voluntary movement is illustrated by the finding that significant upper limb recovery after stroke depends on the CST remaining functionally intact (71, 77).

Humans also have ipsilateral motor pathways that are more scarce than contralateral pathways. Approximately 10 – 25% of CST fibres do not decussate, and these form the anterior CST (200). The anterior CST terminates in the ipsilateral spinal cord either directly onto α-motoneurons or indirectly via other pathways such as the corticoreticulospinal and corticopropriospinal tracts (202). The anterior CST contributes towards ipsilateral movements, particularly movements involving axial muscles (202, 203). Voluntary unimanual muscle activation can also increase excitability in the ipsilateral M1 (204-207) and individual neurons in M1 are modulated based on ipsilateral movements (208). This means M1 controls both contralateral and ipsilateral voluntary movements, although its influence is far greater for contralateral movements.

Several other descending motor pathways also contribute to voluntary movement. The most important of these is the reticulospinal tract (RST) that descends both contralaterally and ipsilaterally (209). RST neurons involved with limb movement arise from the pons and medulla (210). The RST primarily innervates trunk and proximal limb muscles which means it assists more with gross upper limb reaching than dexterous hand control (203, 210). The RST does have some projections to hand muscles though but is more involved with hand grasping rather than individual finger movement (210, 211). There is evidence that the RST plays a more significant role during bimanual movements than unimanual movements which may reflect its bilateral descending projections (212-214).

6.2 Theoretical Frameworks

The neural control of bimanual movements has been a debated topic for decades. Producing bimanual movements does not simply reflect the summation of two unimanual movements because the spatial and temporal demands of coordinating both upper limbs need to be accounted for (159, 169). Several of the more popular theories of motor control and handedness that relate to bimanual coordination will be discussed here.

6.2.1 Theories of Motor Control

Numerous theories have been proposed over the past half-century to explain how humans are able to coordinate movements using combinations of muscles across multiple joints. The challenge is to identify how the motor system decides on a given solution for achieving a task given there are usually numerous options (215). Although an in-depth evaluation and comparison of each theory is beyond the scope of this thesis, the most common theories will be discussed here as they relate to bimanual coordination.

The dynamical systems framework for motor control relies on mathematical concepts of nonlinear dynamics to explain bimanual coordination patterns. This approach posits that the arrangement of muscles and movements for a task are assembled via self-organising processes and occur through the stability of interactions within the system (216). These self-organising arrangements can form and dissipate spontaneously in response to internal and external constraints. The Haken-Kelso-Bunz (HKB) model was proposed in 1985 and uses a dynamical systems approach to explain the stability of different movement patterns during rhythmic bimanual tasks (217, 218). According to the HKB model the rhythmic movements of each hand are viewed as nonlinearly coupled oscillators. Rhythmic patterns with a 1:1 frequency and a relative phase of 0° or 180° between the hands are termed “attractors” because their stability makes them the motor system’s preferred coordination patterns. Bimanual movements with other relative phases, such as 90°, are less stable and are drawn towards the stability of 0° or 180° (219, 220). It should be noted the HKB model was developed to explain coordination during rhythmic tasks and so does not provide an explanation for coordination during bimanual tasks involving discrete movements.

The information-processing perspective provides another framework for understanding bimanual coordination (169). This perspective views bimanual movements as two movements being performed simultaneously that are subject to interference due to limitations in neural resources. The focus using this perspective has been on the difficulties in performing asymmetric bimanual tasks because of interference. A source of interference that can hinder asymmetric movements is neural crosstalk (221-223). One source of neural crosstalk is that when both hemispheres send descending motor commands to contralateral muscles via the lateral CST a small fraction of the same motor command is sent to ipsilateral homologous muscles via the anterior CST. This ipsilateral influence is weaker than the contralateral influence because 75 – 90% of CST fibres decussate (200). Thus, muscles receive dissonant motor signals from each hemisphere when performing asymmetric tasks and this neural crosstalk can interfere with task performance.

An additional source of neural crosstalk is the interhemispheric exchange of sensorimotor information through the corpus callosum. These interhemispheric interactions occur predominantly between M1s but there is evidence they also occur at higher levels of motor planning prior to M1 such as the SMA and PMd (224). During asymmetric movements each hemisphere sends different motor commands to contralateral muscles, and some of the temporal and spatial properties of the motor commands are shared with the opposite hemisphere which causes interference. Neural crosstalk has been used to explain interference effects during asymmetric rhythmic tasks (223, 225) and discrete movements (164, 226) in addition to functional magnetic resonance imaging (fMRI) findings from bimanual tasks (159, 224, 227).

Lastly, the optimal feedback control theory (OFCT) posits that motor commands are learned and optimised for a given task to require minimal effort (228, 229). Optimal control uses feed-forward motor signals along with sensory feedback regarding the body and the environment to create an accurate estimate of optimal state variables for movement such as limb position and forces. These state variables are converted to generate motor commands, and if any variations in the optimal state variables occur during movement then the motor plan can be continually updated as needed to remain optimal. There are two important features of state variables. First, corrections are only made to optimal state variables that negatively impact motor performance, for example external perturbations while reaching. This allows for greater flexibility in redundant variables that do not affect performance. Secondly, how state variables are converted to generate motor commands is not fixed but is adjusted based on the task parameters. As a result, the OFCT model states that motor control is extremely task-dependent, and this idea has been supported elsewhere in the context of bimanual coordination (169, 230).

The OFCT describes the neural control of bimanual movements in terms of goal conceptualisation. This contrasts with the HKB model and information-processing perspective that both focus on the movement symmetry of bimanual tasks. How each of these models have been used to explain bimanual coordination will be discussed in the following sections alongside behavioural results from healthy adults.

6.2.2 Theories of Handedness

Handedness refers to the consistent preference to use one hand over the other for a given task (231). Approximately 90% of adults self-report as being right-hand dominant, 10% as left-hand dominant, and 1% as ambidextrous with no preference in hand choice (114, 232, 233). Adults have a bias to use their dominant limb for unimanual tasks if given the choice although this bias is weaker for left-hand dominant adults (234-237). Numerous factors influence hand choice for a task including age, task complexity, the location of objects, and whether the task is unimanual or bimanual (234, 235, 237, 238).

Handedness and hand choice are particularly important to consider for common-goal bimanual tasks that require one hand to act as a manipulator while the other hand acts as a stabiliser. Two studies examined spontaneous hand use when healthy adults performed common-goal tasks with no instructions of how to complete the task. Participants preferentially used their dominant limb as the manipulator during a high-precision watch making task (150) and when constructing models using blocks (158). Both tasks have high ecological validity and likely reflect real-world spontaneous hand use. The question then arises as to why participants spontaneously use their dominant hand as a manipulator during common-goal bimanual tasks. There are currently two prominent theories of handedness that address this question: the global dominance hypothesis and the complementary dominance hypothesis.

The global dominance hypothesis posits that the dominant upper limb is superior for all aspects of motor performance compared to the non-dominant upper limb. This view was originally based on the observation by Hugo Liepmann in the early 20th century that apraxia almost exclusively occurred following left-hemisphere stroke and not right-hemisphere stroke (239). Supporting evidence in healthy adults includes findings that the dominant M1 has a larger cortical representation than the non-dominant M1 (240, 241) and the dominant hemisphere exerts greater control over the non-dominant hemisphere than vice versa (227, 242, 243). Thus, according to the global dominance hypothesis, people use their dominant limb as a manipulator because it is the superior limb for motor performance and the manipulator role in bimanual tasks is typically more difficult than the stabiliser role.

A more recent theory proposed by Sainburg was termed the dynamic dominance theory and renamed to the complementary dominance hypothesis. Sainburg proposed the complementary dominance hypothesis based on his own results showing unimanual reaching with a 2kg load attached to the upper limb during random trials decreased accuracy for the dominant limb but not the non-dominant limb (244). This finding of superior task performance by the non-dominant limb contradicted the global dominance hypothesis. Instead, the complementary dominance hypothesis proposes that the dominant hemisphere is specialised for predicting the control of limb dynamics to efficiently coordinate movement whereas the non-dominant hemisphere is optimised for impedance control mechanisms to maintain accuracy and stability during movements (115). Thus, each hemisphere is specialised for different aspects of motor control. Based on this hypothesis it is the specialised roles of the dominant and non-dominant hemispheres that lead to the preference to use them as a manipulator and stabiliser, respectively. The complementary dominance hypothesis is largely incompatible with the global dominance hypothesis since the latter states the dominant upper limb would be superior at both coordinating movement and maintaining accuracy.

It is of ecological interest whether the complementary dominance hypothesis is supported by findings from cooperative bimanual tasks with clear manipulator and stabiliser roles. One task had participants mimic bread slicing while both hands were physically connected with a spring (245, 246). One hand was required to accurately reach forwards to a target while the other hand stabilised the spring load to remain stationary. Both studies reported the dominant limb demonstrated superior performance than the non-dominant hand while reaching but the non-dominant limb was superior at stabilising. These findings support the complementary dominance hypothesis but it remains to be seen whether findings from actual real-world tasks support this hypothesis.

Overall, contemporary thinking supports the complementary dominance hypothesis over the global dominance hypothesis. Future work will be needed to better understand how the lateralisation of motor control affects bimanual tasks, particularly using tasks that more closely resemble ADLs. This work could have direct implications for individualising rehabilitation following stroke depending on whether the dominant or non-dominant upper limb is impaired (247).

6.3 Bimanual Coordination and Task Performance

There are two broad categories of tasks used to study bimanual coordination. The more common category, especially with healthy adults, includes simple tasks performed in highly controlled laboratory environments. These lab-based tasks are highly standardised and useful for studying the behavioural and neural characteristics of bimanual coordination, particularly kinematic and kinetic parameters. Kinematic parameters refer to the spatial and movement aspects of coordination whereas kinetic parameters refer to the coordination of muscles and forces (248). Examples of lab-based tasks include simple rhythmic bimanual movements, discrete reaching movements, and isometric force production. This chapter will focus on rhythmic and discrete reaching tasks as these tasks were used in the experiments of the current thesis. The second broad category of bimanual coordination tasks includes naturalistic, real-world tasks such as retrieving an item from a drawer or pouring a glass of water. Real-world tasks are less common than lab-based tasks because they are often harder to standardise, however they do provide greater ecological validity for understanding how people coordinate their hands during ADLs. Both lab-based and real-world tasks have complementary advantages and have been useful in discerning the behavioural and neurophysiological characteristics of bimanual coordination in healthy adults.

6.3.1 Lab-based Tasks

6.3.1.1 Movement Symmetry

The influence of movement symmetry on bimanual coordination has been studied for many decades. Movement symmetry can be described relative to an egocentric or allocentric reference frame (221). Symmetric movements in the egocentric frame refer to the simultaneous activation of homologous muscles relative to the individual's internal midline, for example flexing both wrists towards the midline. Asymmetric movements involve the simultaneous activation of non-homologous muscles or the recruitment of homologous muscles at different times. Conversely, symmetric movements in the allocentric frame involve homologous body parts moving in the same direction in extrinsic space, such as simultaneously lifting your hand and foot superiorly. Figure 6.1 demonstrates the difference between the egocentric and allocentric frames in relation to a bimanual circle drawing task.

The egocentric reference frame is more commonly used in upper limb coordination studies and so symmetry will refer to the egocentric frame from this point unless stated otherwise.

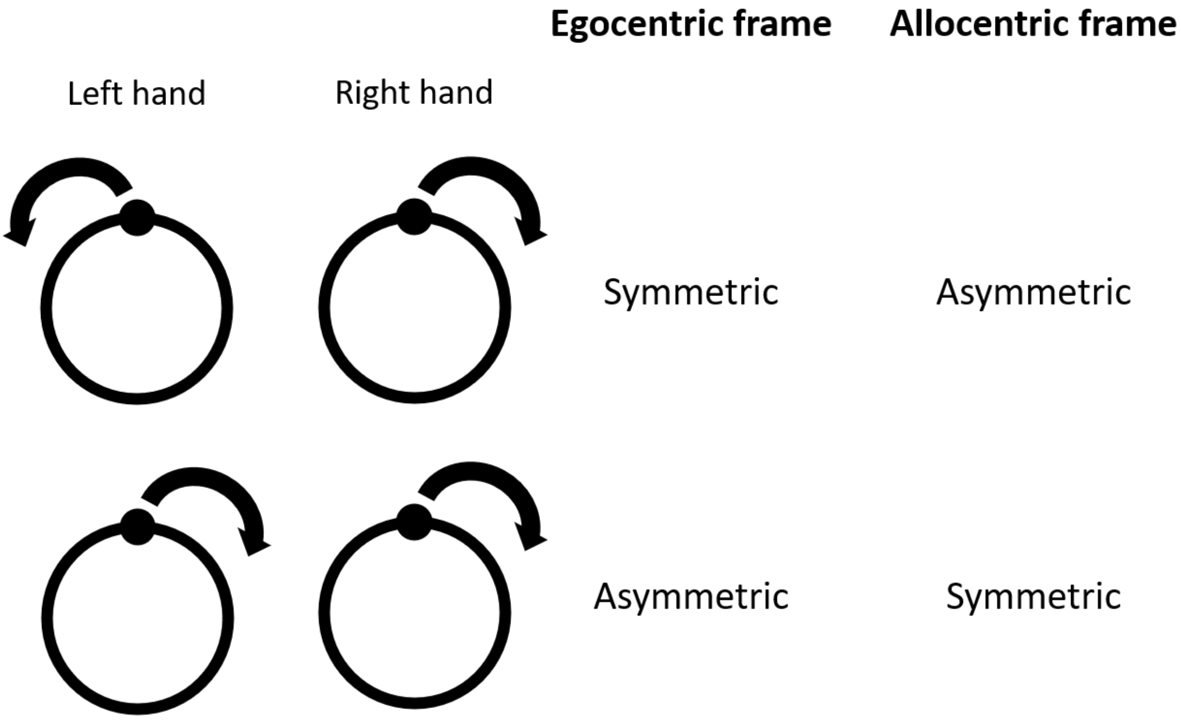


Figure 6.1. Symmetry of bimanual circle drawing in the egocentric and allocentric reference frames. The solid dot at the top of the circle indicates the starting position and arrows represent the directions of movement. The top row demonstrates a symmetric pattern in the egocentric frame as both hands are activating homologous muscles simultaneously but this pattern is asymmetric in the allocentric frame as one hand is moving to the left and the other to the right. Conversely, the bottom row is asymmetric in the egocentric frame as different muscles are being activated simultaneously but is symmetric in the allocentric frame as both hands are moving in the same direction in extrinsic space. The movement patterns in the top and bottom rows can also be termed in-phase and anti-phase, respectively.

A separate distinction to be made is between spatial and temporal asymmetry. Spatial asymmetry is when the upper limbs have different movement or force amplitudes, for example reaching in different directions or drawing a circle with one hand and a straight line with the other (221). In contrast, temporal asymmetry involves different movement durations, timings, or frequencies. An example of temporal asymmetry is tapping both index fingers at different frequencies.

Several of the earliest bimanual coordination studies found symmetric movement patterns were more stable than asymmetric patterns using rhythmic bimanual tasks at various frequencies. Bimanual circle drawing is one of the most studied rhythmic tasks and involves drawing circles with both hands simultaneously in a mirror symmetric or asymmetric pattern. The spatial symmetry of these tasks is described based on the relative phase difference between the hands. A relative phase of 0° indicates a symmetric pattern, also known as in-phase. Phase differences other than 0° indicate an asymmetric movement pattern and the most studied phase difference is 180°, also termed anti-phase. The top and bottom rows of Figure 6.1 indicate in-phase and anti-phase circle drawing patterns, respectively. Bimanual circle drawing with an anti-phase pattern is stable at low movement frequencies but becomes less stable as participants are continuously paced to increase their frequency (249). A critical frequency is eventually reached where the non-dominant limb spontaneously and involuntarily switches direction so both hands are moving in-phase. An in-phase pattern is more stable at higher frequencies and does not spontaneously switch to an anti-phase pattern if movement frequency is decreased. This phenomenon of a critical frequency transition from an anti-phase pattern to an in-phase pattern has been replicated with other rhythmic movements such as wrist flexion-extension and index finger abduction-adduction (250-252). Moreover, polyrhythmic tasks are more stable with temporal symmetry than temporal asymmetry, for example tapping the hands at a 1:1 ratio compared to 5:3 (253-257). Difficulty does vary amongst asymmetric conditions though as relative phases such as 30° or 90° are even less stable than an anti-phase movement pattern, and complex asymmetric polyrhythms are more difficult than simpler ones (178, 219, 255, 258, 259). Together, these studies demonstrate that healthy adults are more stable and coordinated on rhythmic tasks with symmetric parameters than asymmetric parameters.

The HKB model that is based on the dynamical systems approach for motor control has been widely used to explain findings from rhythmic bimanual tasks (217, 218). The HKB model asserts that a symmetric pattern with a relative phase of 0° is the most stable attractor state and the body's preferred movement pattern. This explains why spontaneous phase transitions occur from anti-phase to in-phase patterns and not vice versa, and why voluntarily switching from anti-phase to in-phase patterns is easier than vice versa (249, 260-263). Asymmetric relative phases such as 30° and 90° are difficult to perform because these movement patterns are not attractor states. As a result, performing rhythmic movements with a non-attractor relative phase results in fluctuations towards in-phase or anti-phase patterns unless training or feedback is provided (220, 264, 265). Similarly, hand tapping with difficult frequency ratios such as 3:7 are drawn to simpler ratios such as 2:3 (255). In contrast, the information-processing perspective proposes the instabilities of asymmetric patterns are caused by interference from ipsilateral descending motor pathways and the interhemispheric exchange of sensorimotor information (169). There is still ongoing debate about which of these perspectives best explains the results from rhythmic bimanual tasks.

Discrete bimanual movements are also performed easier with symmetric parameters than asymmetric parameters. Discrete movements provide better ecological validity than rhythmic movements because upper limb movements during everyday life predominantly involve discrete movements to interact with objects. There is evidence that at least partially separate neural mechanisms mediate discrete and rhythmic movements (266, 267). Bimanual coordination during discrete movements is often studied using independent-goal tasks that involve reaching to press a target with each hand. The symmetry of parameters such as reaching amplitude, reaching direction, and target size are manipulated. One of the most influential studies using discrete movements was published by Kelso et al (268). Twelve healthy adults in this study reached as quickly as possible either unimanually or bimanually to press a home key with their index finger(s). As expected, participants' unimanual movements and bimanual symmetric movements followed Fitts' speed-accuracy trade-off law (269). However, when asymmetric target widths or distances were used the movement time for the hand performing the easier reach was longer compared to the same task performed symmetrically or unimanually. There was also no difference in total task time between the hands performing the easier and more difficult roles during asymmetric conditions. These results indicate the reaching performance of one hand is affected by what the other hand is doing, and asymmetric conditions worsen the performance of the hand executing the easier task. The tendency for both hands to produce similar movements during asymmetric conditions has been termed assimilation, or bimanual interference. An assimilation effect during asymmetric discrete movements has been replicated numerous times since it was first observed, and this includes a study reproducing Kelso et al's original protocol over three decades later (217, 261-263, 270). Thus, assimilation effects negatively affect performance for the hand performing the easier role during discrete asymmetric tasks.

Neural crosstalk is the most common model used to explain behavioural differences between symmetric and asymmetric discrete reaching tasks. Symmetric movement patterns are thought to strengthen neural crosstalk via the interhemispheric exchange of sensorimotor information because both upper limbs are performing the same movement, causing them to what is termed functionally coupled (271). Functional coupling during symmetric movements predominantly increases the exchange of sensorimotor information at the cortical level (272, 273) but also at the subcortical (214) and spinal level (274). For example, functional connectivity assessed using fMRI is increased between M1s and between SMAs during rhythmic symmetric bimanual movements compared to unimanual movements (198). Identical motor signals being dispatched to the contralateral and ipsilateral upper limb from each hemisphere may also strengthen functional coupling during symmetric movements. Functional coupling between M1s is hypothesised to be mediated via interhemispheric projections that mediate GABA-mediated inhibitory circuits within M1 (252, 272, 275). Overall, functional coupling is thought to improve stability and performance during symmetric bimanual tasks.

Asymmetric movements are thought to require a suppression of neural crosstalk so that each hand can perform disparate actions (276-278). However, neural crosstalk cannot be completely suppressed during asymmetric movements and so conflicting sensorimotor information is still exchanged between hemispheres. This leads to increased task difficulty and assimilation effects observed during tasks with asymmetric parameters. The suppression of neural crosstalk has been hypothesised to occur via interhemispheric inhibition between M1s (243) but this view has been challenged as overly simplifying the contralateral influence from each hemisphere (196). Interhemispheric influences from regions such as PMd and SMA have also been proposed to contribute to the suppression of neural crosstalk (226, 279). The corpus callosum likely mediates these interhemispheric influences because callosotomy patients do not exhibit assimilation effects on certain asymmetric bimanual tasks (191, 280). Support for the critical role of secondary motor areas during asymmetric tasks comes from

MRI findings that the SMA, PMd, and cerebellum are more active during asymmetric tasks than symmetric tasks (177, 178, 224, 279). Furthermore, permanent (175, 176, 281) and transient (182, 282, 283) disruption of the SMA or PMd impairs performance on asymmetric tasks but not symmetric tasks. Overall, neural crosstalk and functional coupling are thought to be key processes influencing bimanual coordination that result in greater stability and better performance on tasks with symmetric parameters than asymmetric parameters. Further work needs to be done to elucidate the exact mechanisms mediating neural crosstalk and how it is strengthened and suppressed during symmetric and asymmetric tasks, respectively (196).

6.3.1.2 Goal Conceptualisation

Goal conceptualisation is a growing area of bimanual coordination research. Here, common-goal and independent-goal refer to tasks where both hands share a single goal or have separate goals, respectively (151). Common-goal tasks are subdivided into cooperative tasks where coordination between the upper limbs is essential to complete the task and parallel tasks where coordination is not essential but is preferred for optimal task performance. To date, no studies have directly compared the performance of cooperative and parallel tasks. This is potentially because healthy adults naturally perform parallel tasks concurrently with both hands, such as retrieving an item from a drawer (168, 284, 285) or reaching to pick up a box (168), and so there are likely few differences between cooperative and parallel task performance. These common-goal subclasses will be discussed in a later chapter in relation to stroke; this section will focus on cooperative versus independent-goal tasks in healthy adults.

Only a few studies have specifically compared performance of cooperative and independent-goal lab-based tasks and there is little consensus. One study had 12 healthy adults perform a novel rhythmic task in which they made circular movements with a joystick in each hand (153). Participants received visual feedback in the form of two rotating balls which would change colour if participants were moving too fast or slow. Participants were provided with an asymmetric frequency ratio to maintain during the cooperative condition while in the independent-goal condition they had to match the speed of two rotating balls presented to them. Participants performed similarly on both tasks initially but following a training session they performed better on the cooperative condition than the independent-goal condition. This result indicates cooperative tasks may be more readily improved with practice than independent-goal tasks.

Several studies have used discrete reaching tasks with different methods for altering goal conceptualisation. No differences in temporal or spatial coordination were reported when healthy older adults reached to move a single virtual brick with both hands or two independent virtual bricks presented to them on a computer screen (286). Participants demonstrate no differences in movement time, accuracy, or temporal coupling when reaching towards separate targets with a virtual cursor for each hand or towards one target with a single cursor displayed at the spatial midpoint between the hands (287). Another study had separate groups of healthy adults perform out-and-back reaching movements while holding onto a robotic handle in each hand either independently or with the handles virtually coupled together with a stiff spring (288). It was not specified whether participants were younger or older adults but both groups had similar initial error rates and displayed similar levels of learning over ten blocks of trials. In contrast, one study reported healthy adults had faster movement times when bimanually reaching to two targets rather than one target (289). This contrasting result is possibly because separate cursors were displayed for both hands during the cooperative condition whereas other studies display a single cursor which likely decreased the visual demands of the cooperative condition (286, 287). Collectively these studies demonstrate that healthy adults perform similarly during cooperative and independent-goal discrete reaching tasks.

A frequent focus of studies comparing cooperative and independent-goal conditions is how participants respond to unilateral perturbations during task performance. These perturbation studies are used to better understand the neurophysiological differences between cooperative and independent-goal tasks. Diedrichsen was the first to investigate how both upper limbs responded to a unilateral force field applied during bimanual reaching with either one shared virtual cursor or two independent virtual cursors (165). When the unilateral force field was applied participants initially experienced a change of direction in both upper limbs if a single cursor was used but a change of direction only occurred in the perturbed limb when independent cursors were used. Later studies extended Diedrichsen’s findings by demonstrating that unilateral perturbations during bimanual reaching result in bilateral reflex responses during cooperative reaching but not independent-goal reaching (166, 290). A task in which participants “held onto” a virtual bar with both hands and symmetrically reached forwards demonstrated the extent of these bilateral responses depends on hand dominance (167). When the dominant arm was perturbed during bimanual reaching the non-dominant arm decelerated to wait for the dominant arm to recover. In contrast, there was no response in the dominant limb when the non-dominant arm was perturbed and so the non-dominant arm accelerated to catch up with the dominant arm. Only right-hand dominant participants were included so it remains to be determined if this asymmetry exists in left-hand dominant people. Bilateral responses to unilateral perturbations have also been reported during a rhythmic cooperative task but not an equivalent independent-goal task (291-293).

The OFCT was used by Diedrichsen as an explanation for why unilateral perturbations cause bimanual responses during cooperative tasks (165, 228). According to the OFCT the distribution of work from motor commands can affect multiple effectors if it optimises task performance, even if the task could be completed using a single effector. It was proposed that during cooperative reaching the motor system exploits the redundancy of the task by distributing the perturbation corrections across both arms to minimise effort (228). During the independent-goal condition the motor commands for each hand do not depend on the state of the contralateral hand, and so unilateral perturbations only cause corrections in the perturbed limb.

Diedrichsen did not propose what neural mechanisms may underlie this distribution of work to the contralateral limb following unilateral perturbation during cooperative tasks. However, other studies have used MRI and transcranial magnetic stimulation (TMS) to provide information regarding the neural control of cooperative and independent-goal tasks. The presence of bilateral responses to unilateral perturbations during cooperative tasks has been proposed to represent a neural coupling between both sides of the body (294). This neural coupling is thought to assist with cooperative tasks by increasing the exchange of sensorimotor information between both hemispheres that leads to more equal control of each upper limb by both hemispheres. Three findings indirectly support the idea of neural coupling during cooperative tasks. First, the amplitude ratio of ipsilateral to contralateral somatosensory evoked potentials (SSEPs) is higher during cooperative tasks than independent-goal tasks (292, 293, 295). Second, ipsilateral motor evoked potentials are elicited more frequently using TMS during cooperative tasks than independent-goal tasks (296). Third, fMRI studies have shown that activation in the bilateral secondary somatosensory cortices (S2) and functional connectivity between S2s is increased during a cooperative task compared to an equivalent independent-goal task (291, 297). Each S2 receives afferent input from both hands and is thought to be involved with the processing of afferent sensory information in addition to the exchange and integration of information from both sides of the body (298, 299). Together these findings indicate that cooperative tasks may strengthen the interhemispheric exchange of afferent somatosensory information to increase control of each hand by the ipsilateral hemisphere to help coordinate both upper limbs together.

It should be noted that with one exception all these studies utilising SSEPs, TMS, and fMRI have come from the same lab group and use the same rhythmic asymmetric cooperative task that imitates opening a bottle. A version of this task that imitated screwing a nut onto a bolt did lead to stronger ipsilateral SSEPs than the bottle-opening task, although the tasks were identical apart from the precision requirements (292). The only study by a different group to compare activation patterns between cooperative and independent-goal tasks had participants rotate a joystick in each hand at asymmetric frequencies with on-going visual feedback (153). Greater activation of the right superior temporal gyrus, SMA, and M1 occurred when the hands were virtually coupled together compared to an independent-goal condition. The involvement of these regions may reflect the increased task complexity and greater spatial attention demands of the task compared to the bottle-opening task that physically couples both hands together (291, 297). These contrasting fMRI results also reinforce that the coordination strategy to achieve a cooperative goal is likely task-dependent. Further research is required to elucidate the neural mechanisms underlying cooperative movements.

In contrast, independent-goal tasks may decrease neural coupling so afferent information from each upper limb is processed locally within the contralateral hemisphere. This allows each upper limb to be controlled separately to achieve their unrelated goals, and possibly explains why unilateral perturbations do not elicit responses in the contralateral limb during independent-goal tasks. It was found that participants rotating a joystick in each hand had increased activation in the right inferior parietal gyrus and fusiform gyrus when on-going visual feedback was provided for each hand compared to when the hands were virtually coupled together (153). These two gyri are involved in attention and visual processing, respectively, and so their activation may reflect the demands of attending to visual feedback for each hand in the independent-goal condition (300, 301). Other studies found no differences in activation patterns between cooperative and independent-goal tasks (291, 297). The neural control of independent-goal tasks may vary with context.

6.3.1.3 Interaction between Symmetry and Goal

The previous sections have highlighted how the performance and mechanisms of bimanual tasks can depend on the movement symmetry and goal conceptualisation. Only a few studies though have investigated movement symmetry and goal conceptualisation together in the same experiment. This includes a pair of studies that found an interaction during movement preparation of an isometric force task. Hoyer and Bastian performed two experiments in the same study that had healthy adults learn a novel bimanual task (302). Participants pinched an isometric force sensor in each hand to vertically displace a virtual cursor for each hand towards separate targets. The targets required symmetric or asymmetric forces and the cursors were either independent or had a line unifying them to create a common goal, for a total of four task conditions. How the cursors appeared to participants during the four task conditions is shown in Figure 6.2. One of the experiments involved separate groups of eight people each learning one of the four task conditions with the practice briefly interrupted by a unimanual condition. The group learning the asymmetric independent-goal condition had longer reaction times than participants learning the other three conditions, as demonstrated in Figure 6.2. A different study reported the same finding using a near identical protocol, except participants did not train on the task and no task switching was involve (303). Interestingly, the second experiment from Hoyer and Bastian's study showed participants learning the symmetric common-goal and the asymmetric independent-goal conditions had similar error rates and reaction times if their practice was not interrupted with a unimanual condition. Symmetric independent-goal and asymmetric common-goal conditions were not included in this second experiment by Hoyer and Bastian. Together, the results from these two studies indicate that movement symmetry affected planning of independent-goal tasks but not common-goal tasks, and planning was most difficult for the asymmetric independent-goal task.

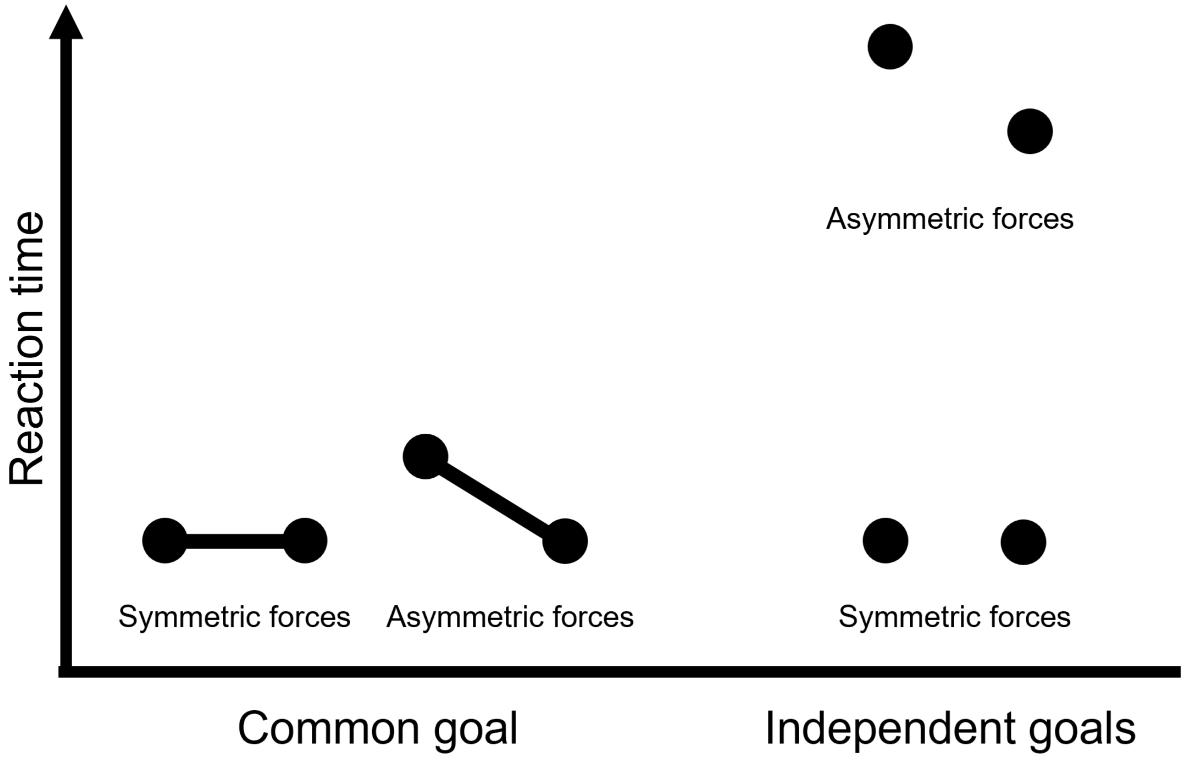


Figure 6.2. Simplified diagram showing how disrupting the learning of a novel isometric force task affected reaction time in a study (302). The circles represent cursors and a line unifying them was shown for the common-goal conditions. Interference of learning led to longer reaction times during the asymmetric independent-goal condition compared to the other three conditions. There were no differences in reaction time between the symmetric independent-goal condition and the symmetric and asymmetric common-goal tasks.

More important for the interaction between movement symmetry and goal conceptualisation is how they affect performance during tasks rather than during preparation. As discussed, healthy adults perform better during symmetric conditions than asymmetric conditions on lab-based tasks. However, performance of asymmetric tasks can be improved by manipulating how participants conceptualise the task. This is most successfully done using Lissajous feedback, which incorporates the position of both limbs into a single point to provide participants with a unified representation of the task and real-time visual feedback (259). Lissajous feedback is thought to improve performance by reducing visual and perceptual demands, promoting an external focus of attention on the task, and simplifying error detection and correction during the task (304). Lissajous feedback makes normally difficult rhythmic asymmetric tasks achievable after only a few minutes practice, such as rhythmic movements with a 90° relative phase (259, 305-307) and polyrhythmic movements with ratios such as 3:2 and 5:3 (308, 309). Assimilation effects during asymmetric discrete movements can also be overcome using Lissajous feedback (217). Lissajous feedback thus appears to be an effective method of improving performance during asymmetric laboratory tasks by creating a cooperative condition.

In contrast to most studies that use virtual feedback to manipulate goal conceptualisation, one study had different groups of healthy adults grip separate boards with each hand or with the boards physically joined together with a spring (310). Participants had to move and rotate the boards to symmetric or asymmetric orientations. Spatial coordination during the acceleration and deceleration phases of the task was determined using the difference in velocity between the hands. There were several interactions between movement symmetry and goal conceptualisation. Peak velocity for the symmetric independent-goal task was greater than the asymmetric independent-goal task, with no effect of symmetry for the common-goal task. During acceleration and deceleration participants were more spatially coordinated during the symmetric conditions than the asymmetric conditions, however this difference was greater for the common-goal group than the independent-goal group. These differences in coordination however did not affect overall performance as there was no interaction between factors for task completion time. The spring connecting the boards required approximately 10N of force to overcome which may have negatively affected coordination for the common-goal group, however this was not addressed by the authors. Regardless, the fact the objects were physically connected increases the task's ecological validity compared to tasks that perceptually unify the goal using Lissajous feedback.

Whether an interaction occurs between movement symmetry and goal conceptualisation at a mechanistic level also remains uncertain as no studies to date have attempted to answer this question. Both symmetric movements and cooperative tasks are thought to increase coupling between hemispheres, but whether tasks that are both symmetric and cooperative involve an additive effect of coupling remains unknown. Evidence against this idea comes from the finding of greater bilateral S2 activation and functional connectivity during an asymmetric cooperative task compared to a symmetric cooperative task and an asymmetric independent-goal task (291). Bilateral reflex responses to unilateral electrical stimulation were also elicited during the asymmetric cooperative task but not the symmetric cooperative task in the same study. Unfortunately a symmetric independent-goal condition was not included but it is still the only study to compare mechanisms underlying three of the four possible task conditions when considering movement symmetry and goal conceptualisation together. This finding of enhanced coupling during the asymmetric common-goal condition may be surprising given asymmetric movements are thought to decrease coupling between hemispheres and indicates the interaction between movement symmetry and goal conceptualisation on the neural control of bimanual tasks is more complicated than simply an additive effect of the coupling from symmetrical and common-goal task aspects. MRI and TMS studies with a 2x2 task paradigm varying both movement symmetry and goal conceptualisation will be necessary to provide a more complete picture of how these factors interact with one another on a neural level.

Lab-based tasks have provided rich information regarding the behavioural and neurophysiological processes underlying movement symmetry and goal conceptualisation in healthy adults. Lab-based tasks do have limitations though. Early studies of bimanual coordination often had low sample sizes of approximately 5 participants (219, 250, 251, 253, 255) which increases the likelihood of type II errors occurring (311). These low sample sizes were likely due to the technical challenges related to the recording and analysis of bimanual coordination measures compared to the present. More recent studies with healthy adults typically include at least ten participants, and commonly 20 – 30 participants (164, 259, 260, 312-314). Furthermore, parallel tasks have been largely unstudied in healthy adults using lab-based tasks. Parallel tasks have been studied in people with stroke though and it is based on those findings that common-goal tasks were subdivided into cooperative and parallel tasks in the Kantak taxonomy (151). Distinguishing between cooperative and parallel tasks may be important when discussing bimanual coordination in people with stroke but less so in healthy adults.

The most significant limitation of lab-based tasks is their ecological validity. Healthy adults coordinate their hands together for ADLs including opening a jar or shooting a basketball, which are very different to lab-based tasks such as continuously drawing circles with both hands at increasing frequencies or reaching bimanually to press arbitrary buttons. Assistance such as Lissajous feedback provided during lab-based tasks is also not available during everyday life. Moreover, lab-based tasks typically have each hand achieve an independent goal whereas most real-world tasks use both hands together to achieve a single common goal. ADLs have a wide range of additional considerations that are often controlled in lab-based tasks such as greater degrees of freedom for movement, the influence of the surrounding environment, and task familiarity. A disparity between laboratory performance and real-world upper limb performance has been highlighted for healthy adults (315). Capturing real-world bimanual performance and its underlying mechanisms thus requires studying participants performing tasks that more closely replicate ADLs.

6.3.2 Real-World Tasks

Behavioural studies using real-world tasks often examine similar kinematic measures as lab-based tasks but are far less common. The greater degrees of freedom when performing real-world tasks can make them challenging to standardise and replicate, which in turn can make it difficult to directly compare results between studies using different tasks (285). An additional challenge is finding tasks that can naturally be performed symmetrically and asymmetrically, and goal conceptualisation is difficult to study using real-world tasks for a similar reason. As a result, only a few tasks have investigated movement symmetry and goal conceptualisation during real-world tasks. Instead, real-world tasks are primarily used to compare coordination between people with and without neurological disorders. Only the results from healthy adults will be discussed here.

A naturalistic bimanual task that is commonly studied in healthy adults is the asymmetric parallel item retrieval drawer-task. Participants use one hand to grasp a handle to open a drawer and use their other hand to reach inside the drawer to retrieve an item or press a button (168, 284, 285). Healthy younger and older adults move both upper limbs simultaneously when performing this task as they begin reaching forward with the item-retrieving hand while the other hand begins to pull the drawer backwards. Interestingly, prolongating the drawer pulling phase by increasing the force required to open it also leads the hand retrieving the item to slow down to maintain temporal coordination between the hands (285). These results indicate that healthy adults will instinctively coordinate to move both hands simultaneously to complete a parallel task even when it is not necessary, likely to increase task efficiency. Healthy adults are also highly temporally and spatially coordinated during real-world asymmetric common-goal tasks such as pouring a glass of water (316) and opening a jar (317), as well as the symmetric parallel and cooperative tasks of reaching to grasp a box and picking up a box, respectively (168).

There are several biological and practical reasons why healthy adults are highly coordinated during real-world asymmetric tasks but struggle with lab-based asymmetric tasks. Unimanual reaching to grasp a tool becomes more coordinated with greater practice using the tool, although it remains to be determined whether this effect occurs during bimanual tasks (318, 319). Other studies have shown the kinematics of reach-to-grasp movements differ between instructed movements and natural movements (320, 321). Practically, most real-world tasks are relatively simple to complete whereas many lab-based asymmetric tasks are intentionally very difficult or are performed until failure, such as increasing movement frequency during bimanual circle drawing. Thus, healthy adults can easily coordinate their hands to perform both symmetric and asymmetric bimanual tasks in everyday life. It should be noted however that real-world tasks performed in the lab such as the item retrieval drawer-task still do not perfectly capture bimanual coordination during ADLs as they do have several constraints necessary for some level of standardisation.

Only one real-world task to date has been used to directly compare common-goal and independent-goal conditions. Thirteen healthy older adults reached forward symmetrically to grasp one large tray with both hands or a smaller tray in each hand before lifting and placing them on a ledge forward from their starting positions (322). The first phase of reaching to grasp the trays was comparing a parallel condition versus an independent-goal condition. Participants had comparable spatial and temporal coordination between conditions although the non-dominant hand reached slower during the independent-goal condition than the parallel condition. The authors did not comment on this finding but it could reflect the additional demands of needing to visually attend to two objects during the independent-goal condition.

The second phase of the task involving lifting and moving the tray(s) compared a cooperative condition versus an independent-goal condition. There were no differences in coordination or task performance between conditions. It could be argued this tray-lifting task is closer to a lab-based task than a real-world task but the fact participants transported real objects with complete vision of their arms makes it similar to ADLs such as lifting one or two briefcases by the handle. Furthermore, the common-goal condition involved a single physical object in comparison to the many lab-based studies that perceptually unify the task using Lissajous feedback. It should be noted however the trays were intentionally made light and easy to transport so whether needing to account for a heavy mass would affect coordination is uncertain. Regardless, the results mirror those from lab-based tasks demonstrating similar task performance during independent-goal and common-goal tasks.

Several important questions remain to be answered regarding bimanual coordination during real-world tasks. Coordination during real-world independent-goal tasks has yet to be investigated except using the tray-lifting task (322). The constraints on what tasks can be performed during MRI or TMS has meant that the neural mechanisms of bimanual coordination have yet to be examined during real-world tasks. Furthermore, although the tasks described here have higher ecological validity than most lab-based tasks, they are still far removed from how adults coordinate their hands in everyday life. One reason is that the real-world tasks used in studies predominantly require a single step to complete compared to many tasks in real-world situations that require multiple steps. This was addressed in one study using a reach-to-lift box task by examining the kinematics of the symmetric parallel reaching and symmetric cooperative lifting aspects separately, and this could be extended to more complex tasks such as a making a cup of tea and gardening (168, 323). This method of segmenting the task based on the bimanual coordination conditions would allow greater insight into how changing bimanual coordination requirements affects task performance in more natural situations.

6.4 Bimanual Coordination and Aging

It is important to briefly discuss how healthy aging affects bimanual coordination because most strokes occur in older adults but most studies with healthy participants use younger adults (6, 37). A meta-analysis of 47 studies found that older adults are overall less accurate, more variable, and have longer movement times compared to younger adults across a range of bimanual lab-based tasks (324). However, this can depend on the movement symmetry and goal conceptualisation of the task. This section will only discuss how aging affects bimanual coordination comparing healthy younger versus older adults, who are typically aged between 20 – 30 and 60 – 80 in studies respectively.

Healthy aging affects symmetric and asymmetric tasks differently. Younger and older adults perform similarly on continuous rhythmic tasks regardless of the spatial symmetry (325, 326) but older adults perform worse on polyrhythmic tasks with temporal asymmetry (327).

Moreover, older adults perform worse than younger adults during intermittent asymmetric bimanual drawing as well as rhythmic tasks with discrete movements such as bimanual finger tapping (325, 326, 328, 329). These specific deficits might reflect difficulties with repeated stopping and starting (326).

The effects of aging on bimanual coordination during discrete reaching were studied using a task that had younger and older adults pick up a ball with each hand and place them on a tray synchronously (330). The distance from the tray to the balls was either symmetric or asymmetric. No group difference in task time was present but older participants reached higher peak velocities during movement in addition to spending longer and making more adjustments immediately prior to placing the balls. The authors suggested this was possibly because older adults needed to visually attend to both balls at the same time to synchronise placing them, which may relate to a decline in proprioception with aging (331). Thus, vision may be more important for bimanual coordination during difficult tasks in older adults than younger adults.

To date, no studies have investigated how aging affects common-goal tasks and independent-goal tasks with the same cohort. Instead, several studies have focused on how aging affects cooperative tasks. For example, younger and older adults performed a task mimicking bread slicing where both hands were physically connected with a spring (246). One hand needed to accurately reach forwards while the other hand stabilised the spring load to remain stationary. Compared to the younger cohort, the older adults had lower velocity and greater path deviations for the reaching arm while the stabilising arm experienced greater and faster deviation. These results were present regardless of which roles the dominant and non-dominant hand played. Both groups had superior stabilising performance with their non-dominant hand, which supports the complementary dominance hypothesis of handedness (115). However, there was a greater difference in stabilising performance between the dominant and non-dominant limb in older adults than in younger adults which the authors suggested may reflect a decreased ability of the nonspecialised dominant hemisphere for stabilising performance. Older adults were also slower than younger adults during each phase of a separate task which required them to hold and stabilise a tray with their non-dominant hand while placing two balls onto it with their dominant hand (332). Younger and older adults displayed similar performance stabilising the tray with their non-dominant hand, potentially because the hands were not physically coupled together as they were for the task mimicking bread slicing in which older adults stabilised worse than younger adults (246). Together these two studies indicate that older adults perform worse on asymmetric cooperative tasks than younger adults.

Several real-world tasks have been used to examine the effects of aging on bimanual coordination. A unique study examined bimanual coordination in younger adults and two groups of aged participants with mean ages of 63 and 71 (333). These groups of aged participants were termed the older and retiree groups, respectively. It is one of the few studies to include real-world tasks requiring multiple steps to complete. One task was to prepare a letter to be sent which included folding and placing a piece of paper in an envelope before stamping and sealing the envelope. The second task involved preparing a glass of ice-tea. When performing the tasks at their natural speed all three groups displayed similar performance and bimanual coordination, which was defined in this study as simultaneous movement of both hands on each task. All groups also displayed similar coordination when performing the tasks at the maximum speed possible, with the main difference being the retiree group taking longer to complete the ice-tea task compared to the other two groups. The authors suggested the increased task duration in the retiree group may be due to general cognitive decline on the basis that the retiree group performed significantly worse than the other two groups on a trail making task testing sequencing and task switching. A separate study had younger and retiree adults prepare a hot cup of tea which included more steps than the ice-tea task (334). Retiree adults moved slower, made more errors, and took longer to complete the task than younger adults. Together these studies demonstrate that bimanual ADL performance is influenced by age in a task-dependent manner. Further studies may examine how bimanual coordination and task performance is influenced by age amongst older adults.

Bimanual coordination deficits with aging reflect structural and functional neurological changes. Both grey and white matter volume is decreased in older adults compared to younger adults (335). One hypothesis is that older adults recruit more facilitatory interhemispheric interactions and hyperactivate motor regions compared to younger adults in order to compensate for this structural decline (336). Several studies have demonstrated that greater integrity of the corpus callosum, which mediates interhemispheric interactions, is associated with better bimanual task performance in older adults (327, 328). Another study reported older adults with greater corpus callosum integrity had lower levels of interhemispheric inhibition during bimanual tasks, and lower levels of inhibition were associated with better bimanual task performance (337). Greater activation of motor regions in older adults compared to younger adults has also been observed during bimanual tasks (297, 338). It was reported that separate groups of younger and older adults were similarly coordinated and stable performing symmetric and asymmetric wrist flexion-extension movements but older adults had greater activation of bilateral sensorimotor cortices, SMA, PMd, and the cerebellum during the tasks (338). Thus, greater activation of motor regions and increased facilitatory interactions between these regions may be required for older adults to perform similarly to younger adults during bimanual tasks.

TMS has been used to study how aging affects the involvement and influence of secondary motor regions during bimanual tasks, particularly the PMd and SMA. Resting facilitation and inhibition from the left PMd to the left M1 is lower in older adults compared to younger adults, indicating the intrahemispheric influence from the PMd may be reduced with aging (339). Resting interhemispheric inhibition from the left PMd to the right M1 is similar between younger and older adults though, and aging has been reported to have no effect on inhibition from the left PMd to the right M1 during preparation of a complex asymmetric task (327, 340). Therefore, alteration to the intrahemispheric role of the left PMd or the interhemispheric role of the right PMd may contribute to older adults’ worse performance on asymmetric tasks. Facilitatory interactions from the SMA may also be impaired in older adults as facilitation from the SMA to the ipsilateral M1 has been reported using TMS in younger adults at rest but not older adults (341, 342). It remains to be determined whether this absence of facilitation from the SMA in older adults also occurs during bimanual movements. Given their roles, age-related declines of PMd and SMA function may worsen performance on asymmetric tasks by impairing processes such as motor planning and task sequencing.

The ability for humans to coordinate their upper limbs together to achieve a plethora of tasks has been studied for decades. Symmetric movement patterns are consistently more stable and easier to perform than asymmetric patterns on lab-based tasks, but healthy adults seem adept at performing real-world tasks regardless of movement symmetry. Healthy adults perform similarly on independent-goal and cooperative tasks but there is evidence that separate coordination strategies are employed for each condition. Behavioural studies indicate an interaction between movement symmetry and goal conceptualisation on bimanual coordination is present in healthy adults, but future studies will be needed to elucidate the extent and relevance of this interaction.

Two of the most common techniques used to explore the mechanisms underlying bimanual coordination are MRI and TMS, and results using these techniques have been discussed throughout this chapter. TMS in particular has emerged as a useful method for assessing the role of individual brain regions such as the SMA. Moreover, TMS has provided greater understanding of the brain networks engaged in bimanual coordination by probing facilitatory or inhibitory influences onto M1 from contralateral motor areas (343). The next chapter will provide a comprehensive overview of TMS and will lead into the following experimental chapter using TMS to study bimanual coordination in healthy adults.

7 Transcranial Magnetic Stimulation

TMS is a non-invasive technique used to stimulate specific regions of the brain. This chapter will provide an overview of TMS and its mechanisms as well as protocols used to investigate interhemispheric pathways. TMS measures of inhibition between M1s (IHI) will be the focus because they were recorded as part of an experiment in the next chapter.

7.1 Overview

In the mid-1900s there was a desire to develop a method of noninvasively stimulating the brain to study its cellular mechanisms. The first successful non-invasive stimulation method was transcranial electrical stimulation (TES) but its use was limited because it was painful for participants (344). TMS was first introduced in 1985 as a painless alternative to TES (345). Since then, the popularity of TMS for studying the brain has continually increased.

TMS involves holding an insulated coil of wire against the participant's head to stimulate a specific region of the brain. Stimulation is produced by discharging a capacitor to send a powerful electric current through the coil that generates a magnetic field perpendicular to the surface of the cranium lasting approximately 100 ms (346). The magnetic field passes through the cranium to produce an eddy current in the brain that excites neuronal axons underlying the TMS coil. Stimulation of M1 activates corticospinal neurons directly or trans-synaptically via excitatory post-synaptic potentials from interneurons. A series of action potentials from corticospinal neurons propagate down the lateral CST, synapse with α-motoneurons, and can ultimately lead to the contraction of muscles whose representations in

M1 were activated by the TMS pulse. Higher TMS intensities lead to a greater number of corticospinal neurons being activated and generate a stronger muscle contraction.

The descending responses following TMS can be recorded and quantified in two ways. The first is to use epidural recordings to record responses at the spinal cord level, typically around C2 (347). This has the advantage of being a direct recording early in the descending volleys' pathway but is extremely rare as it requires implanted electrodes in the epidural space of the participant. Responses are more commonly recorded indirectly with electromyography (EMG) by using electrodes to measure the electrical potential from the ensuing muscle contraction following TMS. These electrical responses are termed motor evoked potentials (MEPs). MEPs are influenced by synaptic connections at the spinal cord level but the feasibility and widespread applicability of EMG makes it superior to epidural recordings for almost all TMS studies. An overview of MEP generation using TMS is displayed in Figure 7.1.

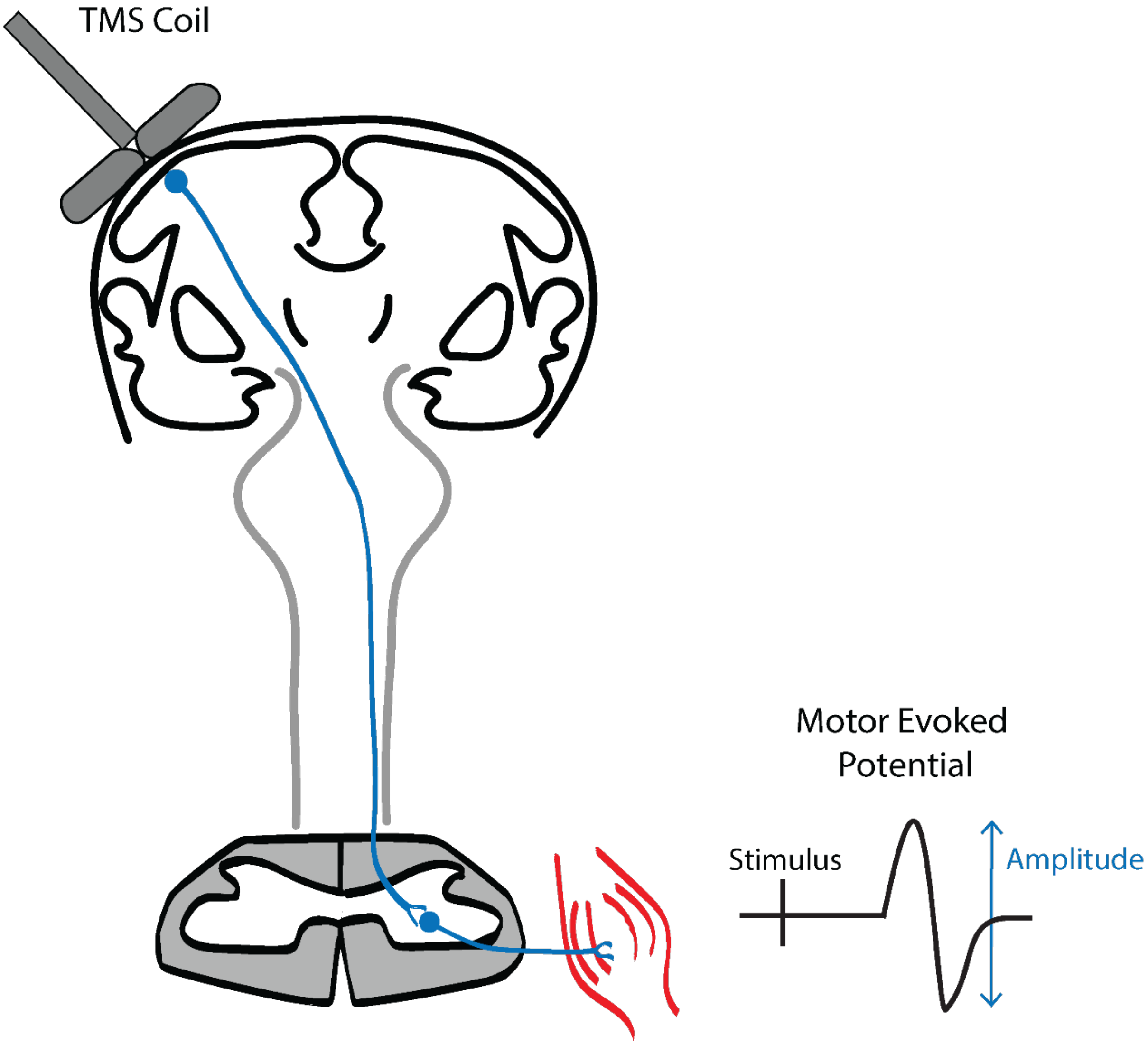


Figure 7.1. Overview of MEP generation. TMS delivered over M1 causes a series of descending waves to propagate down corticospinal neurons of the lateral CST. These corticospinal neurons project to the spinal cord where they synapse with α-motoneurons. From here, α-motoneurons project to skeletal muscles and cause them to contract. The electrical potential from the muscle contraction can be recorded as an MEP using EMG. The amplitude of the MEP response is commonly used as a measure of corticomotor excitability.

7.2 Mechanisms

Early TMS studies focused on understanding the neural mechanisms of TMS. Epidural recordings and EMG were both used to determine which types of neuronal cells are activated by TMS and how action potentials propagate down the CST. Following TMS, a series of descending waves propagate down corticospinal axons. The first descending wave has been termed the direct wave, or D-wave, because it originates from the direct activation of corticospinal neuron axons in M1 (346). A series of descending waves occur following the D-wave at regular intervals of 1.5 ms. These later waves have been termed indirect waves, or I-waves, because they are produced through the trans-synaptic activation of corticospinal neurons by interneurons. More specifically, the three predominant I-waves are termed I1-, I2- and I3-waves based on their latencies of 1.5 ms, 3 ms, and 4.5 ms, respectively. Numerous models have been proposed for how the train of I-waves are produced by TMS. Models include I-waves being generated through chains of interneurons, by corticospinal neurons themselves, or based on which parts of corticospinal neurons receive synapses from interneurons (348-350).

The direction of the current induced in the brain determines which I-waves are preferentially recruited by TMS. All current directions mentioned from here on will refer to the direction of the intracortical current rather than current in the TMS coil. I1-waves are preferentially generated using a posterior-anterior (PA) current at a 45° angle from the midsagittal line with low stimulus intensities, however late I-waves and eventually a D-wave are recruited with higher intensities (348, 351-353). Conversely, anterior-posterior (AP) and medial-lateral (ML) currents preferentially recruit I3-waves (348, 351, 354, 355). Current in a lateral-medial (LM) direction at threshold produces a D-wave and higher stimulus intensities elicit both early and late I-waves (348, 353). PA stimulation is most often used when recording from upper limb muscles as this direction generates the strongest electrical current within M1 and is most reliable for generating MEPs (356-359).

7.3 Single-Pulse TMS

TMS can be used to obtain excitatory, inhibitory, and facilitatory measures from M1. The simplest form of TMS is single-pulse and involves administering a single stimulus from one coil (360). Most TMS studies use single-pulse TMS to locate the ideal coil location on the scalp for activating the muscle of interest. This process is called hotspotting and is often done by finding the coil location over M1 that generates the largest amplitude MEPs in the muscle of interest.

A common use of single-pulse TMS is to determine corticomotor excitability (CME). CME can be assessed with several measures including MEP amplitude, stimulus-response curves, or the resting motor threshold (RMT) that is defined as the lowest stimulus intensity that can reliably elicit an MEP (360). The most used measure of CME is MEP amplitude. Larger MEP amplitudes for a given stimulus intensity indicate higher CME as a greater number of corticospinal neurons were closer to their membrane threshold and activated by the stimulus.

Measuring CME can be used to evaluate whether interventions or the independent variable of interest influences corticomotor system excitability. For example, positive modulators of $GABA_A$ receptors lower MEP amplitude at rest which indicates that GABA-mediated inhibition at least partially regulates CME (361). Measuring CME can also be used to understand the pathology of neurological disorders. An example is Parkinson’s disease which increases resting CME compared to healthy adults (362, 363).

One limitation of single-pulse TMS is that it cannot distinguish whether the modulation of MEPs is due to cortical or subcortical influences. Furthermore, MEP amplitude is highly variable between trials due to physiological and technical factors such as the intrinsic excitability of α-motoneurons, the participant's level of arousal, and small deviations in TMS coil position. Recent studies have suggested that 20 – 30 MEPs are needed to ensure excellent inter-individual and between-session reliability of CME results (364, 365). However, studies still commonly record between 12 and 16 MEPs for CME due to time constraints and the participant's tolerance to repeated stimulation.

7.4 Dual-Coil TMS

Dual-coil TMS involves using two TMS coils to each deliver a single stimulus at separate locations. The first and second stimuli delivered are termed the conditioning stimulus (CS) and test stimulus (TS), respectively. The influence of the CS can be determined by comparing the amplitude of MEPs produced by the TS alone and those with the TS and CS together. These are referred to as non-conditioned (NC) and conditioned (C) MEPs, respectively. Protocols that result in greater amplitude for the C MEP than the NC MEP are called facilitatory, while protocols resulting in a lower C MEP amplitude are called inhibitory. The influence of the CS depends on the time between the CS and TS, also known as the interstimulus interval (ISI), as well as the intensity of both stimuli.

Dual-coil TMS is used to examine connections and interactions between separate areas of the brain. One limitation is that it can only be used to measure the influence of regions onto M1 because the TS must be administered to M1 to generate an MEP. Dual-coil TMS is predominantly used to study the inhibitory influence of one M1 onto the contralateral M1 that is mediated by interhemispheric pathways. These interhemispheric pathways are studied using IHI protocols.

7.5 Interhemispheric Inhibition

IHI is elicited by delivering a suprathreshold CS to a brain region in one hemisphere and a suprathreshold TS to the contralateral M1 (366). IHI here will always refer to inhibition between M1s unless stated otherwise. The CS activates excitatory transcallosal fibres in the stimulated M1 (conditioned M1) that project via the corpus callosum to the contralateral M1 (test M1). The excitatory transcallosal fibres exert their inhibitory effect in the test M1 by activating intracortical inhibitory interneurons (366-369).

There are two distinct phases of IHI, a shorter phase with an ISI of approximately 10 ms (SIHI) and a longer phase with an approximately 40 ms ISI (LIHI). SIHI and LIHI are mediated by discrete mechanisms and transcallosal pathways. One study recorded MEPs from bilateral first dorsal interosseous muscles and measured SIHI and LIHI from five brain regions to the contralateral M1 (366). These five regions were the M1 representations for the hand and face, PMd, dorsolateral prefrontal cortex, and the primary somatosensory cortex. Two key differences between SIHI and LIHI emerged. LIHI had a lower threshold to elicit compared to SIHI, and LIHI was present when conditioning all five brain regions while SIHI could not be elicited when the CS was applied to the dorsolateral prefrontal cortex and primary somatosensory cortex. Differing effects of SIHI and LIHI have also been reported during muscle activation, movement preparation, and fine-motor tasks (370-372). Common protocols for eliciting SIHI and LIHI are shown in Figure 7.2.

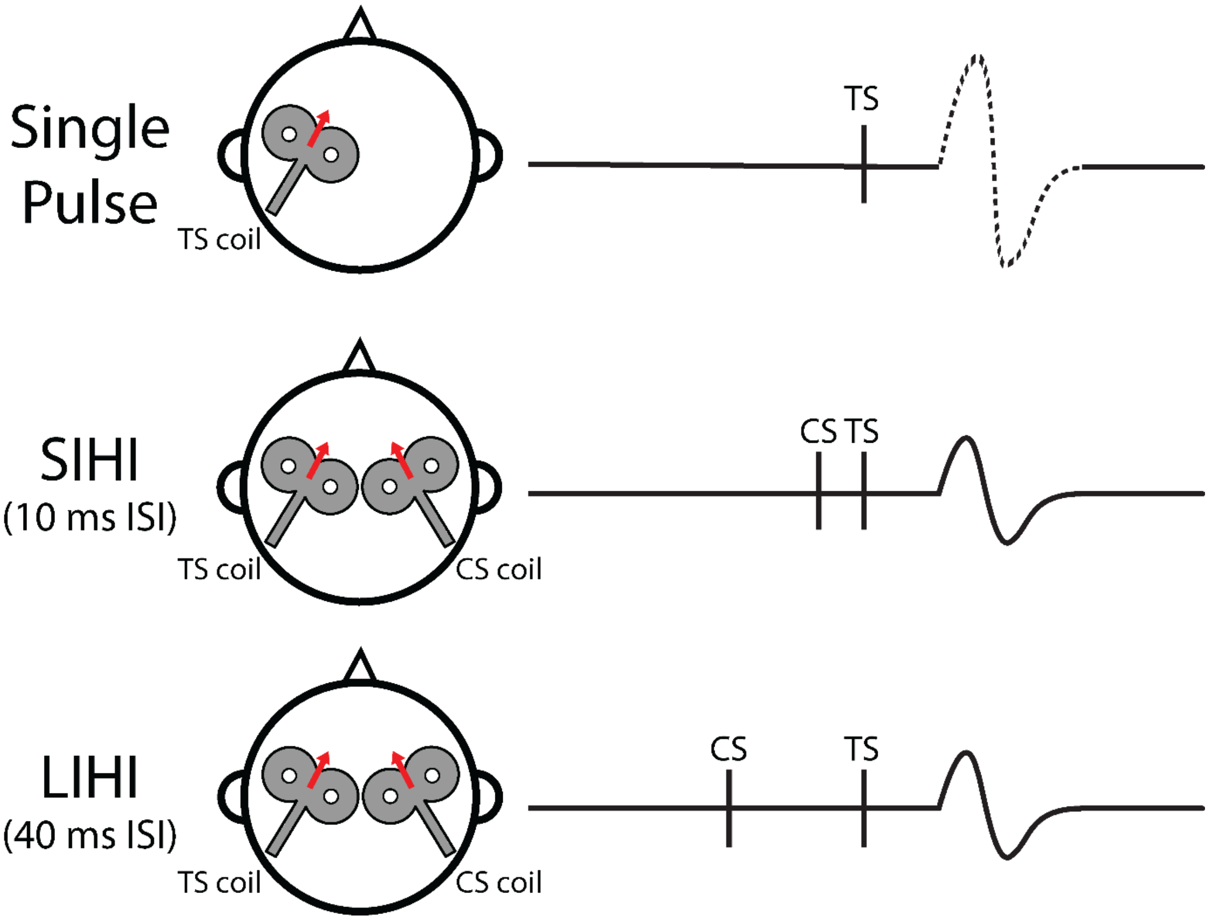


Figure 7.2. TMS protocols for measuring SIHI and LIHI. The dashed line represents a NC MEP from a single TS and solid lines represent C MEPs resulting from a CS and TS. Red arrows indicate the direction of the intracortical current induced by the TMS coil. SIHI and LIHI inhibit MEPs.

7.5.1 SIHI and LIHI Parameters

The intensity of the TS for eliciting SIHI and LIHI can be set using several methods. One method is setting the TS to produce a NC MEP of a given amplitude, such as 1 or 1.5 mV, to ensure that inhibition can be detected (366, 373, 374). One limitation of this method is that some participants are unable to produce MEPs of the target amplitude, especially at rest. An alternative method is setting the TS to a percentage of the participant's RMT. The TS is typically set to 120% or 130% RMT and has the advantages of being individualised to the participant and usually avoiding ceiling effects (375, 376). However, this method can produce NC MEPs with very low amplitudes in some participants which can make it difficult to detect inhibition. Initial studies measuring IHI often set the TS based on a percentage of the maximum stimulator output of the TMS capacitor but this method has fallen out of favour as it has the significant disadvantage of not being individualised to the participant (367, 368). In general, SIHI and LIHI have an inverse relationship with TS intensity as there is less inhibition with higher TS intensities (367, 369, 377).

The CS for SIHI and LIHI can be determined with similar methods as the TS, such as 120% RMT or an intensity that produces a 1 mV MEP (366, 373, 374). The TS and CS are often set to the same intensity for this reason. An alternative method is to set the CS to produce approximately 50% inhibition to ensure that any modulation of IHI can be detected (378). In contrast to the TS, the amount of SIHI and LIHI increases with higher CS intensities (366, 368, 370, 379). This is likely because higher CS intensities activate a greater number of transcallosal neurons, leading to greater inhibition of the test M1.

SIHI and LIHI largely do not depend on the induced direction of current in the brain. PA and AP currents for the TS induce similar levels of SIHI and LIHI (368, 374). SIHI and LIHI can be elicited using a CS with PA, AP, LM, or ML current directions (366, 368, 370). Most SIHI and LIHI protocols use a PA current for both stimuli unless D-waves or late I-waves are being specifically investigated.

Early IHI studies often focused on determining the range of ISIs that produced inhibition. SIHI can typically be elicited with ISIs from approximately 6 to 12 ms whereas LIHI is more variable and can be obtained using ISIs from 20 to 60 ms (366-368, 370). The most common

ISIs for SIHI and LIHI are 10 ms and 40 ms respectively as they produce the greatest inhibition (366, 374, 378).

7.5.2 SIHI Mechanisms and Roles

SIHI likely acts via fast and direct excitatory transcallosal fibres based on its short ISI (366). The neurotransmitters mediating SIHI are not yet known but it is unaffected by $GABA_A$ and $GABA_B$ agonists (376, 380). The effect of other neurotransmitters on SIHI needs to be investigated to better understand its mechanisms. This is especially true when compared to the pharmacological work done on other TMS measures. For example, agonist and antagonist drugs modulating $GABA_A$, $GABA_B$, dopamine, and noradrenaline have been studied with inhibitory single-coil TMS measures whereas only $GABA_A$ and $GABA_B$ agonists have been studied with SIHI (361).

SIHI has been proposed as an important interhemispheric mechanism for performing unimanual upper limb movements (379, 381, 382). The M1s controlling the active and resting limbs during unimanual movements are referred to as the active and rest M1, respectively. SIHI from the active M1 to rest M1 during unimanual movements is thought to actively suppress contralateral homologous muscles and prevent bilateral mirror movements. Indeed, studies have found SIHI from the active M1 to the rest M1 increases during unimanual movements compared to rest (382-384) whereas SIHI from the rest M1 to the active M1 decreases (370, 385). In contrast, several other studies have found SIHI from the active M1 to the rest M1 decreases during unilateral contraction (375, 378, 385). One proposed explanation is that a reduction of SIHI to the rest M1 may prepare the rest limb to initiate movement if sudden bimanual movements are necessary (375). Two other studies found SIHI increased from the active M1 to the rest M1 during a fine motor task in which participants transported glass balls with chopsticks compared to rest, but no difference in SIHI when participants mimicked the task without using chopsticks or performed a unilateral isometric contraction (372, 386). Thus, SIHI may act to prevent bilateral mirror movements only during certain unimanual tasks.

SIHI may also play an important role during bimanual tasks. A decrease in SIHI may mediate the functional coupling and resultant increase in the interhemispheric exchange of sensorimotor information that has been hypothesised to occur during symmetric movements. Symmetric active-passive wrist flexion-extension movements decrease SIHI to the rest M1 for up to 15 minutes after the task compared to rest or the same movements performed asymmetrically (272). Although one upper limb was at rest during the task, symmetric bimanual movements were still being performed. Another study found a decrease in SIHI was associated with greater maximum tapping speed during preparation of a symmetric bimanual finger tapping task, but not for asymmetric tapping (279). In contrast, a study found that SIHI to the right M1 was similar during unilateral left first dorsal interosseous isometric force production at 30% maximum voluntary contraction (MVC) and symmetric force production (275). Similar levels of SIHI have also been reported during unilateral abductor pollicis brevis isometric force production at 5% MVC and symmetric force production (387). It is possible that 5% and 30% MVC were too low to influence SIHI during symmetric tasks, or a decrease in SIHI and subsequent functional coupling may be more important during dynamic symmetric bimanual movements rather than isometric force production.

7.5.3 LIHI Mechanisms and Roles

LIHI likely operates through slower or more indirect excitatory transcallosal pathways compared to SIHI based on its longer ISI (366). Potential indirect excitatory pathways have not yet been proposed. LIHI is thought to be mediated through postsynaptic $GABA_B$ receptors on corticospinal neurons following activation of inhibitory interneurons in the test M1 (376, 380). Much like SIHI, further studies targeting neurotransmitters other than GABA are needed to fully understand the pharmacological profile of LIHI.

The role of LIHI is still largely uncertain. LIHI does not appear to be an important mechanism mediating unimanual actions because most studies have found LIHI to both the rest and active M1 is unaffected by unilateral contractions (370, 374, 381, 383). However, one study found that LIHI decreased to both M1s during preparation of unimanual movement regardless of whether participants were provided information about which hand they had to move (371). Another study similarly reported that LIHI to both M1s decreased during preparation of a bimanual index finger tracking task regardless of whether participants were preparing to rhythmically move their hands at the same speed or different speeds (183). A decrease in LIHI may help disinhibit both M1s and prepare for hand movement. Taken together, these results indicate LIHI may provide more global inhibition compared to SIHI but future studies should further explore the role of LIHI during bimanual tasks.

7.5.4 Criticisms of SIHI and LIHI Protocols

The use of TMS to measure inhibition between M1s with SIHI and LIHI protocols has received criticism (196). Carson stated that the terms SIHI and LIHI has led to confusion and over-reliance on TMS results to explain the physiological purpose and mechanisms of inhibition between hemispheres that the SIHI and LIHI protocols aim to measure. Carson proposed that the cortical motor network in each hemisphere is made up of nodes comprising a facilitatory centre and an inhibitory periphery, and this idea has been termed centre-surround inhibition. The idea of centre-surround inhibition is primarily derived from data from animal studies and has been supported by other authors (388, 389). In the centre-surround inhibition model, excitatory interhemispheric neurons from one hemisphere influence descending outputs through the CST depending on whether they synapse with excitatory or inhibitory neurons in the contralateral hemisphere. Increases in surround inhibition of one hemisphere are reciprocal and give rise to symmetrical inhibition in the contralateral hemisphere. Inhibition between hemispheres in the centre-surround model allows greater precision for controlling influences onto corticospinal neurons and increases integrative functions between hemispheres rather than simply acting to suppress activity in the contralateral hemisphere, such as the suggested role of SIHI in preventing bilateral mirror movements (379, 381, 382).

Carson highlighted several features of TMS protocols, such as SIHI and LIHI protocols, that can limit their use in providing conclusions about motor physiology (196). Although the stimulation from TMS is thought of as relatively focal, one study found indirect evidence that TMS delivered at 120% RMT affects an area of several cm^2 which can include several neighbouring gyri to M1 (390). How these inadvertently stimulated neighbouring gyri may influence interhemispheric interactions between M1s is usually not accounted for. Related to this, MEPs only reflect the sum of all the inhibitory and facilitatory processes that occur not only at the cortical level but also subcortically and spinally. Although SIHI and LIHI are likely cortically mediated, using MEPs to measure the extent of inhibition may not accurately reflect more nuanced interhemispheric interactions that are occurring (366-368). Moreover, TMS fundamentally creates a non-physiologically normal brain state as neuronal cells in M1 and neighbouring gyri are excited artificially. Therefore, it should be questioned how accurately TMS results reflect neurophysiological mechanisms underlying processes such as bimanual coordination in everyday life. This notion has been highlighted elsewhere (391). Carson did however mention that theories are largely motivated by the available technology at the time. It will remain to be determined whether our current theories of interhemispheric inhibition, which have been influenced by SIHI and LIHI results, are modified with the advent of new technologies that can better investigate interhemispheric interactions.

TMS is a powerful tool that can be used to investigate the intracortical and interhemispheric mechanisms of bimanual coordination. SIHI and LIHI protocols can study pathways and interactions that have demonstrated some importance for coordinating bimanual actions, but evidence has predominantly come from isometric force tasks. Studying SIHI and LIHI during more complex bimanual tasks that more accurately reflect how both hands are used for ADLs would further our understanding of the neural mechanisms underlying bimanual coordination.

The following chapter presents an experiment performed as part of this thesis using TMS during bimanually active dynamic tasks requiring different types of bimanual coordination. The aim of the experiment was to determine whether movement symmetry and goal conceptualisation modulate CME, SIHI, and LIHI in healthy adults performing bimanual tasks.

8 The Modulation of Short- and Long-Latency Interhemispheric Inhibition during Bimanually Coordinated Movements

This chapter was published as an original article in Experimental Brain Research in 2021.

Jordan HT, Schrafl-Altermatt M, Byblow WD, Stinear CM. The modulation of short and long-latency interhemispheric inhibition during bimanually coordinated movements. *Exp Brain Res*, DOI: 10.1007/s00221-021-06074-z.

8.1 Abstract

Bimanual coordination is essential for the performance of many everyday tasks. There are several types of bimanually coordinated movements, classified according to whether the arms are acting to achieve a single goal (cooperative) or separate goals (independent), and whether the arms are moving symmetrically or asymmetrically. Symmetric bimanual movements are thought to facilitate corticomotor excitability (CME), while asymmetric bimanual movements are thought to recruit interhemispheric inhibition to reduce functional coupling between the motor cortices. The influences of movement symmetry and goal conceptualisation on interhemispheric interactions have not been studied together, and not during bimanually-active dynamic tasks. The present study used transcranial magnetic stimulation (TMS) to investigate the modulation of CME and short- and long-latency interhemispheric inhibition (SIHI and LIHI, respectively) during bimanually-active dynamic tasks requiring different types of bimanual coordination. Twenty healthy right-handed adults performed four bimanual tasks in which they held a dumbbell in each hand (independent) or a custom device between both hands (cooperative) while rhythmically flexing and extending their wrists symmetrically or asymmetrically. Motor evoked potentials were recorded from the right extensor carpi ulnaris. We found CME was greater during asymmetric tasks than symmetric tasks, and movement symmetry did not modulate SIHI or LIHI. There was no effect of goal conceptualisation nor any interaction with movement symmetry for CME, SIHI or LIHI. Based on these results, movement symmetry and goal conceptualisation may not modulate interhemispheric inhibition during dynamic bimanual tasks. These findings contradict prevailing thinking about the roles of CME and interhemispheric inhibition in bimanual coordination.

8.2 Introduction

Many activities of daily living are performed bimanually such as buttoning a shirt and preparing meals (392). There are several ways to classify bimanually coordinated movements and one system proposed by Kantak et al. involves a few key factors (151). One factor is whether the movements are symmetric or asymmetric with respect to the midline. It is well established that symmetric bimanual tasks are easier to perform than asymmetric tasks (221), which is thought to be because symmetric movements engage homologous muscles which leads to a functional coupling between the primary motor cortices (M1) (393). A reduction of interhemispheric inhibition (IHI) acting between homologous M1 representations may facilitate corticomotor excitability and enhance functional coupling for symmetrical movements. However, the potential role of IHI has recently been questioned (196).

Kantak et al. further classified symmetric and asymmetric bimanual movements according to the goal(s) of the task (151). Previous literature has defined goal conceptualisation in terms of spatial or symbolic cues, or having internal or external guidance during the task (394). Kantak et al. however defined goal conceptualisation in terms of the movements of the two hands having either the same goal or different goals, and this definition was used for the present study. Tasks in which both upper limbs must act at the same time to achieve a single goal are termed cooperative, whereas independent tasks involve each upper limb achieving a separate goal. Compared to independent tasks, the neural control of cooperative tasks appears to be more bilaterally distributed across the hemispheres and engage greater functional coupling. Cooperative tasks lead to greater bilateral activation of the secondary somatosensory cortex compared to independent tasks (291), and unilateral upper limb perturbations can elicit bilateral reflex responses during cooperative tasks but not independent tasks (165, 166, 291). Additionally, behavioural studies have found an interaction between movement symmetry and goal conceptualisation that affects bimanual task performance in heathy adults (395) and people with chronic stroke (286), and so these task features should be considered together. Despite these behavioural findings, no studies to date have investigated the neural mechanisms underlying bimanual coordination when considering both movement symmetry and goal conceptualisation.

The role of functional coupling during bimanual coordination has been studied at numerous levels including the spinal cord (274, 396), subcortical areas (214) and cortical regions (272, 273). Interhemispheric interactions between the M1s through the corpus callosum are essential for bimanual coordination and adults with acquired damage to their corpus callosum have great difficulty performing bimanual tasks (189-191). Transcranial magnetic stimulation (TMS) can be used to study the inhibitory effects of interhemispheric pathways on M1 excitability by positioning a stimulating coil over each M1 and delivering a conditioning stimulus to the M1 ipsilateral to the target muscle followed by a test stimulus to the contralateral M1 (366). This protocol is referred to as either short- or long-interhemispheric inhibition (SIHI and LIHI, respectively), depending on the interstimulus interval (ISI). SIHI is elicited with an ISI of 10 – 15 ms and its neurotransmitter system remains uncertain, whereas LIHI is evoked with an ISI of 40 – 50 ms and is thought to operate via post-synaptic $GABA_B$-mediated circuitry in the test M1 (366, 376).

Although many behavioural studies have compared symmetric and asymmetric bimanual movements, only a few have investigated how movement symmetry affects SIHI and LIHI. These studies predominantly investigate static tasks, where isometric forces are produced without a change in muscle length, or dynamic tasks, where variable forces are produced by changes in muscle length. Cunningham et al. found no difference in SIHI when homologous muscles produced symmetric and asymmetric static forces (275). Soteropoulos and Perez found SIHI and LIHI decreased during a static force task using non-homologous muscles compared to homologous muscles (397). In contrast, Byblow et al. found 20 minutes of bilateral priming, in which active flexion-extension of one wrist produced passive flexion-extension of the contralateral wrist, increased CME and decreased SIHI when performed symmetrically but not asymmetrically (272). These results indicate static and dynamic tasks may have differing effects on SIHI, and dynamic symmetric movements may downregulate SIHI. The only study to investigate the effect of goal conceptualisation on SIHI and LIHI found both were greater during a static bimanual cooperative force task than the independent condition but CME did not differ between tasks (398). It remains to be determined whether IHI differs between dynamic cooperative and independent bimanual tasks.

The aim of this study was to investigate whether corticomotor excitability (CME), SIHI, and LIHI differ between categories of bimanual coordination in healthy adults. Participants performed four dynamic tasks in which they rhythmically flexed and extended both their wrists in a symmetric (Sym) or asymmetric (Asym) pattern while holding a custom device between both hands (Coop) or a dumbbell in each hand (Indep). To our knowledge, no TMS studies to date have investigated IHI during bimanually-active dynamic tasks or included bimanual tasks that vary both movement symmetry and goal conceptualisation. We hypothesised CME would be greater and SIHI and/or LIHI would be weaker during the symmetric and cooperative tasks compared to the asymmetric and independent tasks, respectively. This would reflect greater functional coupling between M1s during the symmetric and cooperative tasks. Accordingly, we further hypothesised that CME would be greatest and SIHI and/or LIHI would be weakest during the Sym-Coop task while the inverse would occur during the Asym-Indep task. The results of this study may further our understanding of the interhemispheric mechanisms mediating bimanual coordination.

8.3 Methods

8.3.1 Participants

Twenty neurologically healthy adults with no TMS contraindications participated in this study (Table 8.1). A copy of the safety checklist used to check for TMS contraindications in this study is included in Appendix 6. All participants were right-handed as defined by a laterality quotient greater than zero using the short-form of the Edinburgh Handedness Inventory (146). Participants gave their written informed consent and this study was approved by the institutional ethics committee.

Table 8.1. Participant characteristics and bimanual task parameters (n = 20).

Age years (range)	26 ± 4.8 (20 – 36)
Sex (M/F)	12/8
EHI score	0.9 ± 0.20 (0.3 – 1.0)
Static task dumbbell mass (kg)	1.8 ± 0.80 (0.5 – 3.0)
Independent tasks dumbbell mass (kg)	0.6 ± 0.22 (0.5 – 1.0)
Sym-Coop task dumbbell mass (kg)	1.2 ± 0.43 (0.9 – 1.9)
Asym-Coop task ARCO mass (kg)	0.9 ± 0.00 (0.9 – 0.9)
Asym-Coop ARCO resistance (arbitrary units, range 0 – 15)	8.1 ± 0.19 (8.0 – 8.5)

Values are means ± standard deviation, with range in parentheses. EHI, Edinburgh Handedness Inventory; Sym, symmetric; Coop, cooperative; Asym, asymmetric.

8.3.2 Tasks

Participants were seated comfortably with their elbows flexed at approximately 90° and their forearms pronated and resting on a pillow on their lap. Participants completed four tasks (Figure 8.1). Two of these were cooperative tasks using a custom device called the ARCO. The ARCO consists of two handles with a shoe-type break in-between that allows counteractive rotations of the handles, as described previously (291). These tasks were deemed cooperative because both hands were interacting with the same object. During the Asym-Coop task participants held the ARCO between both hands and rotated the handles by flexing one wrist while extending the other wrist 180° out of phase. The Sym-Coop task involved participants holding the ARCO while simultaneously flexing and extending both wrists. The other two tasks were deemed to be independent tasks because each hand held a separate dumbbell. During the Sym-Indep and Asym-Indep tasks participants held a dumbbell in each hand while flexing and extending their wrists symmetrically and 180° out of phase asymmetrically, respectively. Movements for all tasks were made around the horizontal axis in the sagittal plane. Participants completed flexion-extension cycles paced with a 0.75 Hz auditory metronome.

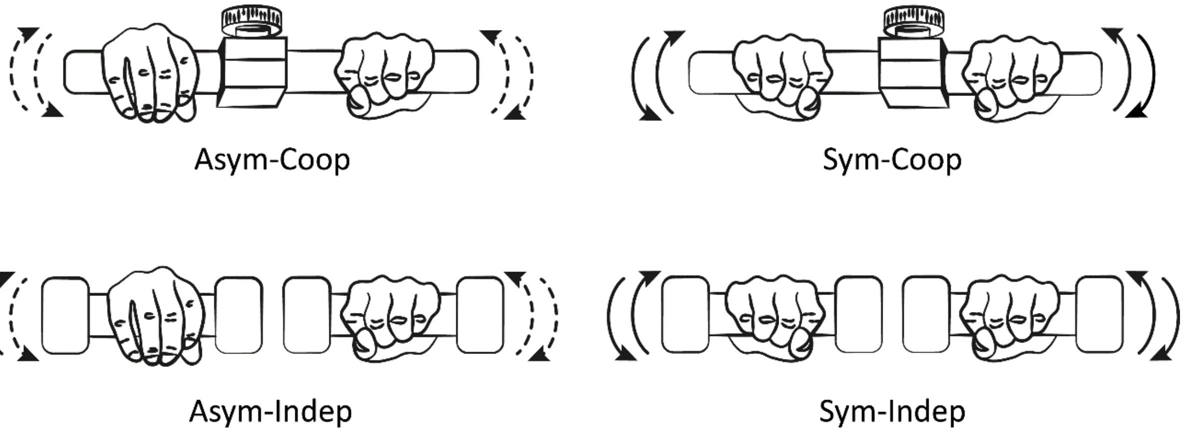


Figure 8.1. Bimanual tasks performed by participants. During the four dynamic tasks participants flexed and extended their wrists asymmetrically (Asym) or symmetrically (Sym) while holding a custom-built device between both hands (Coop) or a separate dumbbell in each hand (Indep). Solid and dashed arrows indicate symmetric and asymmetric movements, respectively

8.3.3 Electromyography

Surface electromyography (EMG) was recorded from the left and right extensor carpi ulnaris (L-ECU and R-ECU, respectively). The R-ECU was the primary muscle of interest and EMG was recorded from the L-ECU to monitor muscle activity in the contralateral muscle. 10 mm Ag-AgCl electrodes (Ambu, Ballerup, Denmark) were placed in a belly-tendon arrangement and a ground electrode strap was placed immediately proximal to the epicondyles of the humerus. The EMG signal was amplified (1000x) and band-pass filtered (10 – 1000 Hz) using a CED1902 amplifier (CED, England, UK), sampled at 2 kHz (Micro 1401 mkII, CED, Cambridge, UK), and analysed offline using Signal software (version 6.03, CED, Cambridge, UK).

Root mean squared EMG (rmsEMG) of the R-ECU was measured during task performance prior to data collection. Adjustments were made to the mass of the dumbbells and the mass of the ARCO to elicit similar levels of R-ECU rmsEMG during performance of the independent tasks and the Sym-Coop task, respectively. The R-ECU rmsEMG during the Asym-Coop task was matched to the other dynamic tasks by varying the resistance needed to rotate the ARCO handles.

8.3.4 Transcranial Magnetic Stimulation

Motor evoked potentials (MEPs) were recorded from the R-ECU using monophasic single-pulse TMS delivered through two figure-of-eight coils (50 mm diameter each) connected to two Magstim 200^2 units (Magstim, Whitland, Wales, UK). A posterior-anterior intracranial current was induced when stimulating the left and right primary motor cortex (L-M1 and R-M1, respectively) by holding the coil on the participant's scalp at 45° from the midline with the handle pointing posteriorly. The optimal scalp locations over each M1 for stimulating the contralateral ECU were identified and marked to ensure consistent coil placement.

The first TMS pulse was triggered during the first half of the wrist extension cycle of the tasks using a R-ECU EMG trigger threshold. This was established prior to data collection by setting an EMG threshold at 25% of the participant's maximum EMG while performing the Asym-Indep task and manually adjusting it to a threshold the participant consistently reached during the first half of the wrist extension, but not flexion, part of the movement cycle.

Resting motor threshold (RMT) was obtained for both ECUs using a maximum-likelihood Parameter Estimation by Sequential Testing (PEST) strategy without a-priori information (399). RMT was defined using an MEP amplitude threshold of 0.05 mV. We anticipated greater target muscle activity than reported in previous IHI studies due to the rhythmic nature of the tasks and the mass of the objects. Increased target muscle activity has been shown to decrease SIHI (385, 400) and LIHI (375, 385). To obtain these measures during the tasks, the maximum MEP amplitude (MEP_{Max}) and the conditioning and test stimuli (CS and TS, respectively) intensities were determined while participants held a dumbbell in each hand and maintained static wrist extension. The mass of these dumbbells was higher than those used for the independent tasks to more closely match the pre-trigger rmsEMG between tasks. First, MEP_{Max} of the R-ECU was determined by increasing the TMS intensity until the MEP amplitude plateaued. The TS was delivered to the L-M1 and set to produce a non-conditioned (NC) MEP amplitude of approximately 50% MEP_{Max}. The same TS intensity was used for SIHI and LIHI. The CS was delivered to the R-M1 and was individually set for SIHI and LIHI at either 120% or 140% R-M1 RMT, depending on which intensity produced greater inhibition. Intensities greater than 140% RMT were not tested due to participant tolerance during the experimental set-up. SIHI and LIHI used ISIs of 10 ms and 40 ms, respectively, as per previous studies (327, 371, 374).

SIHI and LIHI were each recorded in two separate blocks for all tasks, with blocks containing three NC trials and eight conditioned (C) trials. An additional block of six NC trials was also collected for each task. Thus, 18 NC MEPs, 16 SIHI C MEPs and 16 LIHI C MEPs were recorded per task. Two blocks of SIHI and LIHI were also recorded while participants held a dumbbell in each hand and maintained static wrist extension, which was the same action they performed during determination of MEP_{Max} and the stimulus intensities, to confirm inhibition could be successfully elicited. This task is referred to as the static task. The order of the tasks and the measures within each task were randomised for each participant.

8.3.5 Data Analysis

All dependent measures were obtained from the rectified waveform averages of the R-ECU EMG traces. The NC and C trials for each task were rectified and averaged separately. A custom script was used to calculate the mean and standard deviation (SD) of the background EMG over a 200 ms period prior to the first stimulus. MEP onset was defined as the time point when the EMG signal consistently exceeded 2 SD above the mean background EMG at least 13 ms after the first TMS stimulus. MEP area was calculated over a 30 ms period from the MEP onset. The rmsEMG from both ECUs was calculated from 35 ms to 5 ms before the first TMS stimulus to quantify muscle activity immediately prior to stimulation.

CME was evaluated using MEP area from the combined NC trials during the SIHI and LIHI protocols as well as the additional block of six NC MEPs. MEP area was used to measure CME rather than MEP amplitude due to the polyphasic nature of MEPs from forearm muscles. SIHI and LIHI were calculated as percentage inhibition using the equation %INH = 100 – (C/NC*100), with C and NC representing mean conditioned and non-conditioned MEP area respectively. Higher values reflect smaller MEPs and greater inhibition.

8.3.6 Statistical Analysis

Pre-trigger rmsEMG was analysed using a repeated measures ANOVA (RM-ANOVA) with factors Muscle (R-ECU, L-ECU), Symmetry (symmetric, asymmetric) and Goal (cooperative, independent). Paired-sample t-tests were used if any significant effects were found. One-sample t-tests (hypothesised mean = 0) were run for SIHI and LIHI during the static task to ensure these TMS protocols successfully produced inhibition. Separate linear mixed effect (LME) models were performed for NC MEP area, SIHI, and LIHI with the fixed effects Symmetry and Goal. Shapiro-Wilk's tests indicated all dependent measures were normally distributed within each task. Participants were added as a subject-grouping variable and the pre-trigger rmsEMG was added as a covariate because the initial rmsEMG RM-ANOVA detected a significant difference in R-ECU rmsEMG between symmetric and asymmetric tasks. Values of $P < 0.05$ were considered statistically significant. Multiple comparisons were corrected using a step-up procedure based on Rom's exact critical values (401). Reported values in the results text are estimated means from the LME models ± standard error, and graphs display actual values.

8.4 Results

8.4.1 Participants

Participant characteristics are provided in Table 8.1. Group mean TMS parameters and inhibition generated during the static task are provided in Table 8.2. One-sample t-tests revealed SIHI ($P < 0.001$) and LIHI ($P = 0.001$) were successfully elicited during the static task, demonstrating these protocols were able to elicit inhibition (Figure 8.3).

Table 8.2. TMS parameters (N = 20).

RMT R-M1 (%MSO)	42 ± 9 (29 – 64)
RMT L-M1 (%MSO)	45 ± 12 (33 – 83)
SIHI CS intensity (%MSO)	57 ± 12 (40 – 90)
LIHI CS intensity (%MSO)	56 ± 12 (40 – 90)
TS intensity (%MSO)	48 ± 10 (35 – 65)
NC MEP area during static task (mV.ms)	8.3 ± 3.2 (3.9 – 17.9)
SIHI during static task (%INH)	16 ± 14 (-13 – 40)
LIHI during static task (%INH)	17 ± 19 (-15 – 56)

Values are means ± standard deviation, with range provided in parentheses. TMS, transcranial magnetic stimulation; RMT, resting motor threshold; R-M1, right primary motor cortex; MSO, maximum stimulator output; L-M1, left primary motor cortex; SIHI, short-latency interhemispheric inhibition; CS, conditioning stimulus; LIHI, long-latency interhemispheric inhibition; TS, test stimulus; NC MEP, non-conditioned motor evoked potential; INH, inhibition.

8.4.2 Pre-trigger Muscle Activity

The RM-ANOVA for the pre-trigger rmsEMG detected significant effects of Muscle ($F_{1,19}$ = 17.71, $P < 0.001$), Symmetry ($F_{1,19}$ = 52.38, $P < 0.001$), and an interaction between them ($F_{1,19}$ = 91.12, $P < 0.001$). L-ECU rmsEMG was higher during symmetric tasks than asymmetric tasks (t_{19} = 8.89, $P < 0.001$) and rmsEMG for the R-ECU was higher than the L-ECU during asymmetric tasks (t_{19} = 9.23, $P < 0.001$), both of which indicate participants performed the tasks correctly. R-ECU rmsEMG was also higher during asymmetric tasks than symmetric tasks (t_{19} = 2.90, $P = 0.009$) and so it was added into the LME models as a covariate. The pre-trigger rmsEMG values are displayed in Table 8.3.

Table 8.3. Pre-trigger rmsEMG in the R-ECU and L-ECU between 35 ms and 5 ms before the first TMS pulse (N = 20), triggered in the first half of right wrist extension movement.

	R-ECU	**L-ECU**
Static task	0.092 ± 0.029 (0.028 – 0.15)	0.099 ± 0.057 (0.036 – 0.30)
Asym-Coop task	0.123 ± 0.029 (0.045 – 0.16)	0.054 ± 0.037 (0.016 – 0.20)
Asym-Indep task	0.118 ± 0.028 (0.039 – 0.15)	0.047 ± 0.026 (0.017 – 0.12)
Sym-Coop task	0.118 ± 0.036 (0.041 – 0.19)	0.118 ± 0.048 (0.060 – 0.26)
Sym-Indep task	0.106 ± 0.027 (0.039 – 0.14)	0.120 ± 0.059 (0.056 – 0.29)

Values are means ± standard deviation, with range provided in parentheses. rmsEMG, root mean square electromyography; R-ECU, right extensor carpi ulnaris; L-ECU, left extensor carpi ulnaris; TMS, transcranial magnetic stimulation; Asym, asymmetric; Coop, cooperative; Indep, independent; Sym, symmetric.

8.4.3 Corticomotor Excitability

For NC MEP area there was a main effect of Symmetry ($F_{1,19} = 6.38$, $P = 0.014$) but no effect of Goal ($F_{1,19} = 2.02$, $P = 0.16$) or interaction between them ($F_{1,19} = 1.73$, $P = 0.19$). There was also an effect of the covariate rmsEMG on NC MEP area ($F_{1,19} = 13.51$, $P < 0.001$). The main effect of Symmetry was due to greater NC MEP area during asymmetric tasks (12.81 ± 0.75 mV.ms) than symmetric tasks (12.10 ± 0.75 mV.ms), even while controlling for higher pre-trigger rmsEMG during asymmetric tasks (Figure 8.2).

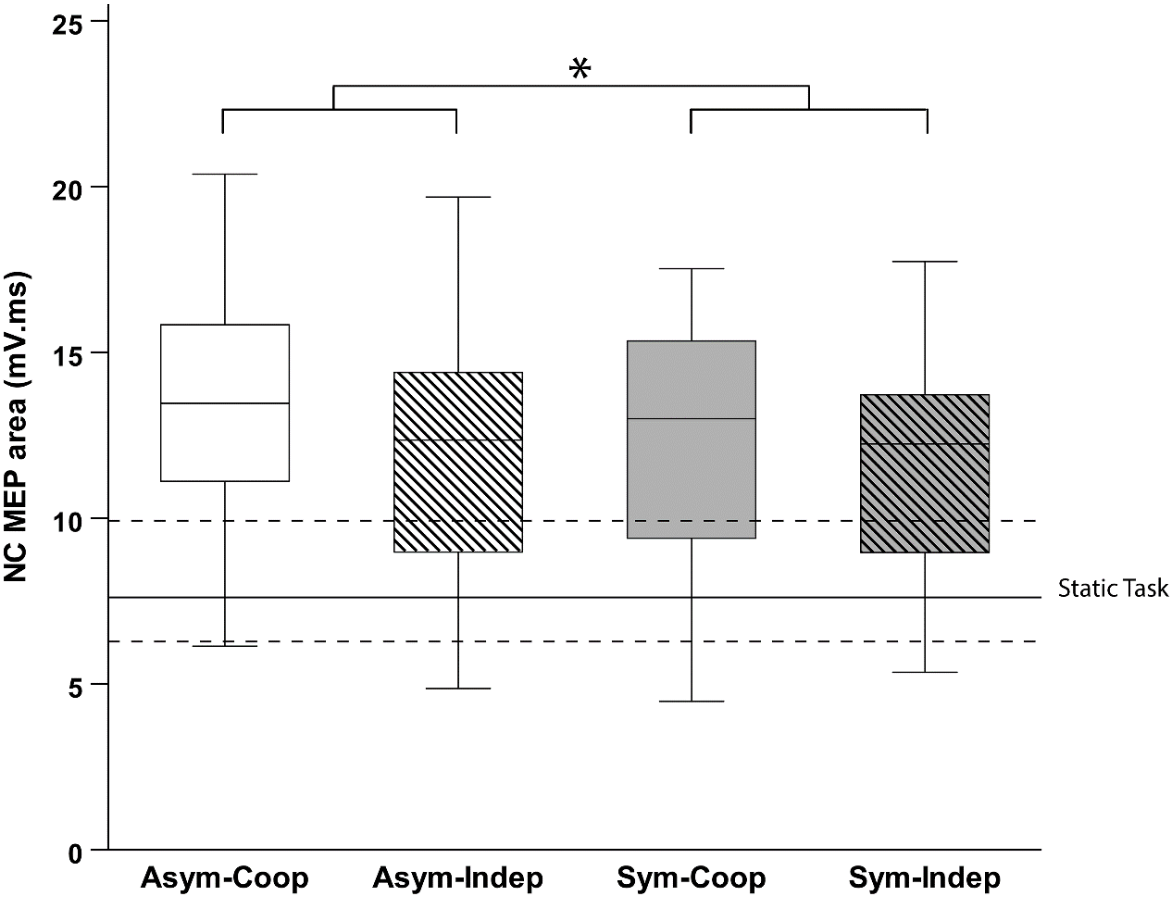


Figure 8.2. NC MEP area during bimanual tasks. Mean NC MEP area was greater during asymmetric tasks than symmetric tasks. No effect of Goal or interaction between Symmetry and Goal was present. Boxes represent upper quartile, median and lower quartile (N = 20), and whiskers represent the largest and smallest observed values that are not statistical outliers. Solid horizontal line represents the median NC MEP area during the static task, and dashed lines represent the upper and lower quartiles. $*P \leq 0.05$. Asym = asymmetric, Coop = cooperative, Indep = independent, Sym = symmetric

8.4.4 Short- and Long-Latency Interhemispheric Inhibition

For SIHI there were no significant effects of Symmetry ($F_{1,19} = 0.11$, $P = 0.75$) or Goal ($F_{1,19} = 0.38$, $P = 0.54$) and no interaction between them ($F_{1,19} = 0.45$, $P = 0.51$) (Figure 8.3). The pre-trigger rmsEMG did not significantly affect SIHI ($F_{1,19} = 0.99$, $P = 0.32$).

For LIHI there were also no significant effects of Symmetry ($F_{1,19} = 0.17$ $P = 0.68$) or Goal ($F_{1,19} = 0.23$, $P = 0.64$) and no interaction between them ($F_{1,19} = 2.44$, $P = 0.12$) (Figure 8.3). LIHI was significantly affected by the pre-trigger rmsEMG ($F_{1,19} = 10.13$, $P = 0.002$).

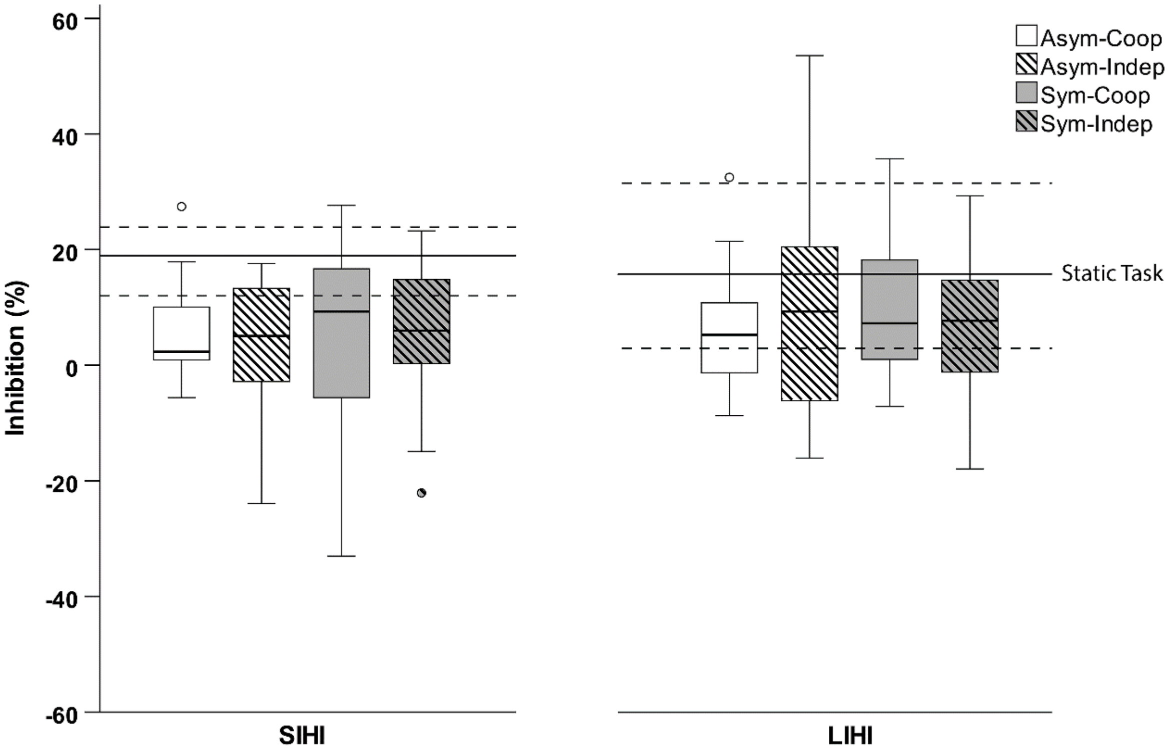


Figure 8.3. SIHI and LIHI during bimanual tasks. There were no significant effects of Symmetry or Goal and no interaction between factors for either measure. Boxes represent upper quartile, median and lower quartile (N = 20), and whiskers represent the largest and smallest observed values that are not statistical outliers. Circles represent outlier values that are greater than 1.5*interquartile range from the upper or lower quartile. Solid horizontal line represents the median inhibition during the static task, and dashed lines represent the upper and lower quartiles. Asym = asymmetric, Coop = cooperative, Indep = independent, Sym = symmetric.

8.5 Discussion

This study investigated whether CME, SIHI, and LIHI were modulated by movement symmetry and goal conceptualisation during dynamic bimanual tasks. Contrary to our hypotheses, CME was greater during the asymmetric tasks than symmetric tasks. There were no effects of goal conceptualisation on CME, and no effects of any task on SIHI or LIHI. Together, these findings indicate that CME is facilitated by asymmetric bimanually-active dynamic movements, but this is not due to a decrease in SIHI or LIHI.

8.5.1 Corticomotor Excitability

Results indicated that CME was greater during the 180° asymmetric tasks than symmetric tasks, regardless of the task goal and accounting for the greater rmsEMG during the asymmetric tasks. Some authors have also found CME is greater during dynamic 180° asymmetric tasks than symmetric tasks, but have attributed this to greater EMG during the asymmetric tasks (258) or found the effect disappears when EMG levels are normalised between tasks (402). One study also found CME was greater during a 90° asymmetric task compared to the symmetric condition, regardless of the background EMG levels (258). The present study compared CME in symmetric versus asymmetric dynamic tasks in the largest sample to date. Overall, it appears that that CME of the target muscle is greater during dynamic asymmetric tasks than symmetric tasks, although it is unclear how physiologically significant this is.

Given that SIHI and LIHI were not modulated by movement symmetry, there must be a different explanation for the greater CME during the asymmetric tasks. A difference in pre-trigger EMG between the symmetric and asymmetric tasks is an unlikely explanation because it was included in the linear mixed effect model as a covariate. The mechanisms underlying crossed facilitation are also improbable explanations. Crossed facilitation occurs when activation of an upper limb muscle raises CME of muscles in the contralateral quiescent limb (403). Crossed facilitation is strongest between homologous muscles (404, 405) but we found CME was greater during asymmetric tasks engaging non-homologous muscles. Another possibility is the modulation of inhibitory or facilitatory intracortical circuits in the test M1. However, previous studies investigating the effect of movement symmetry on short- and long-interval intracortical inhibition during bimanual passive movements (242), active-passive movements (272), and static contractions (406) suggest these are unlikely to account for the increase in CME during asymmetric tasks.

Although this study focused on interhemispheric inhibition between M1s, the role of other cortical, subcortical, and spinal regions cannot be excluded. fMRI and TMS studies have found secondary motor regions such as the supplementary motor area (SMA) and dorsal premotor cortex (PMd) are likely important regulators of asymmetric rhythmic movement patterns (159, 177, 178, 279, 341). At the subcortical level, the cerebellum is thought to help with error corrections as bilateral cerebellar activity is greater during asymmetric tasks than symmetric tasks, and increases as the difficulty of asymmetric tasks increases (178, 407). The basal ganglia are also more active during asymmetric tasks than symmetric tasks, although their exact role during bimanual coordination is uncertain (177, 407). Modulations at the spinal level are another possibility, although H-reflex amplitude is unaffected by movement symmetry during bimanual tasks (272, 402). Future studies are needed to further explore how CME is modulated by movement symmetry during bimanually-active dynamic tasks and the potential role of other motor regions or spinal mechanisms.

8.5.2 Interhemispheric Inhibition

This is the first study to investigate how movement symmetry and goal conceptualisation affect SIHI and LIHI during dynamic bimanual movements. Contrary to our hypothesis, neither factor modulated SIHI or LIHI and there was no interaction between the factors. Despite this, it is possible that inhibition between the hemispheres differed between tasks even though SIHI or LIHI were not modulated. IHI protocols have been widely used during performance of a range of tasks, in both health and disease. However, a recent review by Carson highlighted limitations of using IHI protocols to study inhibition between the hemispheres (196). One concern is that IHI protocols often use a suprathreshold CS intensity, as was the case in this study, which means the CS excites several motor regions in the conditioned hemisphere. The transcallosal fibres from these motor regions project to both homotopic and heterotopic regions in the contralateral hemisphere (195). As a result, Carson suggested the role of inhibitory interhemispheric connections is more complex than only modulating CME of the contralateral M1. This idea is supported by previous TMS studies that have found task effects on IHI measures with incongruous effects on CME (160, 272, 398). Therefore, even though there were no effects of movement symmetry or goal conceptualisation on SIHI and LIHI, these factors may still modulate inhibitory interactions between the hemispheres that are not reflected in commonly used TMS measures. New protocols or techniques that can better target interhemispheric inhibition or facilitation may be necessary to capture how interhemispheric interactions differ between categories of bimanual movements.

8.5.3 Cooperative vs Independent Tasks

This study found goal conceptualisation had no effect on CME, SIHI or LIHI. A previous study using a static force task found SIHI and LIHI were greater during the cooperative condition than the independent condition (398). Similar to the present results though the previous study reported no difference in CME between the cooperative and independent conditions. One possibility is that cooperative tasks engage greater coupling at levels of the corticomotor system other than M1. Previous studies have reported that, compared to independent tasks, cooperative tasks engage stronger bilateral secondary somatosensory region activation (291) and are capable of generating bilateral upper limb muscle reflex responses following unilateral electrical stimulation (157, 291) or perturbations (165, 166). Thus, even though previous studies indicate dynamic cooperative tasks involve greater functional coupling than independent tasks, our results suggest goal conceptualisation may not affect inhibition between M1s.

8.5.4 Limitations

The present study has several limitations. First, the cooperation between upper limbs necessary to complete the cooperative tasks was relatively simple compared to real-world cooperative tasks. The asymmetric cooperative task was similar to wringing out a wet towel and required both hands, however the symmetric cooperative task could also be completed unimanually. This introduces the possibility that the cooperation during the cooperative tasks was not salient enough to modulate CME or IHI compared to the independent tasks. Investigating cooperative tasks requiring more complex upper limb cooperation may help explore this possibility. Second, although SIHI and LIHI were elicited during the static task, the amount of inhibition during the dynamic tasks was relatively low. These low levels of inhibition introduce the possibility of a floor effect, and that any potential differences in SIHI and LIHI between the dynamic tasks were simply not detected. Additionally, the level of pre-trigger muscle activity was not equivalent between tasks despite matching them prior to data collection. This was controlled for in the statistical analysis by including pre-trigger rmsEMG as a covariate. Finally, the rhythmic nature of the dynamic tasks performed during this study means they do not reflect how the upper limbs typically coordinate with one another in everyday life. As a result, movement symmetry and goal conceptualisation may modulate neural mechanisms differently during activities of daily living than during the tasks performed in this study. However, delivering TMS during dynamic tasks while participants were holding objects means the tasks are closer to replicating activities of daily living compared to previous studies using static force tasks.

8.5.5 Future Directions

The tasks performed during this study were still relatively simple compared to many everyday tasks that require bimanual coordination. Given that recent evidence indicates discrete and rhythmic movements are controlled by distinct circuits within M1 (408), performing tasks that more closely resemble everyday bimanual tasks would allow greater understanding of how interhemispheric functions are modulated during real-world activities. Indeed, SIHI and LIHI are modulated to a greater degree during complex unimanual tasks compared to simple unimanual tasks (372, 386) and the same may be true for bimanual tasks.

Another future direction is investigating dynamic bimanual coordination performance in people with stroke. People with chronic stroke have impaired bimanual coordination of asymmetric and cooperative tasks relative to healthy controls (156, 409). Furthermore, the interaction between movement symmetry and goal conceptualisation may be more important in people with chronic stroke because they have coordination deficits during symmetric cooperative tasks, but not symmetric independent tasks, compared to healthy controls (156). Studying how interhemispheric interactions are modulated by different bimanual task conditions in people with stroke may help with understanding why only certain forms of bimanual coordination are impaired after stroke.

A final potential line of inquiry is the role of secondary sensorimotor regions during bimanual tasks, for example the SMA and PMd. TMS protocols can measure facilitation from the SMA (341, 410) and inhibition from the PMd (197) to the contralateral M1, however these measures have only been recorded at rest or during unimanual tasks and so it is not known whether they can be elicited during bimanual tasks. Further study of these secondary regions may advance our understanding of how interhemispheric interactions from regions other than M1 contribute to bimanual motor control depending on movement symmetry and goal conceptualisation.

8.5.6 Conclusion

The present results indicate that CME was greater during bimanually-active dynamic tasks performed asymmetrically compared to symmetrically, but this was not due to modulation of SIHI or LIHI. Conversely, goal conceptualisation did not modulate CME, SIHI or LIHI and there were no interactions between movement symmetry and goal conceptualisation. These results indicate movement symmetry and goal conceptualisation may not modulate inhibitory interactions between M1s during bimanually-active dynamic tasks and contradict prevailing thinking about the roles of CME and interhemispheric inhibition in bimanual coordination.

9 Bimanual Coordination after Stroke

A common result of stroke is impaired upper limb bimanual coordination. This can affect functional independence because many everyday tasks are performed using both hands (91, 411, 412). The focus of paretic upper limb assessments is often on unimanual performance but improvements in the paretic upper limb do not necessarily translate to better performance during bimanual tasks. For example, a study found unimanual training of the paretic upper limb did not increase paretic or bilateral arm use in daily life for any of the 78 participants with stroke, despite significant increases in ARAT scores (413). Ipsilesional upper limb impairments after stroke can also affect functional independence (106). Studies of bimanual coordination after stroke are needed to better understand how impairments can affect functional independence, as well as potentially assist the development of upper limb interventions.

The final component of this thesis will describe the development and use of a behavioural assessment of coordination during bimanual task performance for use after stroke called the Bimanual Coordination After Stroke Scale (BCASS). The next two chapters will discuss the current understanding of bimanual coordination after stroke with reference to the Kantak taxonomy, which was developed to facilitate research and discussion in this field, as well as commonly used bimanual upper limb assessments after stroke. Finally, two experiments using the BCASS with participants at the late subacute and chronic stages after stroke are presented. As a reminder, the acute stage refers to between one to seven days after stroke, the early subacute stage refers to between one week and three months after stroke, the late subacute stage refers to between three and six months after stroke, and the chronic stage refers to six months and later after stroke (70).

9.1 Hand Use after Stroke

It might be assumed there is a positive relationship between bimanual coordination ability and everyday bimanual upper limb use in people with stroke, but this relationship has not been explicitly investigated. However, upper limb activity after stroke has been quantified using accelerometers. Participants usually wear accelerometers for most of the day as they go about their normal activities and so can provide accurate data for how much people with stroke move their upper limbs in everyday life. The most significant limitation of accelerometers is that they cannot provide information regarding the purpose of bimanual movements, or the quality of bimanual coordination. Not knowing the activity being performed can lead to potential issues, for example arm use may be overestimated by accelerometers due to spontaneous arm swing during ambulation (414). Regardless, accelerometery is the most accurate method for capturing the quantity of bimanual upper limb movement in naturalistic settings.

There is reduced unimanual paretic and bimanual upper limb use early after stroke. People at the early subacute stage after stroke move their paretic upper limb less than the equivalent limb in healthy adults, and more severe upper limb impairments is associated with less activity (415-417). The amount of movement can vary substantially between individuals as paretic upper limb movement in the hospital within one month post-stroke has been reported to range from 0.8 hours to 8 hours per day (416). People in the first month after stroke in hospital also have significantly less bimanual upper limb activity than healthy adults (417).

One study found participants with mild, moderate, and severe upper limb impairment all had significantly different amounts of unimanual paretic upper limb activity but bimanual upper limb activity only differed between participants with mild and severe impairment (417). This finding indicates paretic upper limb activity differs between unimanual and bimanual contexts. Finally, one study manually recorded how the upper limbs were being used every 10 minutes over a 12 hour period while participants were in hospital two weeks after stroke (418). The paretic limb was used unimanually and bimanually 8% and 19% of the time, respectively. Bimanual movements were even differentiated depending on whether they were made for common-goal or independent-goal tasks but no statistical analyses were performed between the two task types. Unimanual paretic and bimanual upper limb activity is decreased early after stroke.

Arm movement at the chronic stage after stroke largely mirrors the early subacute stage. The non-paretic limb is used more than the paretic limb, particularly for functional movements, and worse paretic upper limb impairment correlates with less paretic limb use (94, 411, 419, 420). People with chronic stroke predominantly use their paretic limb for bimanual rather than unimanual tasks in everyday life, reinforcing the importance of considering the paretic upper limb in a bimanual context (411, 421). Worse upper limb impairment is also correlated with a lower likelihood of completing tasks bimanually compared to unimanually, but this can depend on the side of the stroke and the task (421, 422). The quantity of bimanual upper limb use is lower in people with chronic stroke than healthy adults because the former spend a significant amount of time being inactive (392, 411, 423). Manual monitoring of daily activities indicates that approximately 50% of upper limb activities performed by people with chronic stroke are bimanual, which is higher than the early subacute stage and is comparable with healthy older adults (411, 412). Together these studies highlight that the absolute amount of unimanual paretic and bimanual upper limb use is reduced after stroke compared to healthy adults. The proportion of time spent using the paretic limb for bimanual movements is decreased soon after stroke but recovers back to normal levels by the chronic stage after stroke.

9.2 Bimanual Coordination at the Subacute Stage after stroke

The study of bimanual coordination has largely been ignored at the acute and subacute stages after stroke. This is possibly because there are no comprehensive clinical assessments of bimanual coordination, and it is simpler to conduct kinematic studies with participants at the chronic stage of stroke who are more likely to be functionally independent and medically stable. No studies at the subacute stage after stroke have examined and compared tasks in different bimanual coordination categories, and so only deficits and recovery using individual tasks can be discussed.

At present, only one study has investigated recovery on a bimanual coordination task at the early subacute stage after stroke. Metrot et al. recruited 12 participants at three weeks after stroke and had them perform a symmetric parallel task that involved reaching to grasp a ball with both hands (424). The same task was also performed unimanually with each upper limb. Assessments were made weekly between three and nine weeks after stroke and at 15 weeks after stroke. Reaching movements of both arms were slower and more segmented during bimanual than unimanual reaching. Moreover, the non-paretic limb hovered over the target as it waited for the paretic hand to catch up so the ball could be grabbed with both hands simultaneously. Over time, participants’ movements became more functionally coupled and synchronised during bimanual reaching. Task performance, smoothness of reaching, and between-hands synchronisation all plateaued for bimanual reaching at six weeks post-stroke. This plateau of bimanual coordination occurs sooner than the recovery of unimanual movement and function (71-73). Unfortunately, unimanual upper limb use and function were not assessed so it is unknown if improved bimanual reaching correlated with unimanual upper limb improvements. This study demonstrates bimanual coordination during a symmetric parallel task is impaired early after stroke and improves up until six weeks post-stroke.

A novel robotic task was developed to examine bimanual coordination impairments during an asymmetric cooperative task at the early subacute stage after stroke (425). People with and without stroke completed a task where they placed their arms in a robot exoskeleton that allowed free movement in the horizontal plane. A virtual bar with a ball resting on it was displayed on a screen that appeared to be grasped between the hands, and participants had to move the virtual bar using their hands so the ball reached several targets. Participants with stroke were on average three weeks post-stroke at time of assessment. All participants were assessed with the task once and so recovery of bimanual coordination after stroke was not examined. Temporal and spatial coordination were impaired in people with stroke as they were worse at keeping the bar steady, had a larger between-hand difference in reaction time, and had a larger difference in between-hand peak speed compared to the control cohort. These coordination deficits affected task performance as participants with stroke hit fewer targets than controls. One limitation with this study is that it included participants who were within one week after stroke as well as those who were between six and nine weeks after stroke. Based on Metrot et al’s finding that bimanual coordination plateaued at six weeks post-stroke it is possible that some participants may have already experienced significant bimanual coordination recovery, or may have even plateaued, at their time of assessment (424). Although bimanual coordination impairments were detected using the robotic task, it is questionable whether they captured the full extent of impairment in the early stages post-stroke.

A recent study included 89 participants with first-ever stroke and upper limb weakness (426). This study is notable because it was the first to use a behavioural assessment to try longitudinally measure spontaneous bimanual activity performance from the early subacute to the chronic stage after stroke. Participants were assessed using the Adult Assisting Hand Assessment Stroke (Ad-AHA Stroke). The Ad-AHA Stroke involves using both hands to prepare a sandwich or wrap a present, with each task including multiple sub-tasks. Both main tasks can be broadly categorised as asymmetric cooperative. Assessments were performed at three weeks, three months, and six months after stroke. Ad-AHA Stroke scores improved over time but a study limitation is that no post-hoc analyses were performed to determine exactly when the recovery occurred. It is therefore uncertain whether improvements on the Ad-AHA Stroke plateaued at three months after stroke or whether they continued until six months after stroke. A significant limitation is that the Ad-AHA Stroke was used as an assessment of bimanual task performance, but it was described by the authors as evaluating the use and effectiveness of the paretic upper limb during spontaneous performance of bimanual tasks. The scoring reflects this description as the use and quality of the paretic limb are the only scoring criteria in the Ad-AHA Stroke, and bimanual task performance is not explicitly scored. This may explain why Ad-AHA Stroke scores plateaued at the same time as unimanual upper limb recovery measured using the Fugl-Meyer upper extremity (FM-UE).

Moreover, Ad-AHA Stroke scores correlated strongly with FM-UE at each timepoint. Further discussion of the Ad-AHA Stroke as an assessment is provided in the next chapter. A lesser limitation is that the upper age limit for inclusion was 70 years old and the mean age was 52 years old. The mean age of stroke is approximately 70 years old and differences in bimanual task performance have been reported between groups with mean ages of 63 and 71 (37, 333). It is unclear how generalisable the results from this study using the Ad-AHA Stroke are to the older stroke population (426). Although the study did provide valuable information regarding the recovery of spontaneous performance of the paretic limb during naturalistic real-world task after stroke, the recovery of bimanual task performance after stroke remains unknown. Overall, deficits with bimanual coordination and task performance are present at the subacute stage after stroke and their recovery may plateau sooner or at a similar time compared to unimanual motor recovery.

9.3 Bimanual Coordination at the Chronic Stage after Stroke

Most studies investigating how movement symmetry and goal conceptualisation affect bimanual coordination and task performance after stroke have been performed at the chronic stage. Bimanual task performance is often measured as task completion time but can also be quantified using other measures such as absolute spatial error, movement stability, or number of targets hit in one minute. Participants with chronic stroke have impaired bimanual task performance compared to healthy adults on all six categories of the Kantak taxonomy (161, 168, 286, 427, 428). This is a robust finding across a variety of protocols including discrete and rhythmic movements, as well as lab-based and real-world tasks. Participants with stroke even perform worse than healthy adults on tasks where both groups display similar bimanual coordination (168, 429, 430). The rest of this chapter will focus on bimanual coordination after stroke because, unlike bimanual task performance, it does appear to depend on movement symmetry and goal conceptualisation.

The interaction between movement symmetry and goal conceptualisation was recently investigated in a meta-analysis of bimanual coordination at the chronic stage after stroke by Kim and Kang (156). The meta-analysis was novel as it categorised all tasks into the six categories of the Kantak taxonomy (151). Only studies comparing bimanual coordination between participants with stroke and healthy controls were included. Seventeen studies were included with a total of 25 tasks, including one asymmetric cooperative, two asymmetric parallel, nine asymmetric independent-goal, seven symmetric cooperative, two symmetric parallel, and four symmetric independent-goal tasks. A limitation of the meta-analysis is that three categories included results from only one or two tasks. Examples of lab-based and real-world tasks from each category of the Kantak taxonomy that have been used with participants with chronic stroke are provided in Table 9.1. The meta-analysis found that participants with stroke displayed impaired bimanual coordination in all categories of the Kantak taxonomy compared to healthy controls except for the symmetric independent category. Interestingly, all four symmetric independent-goal tasks were quite different. Two were discrete reaching tasks, one using virtual reality and the other using real-world objects (286, 322). The other two were rhythmic tasks, one involving continuous circle drawing and the other involving discrete finger tapping (161, 431). Therefore, it appears that the maintenance of bimanual coordination during symmetric independent-goal tasks after stroke is robust across protocols.

Table 9.1. Examples of tasks used to study bimanual coordination at the chronic stage after stroke. Lab-based tasks involve rhythmic or discrete movements. Dashed lines mean no tasks in that category have been used with participants with chronic stroke.

	Lab-based	**Real-world**
Asymmetric Cooperative	Reach with one hand while stabilising with the other hand when both hands are connected via a spring	Open a jar
Asymmetric Parallel	--	Retrieve an item from a drawer
Asymmetric Independent	Reach different distances with each hand to press separate buttons	--
Symmetric Cooperative	Push one virtual object by moving both hands in the same direction	Lift a large box with both hands
Symmetric Parallel	Reach the same distance with both hands towards one virtual object	Reach for a large box with both hands
Symmetric Independent	Reach the same distance with each hand to separate virtual objects	Reach for a small tray with each hand

In contrast to the meta-analysis, a narrative review of bimanual coordination after stroke by Kantak et al. concluded that participants after stroke retained bimanual coordination for symmetric parallel tasks as well as symmetric independent-goal tasks (151). The reason why the meta-analysis found deficits with symmetric parallel tasks may be due to how they categorised the bimanual tasks. Only two symmetric parallel tasks were included in the meta-analysis, one being a real-world task where participants reached to grab one large tray with both hands (322). No differences in bimanual coordination were present between participants with stroke and healthy adults. The other task categorised as symmetric parallel involved mirror-symmetric rhythmic forearm pronation-supination movements (387). It is uncertain why this was categorised as parallel rather than independent-goal, especially because a similar mirror-symmetric rhythmic circle drawing task was classified as independent-goal (161). The results from the forearm pronation-supination study supported a difference in coordination between people with and without stroke on symmetric parallel tasks. Finally, a task that involved reaching forwards with both hands to grab and lift a box was categorised as symmetric cooperative in the meta-analysis even though the reaching and lifting aspects were separately analysed in the original study as symmetric parallel and symmetric cooperative, respectively (168). This study found no bimanual coordination differences between participants with chronic stroke and healthy controls for the symmetric parallel component. Hence, the results from the meta-analysis regarding symmetric parallel tasks is questionable as two tasks that could be categorised as symmetric parallel found no bimanual coordination impairments at the chronic stage of stroke while a questionably included symmetric parallel task did find a difference.

The meta-analysis by Kim and Kang provides a good overview of bimanual coordination deficits after stroke relative to healthy adults, but it made no comparisons between bimanual task categories. The meta-analysis also included both kinematic and kinetic measures of coordination, for example five of the seven symmetric cooperative tasks involved isometric force production. The rest of this chapter will discuss bimanual coordination after stroke with particular emphasis on comparisons between task categories, as well as on kinematic measures as we are predominantly interested in naturalistic bimanual movements.

9.3.1 Movement Symmetry

People with chronic stroke are more coordinated on rhythmic independent-goal tasks when they are performed symmetrically than asymmetrically, regardless of whether it is the spatial or temporal characteristics of the task being manipulated (161, 427, 432). Superior task performance and bimanual coordination during common-goal tasks performed symmetrically rather than asymmetrically have also been reported (286, 428). These findings indicate that the preference for symmetric over asymmetric movements in healthy adults remains present after stroke (249).

Assimilation effects, which are the tendencies for both upper limbs to produce similar movements during asymmetric conditions, still occur when people with chronic stroke perform asymmetric independent-goal tasks. This was most apparent in a study that had 30 people with chronic stroke and 30 age-matched controls move both arms sideways to reach separate targets (433). The distance to the targets was made asymmetric by placing a vertical barrier midway to the target for one arm that participants had to reach over. Temporal and spatial coupling were measured using movement time of each hand and maximum vertical displacement of each hand, respectively. The results indicated that some degree of temporal and spatial coupling were preserved after stroke, although both were impaired relative to healthy adults. A preservation of temporal coupling was seen as the movement time of the non-barrier upper limb increased as the barrier was raised higher for the opposite limb, regardless of which role was performed by the paretic limb. Temporal coupling was stronger than spatial coupling in participants with chronic stroke. These findings indicate that some degree of functional coupling, which is thought to cause assimilation effects, remains intact between the upper limbs at the chronic stage after stroke (271).

Interestingly, assimilation effects have been reported during symmetric task conditions for people with stroke even though they only occur in healthy adults during asymmetric conditions (161, 429, 430, 434). Tasks with symmetric parameters will still have asymmetric difficulties for people with stroke due to a functional difference between the paretic and non-paretic upper limbs. This means the non-paretic upper limb will worsen its performance during symmetric bimanual tasks compared to unimanual tasks to stay coordinated with the paretic upper limb, thus leading to assimilation effects. For example, it was reported in 30 participants with chronic stroke and mild upper limb weakness that paretic and non-paretic upper limb velocity decreased and increased by 4% and 10%, respectively, during a symmetric parallel reaching task compared to the equivalent unimanual conditions (429). The result of these assimilation effects is that temporal coordination during lab-based and real-world symmetric parallel and symmetric independent-goal tasks is largely similar between participants with chronic stroke and healthy controls (161, 168, 286, 431). The only study that used a measure of spatial coordination during a symmetric independent-goal task found it was impaired after stroke (286). However, temporal coordination impairments have been noted during symmetric tasks with a cooperative goal or when symmetric parallel and cooperative components of one task are analysed together, including one task not included in Kim and Kang's meta-analysis (168, 286, 428). Thus, the results from individual studies support that bimanual coordination appears intact after stroke during symmetric independent-goal and symmetric parallel tasks. Participants after stroke retain some ability to functionally couple both upper limbs together, and temporal coupling appears more robust than spatial coupling. Superior performance and coordination during symmetric tasks compared to asymmetric tasks also remain after stroke.

9.3.2 Goal Conceptualisation

Bimanual coordination after stroke during common-goal versus independent-goal conditions depends on the task. Eleven participants with chronic stroke and ten healthy controls performed a task where they reached forward to symmetrically or asymmetrically move one virtual brick with both hands or one virtual brick with each hand (286). Temporal coordination was worse for the common-goal conditions than the independent-goal conditions but spatial coordination was similar. Interestingly, participants completed the common-goal conditions predominantly using their non-paretic upper limb and so the impaired coordination may be due to an inability to accurately control the paretic upper limb. One real-world task included a common-goal condition in which participants with chronic stroke and healthy adults reached for one large tray with both hands before lifting, transporting, and placing it down again (322). The reaching and transport components were symmetric parallel and symmetric cooperative, respectively. A symmetric independent-goal condition involved reaching and transporting one small tray in each hand. The only difference between conditions was that participants with stroke took significantly longer when reaching for two small trays than one large tray but the same effect was present in the control group and so does not indicate a stroke-specific deficit. The different results between these two studies may be due to one study using virtual objects and the other using real objects.

Symmetric parallel and symmetric cooperative bimanual coordination have been separately analysed as part of the same real-world task (168). The task involved reaching for a box and lifting it up with both hands, with the reaching and lifting aspects testing symmetric parallel and symmetric cooperative coordination respectively. Participants with chronic stroke and healthy controls were similarly coordinated when reaching to pick up the box, however participants with stroke struggled to coordinate their hands while picking up the box. The time to pick the box up correlated with paretic upper limb proprioception which indicates that sensory deficits may have caused the need for multiple adjustments while grasping the box with the paretic hand. This task demonstrates that coordination may be impaired during symmetric tasks with a cooperative goal.

One study published since Kim and Kang's meta-analysis used an asymmetric common-goal task to examine the paretic limb as a manipulator and stabiliser more closely. Participants with chronic stroke had their hands physically connected with a spring and performed a task mimicking bread slicing that required one hand to accurately reach forwards while the other hand stabilised the spring load to remain stationary (435). Participants with stroke displayed intralimb coordination and performance deficits with the reaching hand but similar performance with the stabilising hand, regardless of which hand was used for each role. Unfortunately the sample size of 15 participants was not large enough to explore the role of the side of stroke lesion because, according to the complementary dominance hypothesis, lesions affecting the dominant hemisphere produce deficits in the paretic upper limb's ability for predictive control of accuracy whereas lesions to the non-dominant hemisphere produce deficits in the paretic upper limb's ability for stabilising. Although the bread-slicing task could not provide evidence for this theory, the results from unimanual tasks with participants with stroke do support it (109, 436, 437). Understanding how the side of stroke lesion affects the paretic upper limb's ability to perform specialised roles during common-goal tasks could have important implications for upper limb rehabilitation in determining what role(s) the paretic limb should be re-trained to perform (247).

Only one asymmetric parallel task has been used to study bimanual coordination after stroke (168). Participants reached to open a drawer with one hand and press a button inside with the other hand. Healthy adults performed this task by moving their hands concurrently whereas people with stroke moved their hands sequentially as the hand reaching to press the button only began moving once the opposite hand had finished opening the drawer. This indicates people after stroke find it difficult to temporally coordinate both hands to move simultaneously during asymmetric parallel tasks.

Together the studies discussed here indicate that participants after stroke have significant bimanual coordination impairments on a range of common-goal tasks, and comparisons between common-goal and independent-goal conditions depends on the task. Participants with stroke also have trouble coordinating their hands during asymmetric parallel tasks. Parallel and cooperative tasks have not been compared after stroke. The significance of common-goal task deficits has been acknowledged with suggestions to incorporate more bimanual cooperative tasks into upper limb rehabilitation due to the plethora of cooperative tasks performed in everyday life (294, 438).

9.3.3 Interaction between Symmetry and Goal

Broadly, the above studies have demonstrated that participants with chronic stroke display impairments on asymmetric tasks and common-goal tasks. It is also important to consider movement symmetry and goal conceptualisation together to identify which aspect of the task produces these deficits. For example, are participants with stroke less coordinated than controls during the asymmetric parallel item retrieval drawer-task because of the asymmetric upper limb movements, or because of the parallel nature of the task? The only study to examine movement symmetry and goal conceptualisation together after stroke is also the only study to compare common-goal and independent-goal conditions in people with stroke (286). Participants had to either move their hands in a symmetric pattern or in a clockwise or anticlockwise asymmetric pattern in order to move one virtual brick with both hands or one virtual brick in each hand. Spatial coordination was worse for the asymmetric common-goal condition than the asymmetric independent-goal condition, however there was no difference between the symmetric common-goal and independent-goal conditions. Hence, an interaction between symmetry and goal was present as goal conceptualisation influenced spatial coordination only during asymmetric tasks.

In the same study, participants with stroke had worse temporal coordination during the symmetric common-goal task compared to the symmetric independent-goal task as well as controls performing the same symmetric common-goal task (286). This is the only study to include a lab-based task requiring symmetric cooperative coordination and indicates that the cooperative aspect of the task impaired temporal coordination given that temporal coordination appears intact after stroke during symmetric parallel and symmetric independent-goal tasks (161, 286, 431). This study demonstrates how both the symmetry and goal of a task can influence bimanual coordination, with symmetric independent-goal tasks being the easiest to coordinate and asymmetric cooperative tasks being the most difficult. Whether the same findings occur when interacting with real rather than virtual objects is not yet known.

9.4 Neurological Basis of Bimanual Coordination Deficits

It is apparent that some degree of functional coupling between homologous muscles is preserved as early as three weeks after stroke (424). This is presumably what allows people with stroke to retain a high degree of bimanual coordination during certain symmetric tasks. The corpus callosum, which is thought to mediate spatial functional coupling at the cortical level, is often damaged by stroke (439-441). In contrast, temporal coupling may be mediated by pathways or mechanisms not involving the corpus callosum such as at the subcortical or spinal levels (214, 274, 442). Thus, damage to the corpus callosum by stroke may impair spatial but not temporal coordination. People with acquired callosal damage show a similar impairment in spatial coordination but not temporal coordination during discrete bimanual tasks (190, 442-444). One limitation is that each of these studies only included three or fewer participants with callosal damage. It has been hypothesised that stroke causes an increase in the ipsilateral control of the paretic limb, and this may also help preserve functional coupling by strengthening the degree to which the contralesional hemisphere controls both upper limbs (157, 295, 445). Although the mechanisms of how functional coupling is preserved after stroke are not fully understood, attempts have been made to harness it to improve paretic upper limb recovery (434, 446).

Participants with stroke demonstrate clear impairments on asymmetric tasks regardless of the task goal(s). This may be due to altered functional connectivity between motor regions that are critical for performing asymmetric movements such as M1, SMA, and PMd (159, 177, 178, 279, 341). One study found participants with chronic stroke did not exhibit an expected increase in SMA activity when preparing for a rhythmic asymmetric independent-goal task compared to controls but did have a greater increase in SMA activity during the task (447).

Increased resting functional connectivity from the M1 to SMA has been reported in the contralesional and ipsilesional hemispheres (448, 449). Overactivation of the SMA has been suggested as a compensatory mechanism needed to perform asymmetric tasks due to damage from stroke (447). Similarly, normally inhibitory interhemispheric interactions from the contralesional PMd to the ipsilesional M1 are facilitatory in people with stroke (450). This increased activation of the SMA and PMd could be similar to the increased activation of the same regions in older compared to younger adults, which is thought to be necessary during asymmetric tasks to compensate for structural effects of aging (297, 336, 338). Thus, it may be damage to secondary motor regions and impaired connectivity between them that accounts for problems with coordinating asymmetric movements after stroke.

Participants with stroke moved their hands more sequentially than controls during an asymmetric parallel task item retrieval drawer-task (168). The difficulty in moving both hands simultaneously means that parallel tasks may be performed in a similar manner to independent-goal tasks after a stroke. This may also partially explain why participants after stroke perform similarly to healthy controls on many symmetric parallel tasks, because they also display no coordination deficits on symmetric independent-goal tasks. Asymmetric independent-goal tasks are the most difficult to visually attend to in healthy adults and so sequential bimanual movements during the item retrieval drawer-task could be caused by a need to visually attend to the paretic upper limb while it moves during the task (302, 451). In support of this, one study using the same item retrieval drawer-task with three people with callosal damage from stroke found they were synchronised at task onset with normal vision but not in the absence of vision (190). In argument against the importance of vision, a study found temporal coordination on the item retrieval drawer-task did not correlate with proprioception in participants with chronic stroke (168). The role of attention could be explored more thoroughly to explain why temporal coordination is impaired during asymmetric parallel tasks after stroke.

Participants with stroke have clear bimanual coordination impairments during cooperative tasks. Several pieces of evidence support the idea that post-stroke deficits during cooperative tasks may be the result of impaired interhemispheric communication. Unilateral ulnar nerve stimulation during a cooperative task leads to bilateral reflexes responses in healthy adults (291-293). However, nerve stimulation of the paretic hand in participants with chronic stroke during the same task only generates an ipsilateral reflex response (157). It has been hypothesised that the contralesional hemisphere takes greater control of the paretic upper limb during bimanual tasks to compensate for damage to the ipsilesional hemisphere and the corpus callosum (157, 295). Increased reliance on ipsilateral motor pathways has been implicated in control of the paretic upper limb for people with severe weakness, but the influence of these pathways has not been examined in the context of bimanual coordination (202, 452, 453). Damage to the corpus callosum could also account for impairments on cooperative tasks as it likely mediates interhemispheric communication during these tasks (439-441). In support of this, corpus callosum integrity measured with fractional anisotropy correlated more strongly with spatial coordination when participants reached symmetrically to grasp a large box compared to two water bottles (439). However, the same study found no differences between the two tasks on the strength of correlation between spatial coordination and mean kurtosis, another measure of corpus callosum integrity. The fractional anisotropy result however provides further support that bimanual coordination deficits during cooperative tasks after stroke may result from impaired interhemispheric communication.

9.5 Limitations of Current Studies and Future Directions

The evidence base describing bimanual coordination after stroke has several overall limitations. One of the key reasons for studying bimanual coordination after stroke is to assist development of upper limb interventions after stroke. As highlighted in this chapter, almost all research of bimanual coordination after stroke has been conducted at the chronic stage (151). The early subacute stage needs greater research attention because this is the period when the vast majority of contralesional and ipsilesional upper limb motor recovery occurs (71-73, 105). The environment of the brain and the repair processes working within it differ greatly between the early subacute and chronic stages and so findings from one stage cannot be reliably extrapolated to the other. The only study to longitudinally measure bimanual coordination at the subacute stage after stroke reported that it plateaued at six weeks post-stroke, emphasising the importance of studying bimanual coordination very early after stroke (424).

Another limitation is that many measures of temporal and spatial coordination are used between studies which can make comparisons between bimanual coordination categories difficult. For example, temporal coordination during symmetric parallel reaching tasks has been measured as movement time as well as the between-hand delay in movement beginning, movement end, and peak velocity (286, 424, 429). A further limitation is that, like with healthy adults, most studies of bimanual coordination after stroke have used lab-based tasks rather than real-world tasks. Finally, studying bimanual coordination in people with severe upper limb weakness is often not possible because a certain degree of upper limb movement is needed to perform bimanual tasks. Some studies mitigate this issue by supporting the arms or using extremely light objects to minimise strength requirements (168, 322, 425). Other studies simply exclude people if they do not have enough movement in the paretic upper limb to perform the task (322, 428-430). Understanding bimanual coordination is critical in severely affected participants as they likely have limited ability to use their paretic upper limb in bimanual tasks and so it is important to maximise this function.

Several aspects of bimanual coordination after stroke remain to be studied. The most important is the longitudinal recovery of bimanual coordination at the subacute stage after stroke using different categories of bimanual tasks. Understanding recovery could help the development of upper limb interventions or improve rehabilitation practices. The influence of stroke symptoms on bimanual coordination has also been largely unstudied. For example, sensory loss correlates with impaired spatial coordination on a symmetric cooperative box lifting task because participants with stroke struggle to grip the box correctly (168). The effects of other symptoms on bimanual coordination after stroke, such as hemianopia or inattention, have not been examined despite evidence that visual attention is important for bimanual coordination in healthy adults (153, 302). It is possible that bimanual coordination could be enhanced by reducing the effects of other impairments. Lastly, a greater emphasis on using real-world tasks to study bimanual coordination after stroke would provide more ecologically relevant results that better capture how the hands are used in naturalistic settings. Future studies could even compare lab-based and real-world tasks, for example whether bimanual coordination during a symmetric parallel task differs depending on whether the participant is reaching for a virtual object or a real object. One study found that ipsilesional upper limb reaching deficits may be more pronounced in natural settings than laboratory contexts, and the same may be true for bimanual movements (321).

Overall, people with stroke largely retain bimanual coordination during symmetric independent-goal and likely symmetric parallel tasks but have impaired coordination during symmetric cooperative tasks and asymmetric tasks regardless of the goal. Thus, an interaction between movement symmetry and goal conceptualisation is present for bimanual coordination after stroke. Task performance is impaired in people with stroke for all categories of bimanual tasks. Despite the usefulness of the tasks described in this chapter for studying bimanual coordination, there are several factors that make them unsuitable to measure the recovery of bimanual coordination after stroke. The most important factor is feasibility as most of the published protocols take a long time to conduct, require highly standardised techniques and environments, and use expensive equipment. These factors make it difficult to assess people with stroke in hospital or rehabilitation settings. Furthermore, the movements involved do not always accurately reflect everyday tasks and often only assess one or two categories of bimanual coordination. It is for these reasons that it is often preferable to assess people with stroke using clinical assessments, particularly at the acute and subacute stages. The next chapter will provide an overview of bimanual upper limb clinical assessments commonly used after stroke.

10 Bimanual Upper Limb Stroke Assessments

Bimanual upper limb clinical assessments after stroke assess aspects such as participant-reported function on bimanual tasks, spontaneous use and performance of the paretic upper limb during bimanual tasks, and bimanual coordination during a rhythmic task. Bimanual upper limb assessments are rarely used in stroke recovery research though. A review of 477 rehabilitation studies found the most commonly used bimanual assessment was the Chedoke Hand and Arm Activity Inventory (CAHAI) in approximately 1% of studies (454). Moreover, there were no mentions of bimanual upper limb assessments from the most recent roundtable of international experts to determine recommended measurements of sensorimotor recovery after stroke (122). Several established and novel bimanual upper limb clinical assessments will be discussed here. Assessments with a mixture of unimanual and bimanual tasks will not be discussed unless the tasks are predominantly bimanual. Bimanual upper limb assessments can be broadly categorised into behavioural assessments, video-recorded assessments, and questionnaires.

10.1 Behavioural Assessments

Behavioural assessments are used to measure a participant's actual functional performance, are usually performed in-person, and are observed and scored in real-time by an assessor. The biggest advantage of behavioural assessments is that they reliably assess a person's actual functional ability, which may be over or underestimated by their self-perceived function (455, 456). Proper training of assessors along with standardisation of items, positioning, and instructions ensures that reliable results are obtained and can be compared between studies.

The need for a high degree of standardisation however means that a person's performance on a behavioural assessment may not accurately reflect their functional ability in their natural environments.

The CAHAI is an assessment of paretic upper limb functional capacity during bimanual tasks (457). The CAHAI consists of 13 everyday tasks such as pulling up a zipper, opening a jar, and pouring a glass of water. Each task is scored on an ordinal scale from 1 – 7 depending on the participant's level of dependence for the task, with a score of seven indicating complete independence and that the paretic hand can perform all required tasks in safe and timely manner. The CAHAI has been validated and has high between-session and interrater reliability (458-460). All tasks except two in the CAHAI would be classified as asymmetric cooperative using the Kantak taxonomy. Two qualitative studies with occupational therapists indicated several issues with using the CAHAI in clinical settings including its usefulness for severely impaired people who cannot perform any part of the tasks, confusion regarding the scoring system, and low confidence that CAHAI scores are sensitive to improvements in upper limb performance (461, 462). Most occupational therapists used the CAHAI with five or fewer participants and so these concerns may subside with more experience. Despite these limitations, the CAHAI remains the most commonly used bimanual upper limb assessment in stroke rehabilitation studies (454).

The Interlimb Coordination Test (ILC2) is a simple behavioural assessment of bimanual coordination (463). The ILC2 forms part of the Comprehensive Coordination scale which uses several sub-assessments to measure coordination between different limbs. A unique property of the ILC2 is that it uses a rhythmic task rather than real-world bimanual tasks like those in the CAHAI. Participants support their forearms on their knees and perform anti-phase pronation-supination movements with both forearms for ten seconds. Participants are scored ordinally from 0 – 3 on two scales, one measuring how long they can perform the movements for and the other measuring the quality of the movements. Thus, the ILC2 measures both task performance and quality of movement. The ILC2 has only been used in one group of thirteen participants with chronic stroke who were compared to healthy controls (463). Both groups performed the ILC2 under four conditions: at either a fast or slow speed, and with internal or external pacing. Control participants scored near maximal on the ILC2 in each condition while participants with stroke were impaired during all conditions and used compensatory trunk and shoulder movements during the task. Reliability of the ILC2 remains to be determined. The ILC2 has potential as a fast and simple test of bimanual coordination after stroke because it requires no items and only takes approximately one minute to administer. The ecological validity of the results can be questioned though because the ILC2 is a rhythmic task that does not closely replicate how the upper limbs coordinate during everyday tasks.

The Bimanual Assessment Measure (BAM) is described as a comprehensive measure of bimanual function (464, 465). Information about the BAM is scarce as its development has not been published online and has only been presented at a pair of conferences in the mid-2010s (464, 465). Despite no published reports of its use with participants with stroke, the BAM deserves to be briefly mentioned because of its potential. The BAM requires common items and includes 11 everyday bimanual tasks that cover a range of bimanual coordination categories. Parallel and cooperative goal tasks are included as well as tasks requiring symmetric and asymmetric movements. Thus, the BAM is the only behavioural assessment that covers most categories in the Kantak taxonomy, despite it being introduced earlier than the Kantak taxonomy. Scoring is predominantly dependent on whether the paretic upper limb is used as a stabiliser or manipulator, although the time to complete each task also contributes to scoring. The current development status of the BAM is uncertain.

10.2 Video-recorded Assessments

Video-recorded assessments involve overt or covert recording of participants while they perform behavioural tasks. The video recording is the used to score the participant's performance later which is the most significant difference to behavioural assessments that are scored in real-time. Otherwise, both video-recorded and behavioural assessments assess a participant's actual functional ability and are usually performed in-person. Video recording assessments reduces interrater variability because different raters score the same performance, and a participant's performance can be reviewed and re-scored if necessary. Standardisation of assessment items and the environment is critical for video-recorded assessments because any changes to object or participant positioning can alter the visual angles recorded and cause task components to be missed. The need for video recording and high standardisation means that video-recorded assessments are not appropriate to use in hospital settings soon after stroke.

The Ad-AHA Stroke is a video-recorded assessment of a participant's typical bimanual task performance and their spontaneous paretic upper limb use (466, 467). The Ad-AHA Stroke is openly video-recorded and scored later. Participants perform one of two everyday tasks, each containing several subtasks requiring a combination of gross and fine hand use. One of these tasks is "making a sandwich" which includes cutting vegetables, spreading condiments, and opening containers. The other task is "wrapping a present" which includes cutting paper, writing a short note, and opening a jar. Participants complete the task using their hands in whatever way feels natural to them. The Ad-AHA Stroke is described as assessing bimanual activity performance but scoring is only made in reference to paretic upper limb performance and task outcome is not evaluated (426). The participant's paretic arm is scored ordinally on a 4-point scale on 19 movement aspects such as grasping, amount of use, forearm movement, and regulating grip force.

The Ad-AHA Stroke has strengths. First, it has demonstrated high validity and good intrarater and interrater reliability in a large sample of 118 participants at the late subacute stage after stroke (467). High validity was confirmed in a separate sample of 144 participants with stroke (466). The Ad-AHA Stroke assesses specific elements of paretic upper limb movement and function with more depth than similar assessments like the CAHAI. Additionally, the large number of scoring categories and the 4-point scale protect against a ceiling or floor effect. There are several significant limitations of the Ad-AHA Stroke though. The most important limitation is the impractical nature of the tasks. Both tasks of the Ad-AHA Stroke require resources that cannot be reused between assessments, such as wrapping paper and vegetables. Furthermore, there can be safety concerns having people with stroke handle scissors and knives, which could limit its use for people with cognitive impairments. Finally, participants completing the Ad-AHA Stroke only perform one task, although it does include several subtasks. In comparison, the CAHAI includes 13 tasks and the ABILHAND, a questionnaire of bimanual function, includes 23 tasks. It is questionable to what extent Ad-AHA Stroke results reflect task-specific paretic upper limb function rather than overall paretic upper limb function. Based on all these factors, the Ad-AHA Stroke shows potential to be a thorough assessment of paretic upper limb function during real-world bimanual tasks but is likely not appropriate to use with people with stroke in hospital settings.

The Actual Amount of Use Test (AAUT) measures spontaneous paretic arm use and performance after stroke (468). Participants are covertly video recorded while performing 17 everyday tasks such as pulling out a chair, opening a newspaper, and grabbing cards from a box. Participants consent to be video recorded as part of the study but are unaware they are being taped when performing the AAUT. Participants are scored 0 or 1 based on whether they attempted to use their paretic upper limb in the task and are scored ordinally from 0 – 5 depending on the quality of paretic upper limb function. The quality of function scoring aspect has a good level of sensitivity with people with stroke, however the amount of use aspect has low sensitivity due to its binary scoring (468). The most significant and unique advantage of the AAUT is that participants are unaware they are being filmed while performing these tasks, which allows a true insight into how people with stroke spontaneously use their hands. The potential to adapt the scoring of the AAUT to focus on spontaneous bimanual performance rather than paretic upper limb performance could be explored in the future.

10.3 Questionnaires

Questionnaires are used to evaluate a person's self-reported perception of their current function and limitations. Advantages of questionnaires include being simple and fast to conduct, they can usually be administered over the phone, and they do not require any equipment. Another advantage is understanding how people with stroke use their paretic limb in everyday life because questionnaires commonly ask people about their perceived ability to complete tasks around the home. Questionnaires also allow insight into tasks that would not be feasible to have the participant perform as part of an observed assessment, for example cooking and gardening. Cognition needs to be carefully considered though to ensure the participant understands the parameters of the questions and the available answers. One limitation is that questionnaires cannot provide information regarding a person’s actual physical capabilities, but this can be mitigated by using questionnaires in conjunction with behavioural assessments. One established bimanual questionnaire is the ABILHAND while a newer type of questionnaire with potential is Ecological Momentary Assessment (EMA).

The ABILHAND is a self-reported questionnaire that examines a participant’s perceived ease of performing everyday bimanual tasks (469). Participants use an ordinal 3-point scale to rate how difficult it is for them to perform 23 bimanual activities such as peeling potatoes, buttoning up a shirt, and opening an envelope. The ABILHAND is valid and reliable at the chronic stage after stroke (469, 470). The ABILHAND is the most used questionnaire of bimanual activities in stroke studies and is recommended as an upper limb outcome assessment after stroke (460). The ABILHAND has a few limitations. All 23 tasks are asymmetric cooperative and so the ABILHAND does not provide information about a participant’s ability to perform tasks in other categories of the Kantak taxonomy. Additionally, how the participant completes a task is largely not considered. For example, participants may open an envelope by holding it in one hand and tearing it open with their teeth which could be perceived and scored as easy by the participant whereas the task would be impossible if they had to use both hands to complete it. Furthermore, the ABILHAND has limited use for people with stroke in dependent care because people may not know how difficult they perceive a task if they haven’t performed it recently. Similarly, the ABILHAND has not been used in the early subacute stage after stroke with people who are still in hospital because they are unlikely to have performed many of the tasks since the stroke. Longitudinal subacute stroke studies instead use the ABILHAND at three months post-stroke or later as a secondary measure of self-perceived functional ability (83, 471, 472).

EMA is a type of questionnaire used to capture functional behaviours of people in their natural environment (473). EMA has been used to characterise functional behaviours in people with stroke rather than their perceived functional abilities like the ABILHAND assesses. Participants are prompted via smartphone during several pre-determined periods throughout the day to answer a questionnaire about their current activities when they received the notification. For example, one study prompted 212 participants with chronic stroke at a random time during five two-hour blocks throughout the day for two weeks (423). This study focussed on broad functional behaviours and so participants answered questions such as where they are currently, who they are with, and what activity they are performing. A different study using EMA aimed to understand how the paretic hand was being used by participants with chronic stroke in their natural environment (474). Participants were asked questions such as what arm(s) the participant is using for the current activity, what position they are performing the activity in, and whether the activity requires strength and/or dexterity. The EMA has been used in conjunction with accelerometers to mitigate one of the latter’s limitations, which is the inability to know what activities the participant is using their upper limbs to perform (475). Although EMA has not been used specifically to study bimanual coordination after stroke, the above two studies demonstrate how the questions could be adapted to focus on bimanual coordination. For example, the participant could be asked if their current activity requires symmetric or asymmetric upper limb movements.

It is evident that paretic upper limb use and movement quality during naturalistic bimanual tasks can be measured with assessments such as the CAHAI, AAUT, and Ad-AHA Stroke. Assessments measuring bimanual coordination or bimanual task performance however are scarcer. The ILC2 shows potential as a measure of bimanual coordination but it only involves a single rhythmic asymmetric task. The ABILHAND includes a range of everyday bimanual activities but measures self-perceived performance rather than observed performance. Thus, there are currently no comprehensive assessments that considers both bimanual coordination and bimanual task performance while including a range of everyday tasks. Part of the current thesis attempted to fill this gap using a novel assessment called the Bimanual Coordination After Stroke Scale (BCASS).

10.4 Development of the BCASS

The BCASS is a behavioural assessment of coordination during bimanual task performance for use after stroke, or more simply an assessment of bimanual coordination after stroke. This section provides insight into how the tasks and scoring criteria were determined for the BCASS. Details of each task, scoring feature, and how the BCASS is administered are provided in the following experimental chapter which used the BCASS with healthy adults and people at the chronic stage of stroke.

10.4.1 Task Selection

We decided that the BCASS would include real-world tasks that replicate everyday activities to increase its ecological validity. This is like assessments such as the ABILHAND, CAHAI, AAUT, and Ad-AHA Stroke. The tasks aimed to require a range of proximal and distal movements to complete, as well as a mixture of both fine and gross object manipulation. Another important property for the BCASS was clinical feasibility. Designing the tasks and scoring in a way that allowed the BCASS to be reliably performed at the patient bedside would increase its clinical feasibility. This is particularly true for use of the BCASS in longitudinal studies after stroke because baseline assessments are recommended to be completed in the first week after stroke (122). Therefore, the BCASS had to be performed and scored in-person without video-recording, would need to be feasible to perform in a variety of environments, and would need to be completed in a short amount of time. Clinical feasibility was further increased by the decision to use cheap and readily available items. For example, one task in the BCASS uses a plastic cup and paperclip to replicate the commonly studied item retrieval drawer-task because they are much easier to find and use in clinical settings than a drawer (168, 284, 285). Finally, the number of items required for the BCASS was limited by using the same items across multiple tasks.

Many current bimanual upper limb assessments measure performance across a range of approximately 10 – 20 naturalistic tasks. Most bimanual tasks performed in real-world situations are asymmetric cooperative, and this is reflected in the currently available assessments. For example, all 23 tasks in the ABILHAND and 15 of the 17 tasks in the CAHAI are asymmetric cooperative. Additionally, assessments of paretic hand role choice such as the AAUT need to use asymmetric cooperative tasks as they have clear stabiliser and manipulator roles. However, naturalistic tasks that require symmetric movements and tasks with parallel or independent goals are not present in many studies. BCASS tasks cover the full range of the Kantak taxonomy to comprehensively assess bimanual coordination during tasks with differing coordination requirements. A summary of the eight tasks in the current version of the BCASS is provided in Table 11.1.

10.4.2 Scoring Criteria

Scoring criteria in the BCASS focuses on bimanual coordination and bimanual task performance. Participants are scored 0 or 1 across a variety of features for each task, and there are seven scoring features in total. Certain scoring features refer to bimanual task performance such as whether the participant could complete the task, whether compensatory trunk movements were used, and whether the task was performed in a timely manner. The last of these is commonly scored in behavioural assessments, and different methods are used to determine time limits for timely completion. As an example, the ARAT can be performed using a 5 second limit for all tasks or using task-specific limits based on normative times from healthy older adults (130, 131). We decided to collect normative times from healthy older adults to use as time limits for BCASS tasks because we anticipated completion time to vary between tasks. For example, time limits for the ARAT based on normative values range from 2.4 to 7.9 seconds depending on the task (131). Normative times for BCASS tasks were collected from healthy older adults as part of a study described in the next chapter.

Certain scoring features of the BCASS assess bimanual coordination during the task. For example, one scoring feature is whether the participant's hands are moving concurrently or sequentially during the task as a measure of temporal coordination. An evaluation of temporal coordination was included in the scoring because people with stroke have demonstrated impaired temporal coordination during bimanual tasks (168, 286, 428). Similarly, whether the participant's hands were moving at the same speed during the task is evaluated as a measure of spatial coordination. This was included because people with stroke have exhibited dissimilar hand speeds during bimanual tasks (286, 433).

Each BCASS task is scored out of 5, 6, or 7 and this varies between tasks because certain scoring features are not applicable to all tasks. For example, we ascertained that spatial coordination would be too difficult to evaluate for tasks with multiple objects at asymmetric distances from the participant. The need to evaluate at least five binary scoring features of each task does make the BCASS more difficult to score compared to assessments like the CAHAI where overall paretic hand performance in each task is simply scored from 0 – 7. However, this limitation is offset by the advantage of more detailed examination of bimanual coordination using the BCASS. The current BCASS is scored out of a total of 45 points and further details of each scoring feature are provided in the methods section of Appendix 8.

People performing the BCASS are informed of the goal for each task and are instructed to complete the tasks bimanually. An important feature is that participants are not told how they should use their hands to complete each task. Allowing participants to complete the task in whichever way feels most natural or easiest allows insight into their spontaneous upper limb use. Examining spontaneous performance also increases ecological validity. Allowing spontaneous performance is most important for three asymmetric tasks with clear manipulator and stabiliser roles. However, we decided that the BCASS would not score whether the participant uses their paretic upper limb as a stabiliser or manipulator because hand role choice varies in healthy adults depending on the task, object positioning, and object orientation (150, 158, 238).

The following two chapters present experiments using the BCASS with people with stroke. The first experiment evaluated the sensitivity, validity, and reliability of the BCASS in people with chronic stroke, as well as obtain normative values from healthy younger and older adults. The second experiment used the BCASS to longitudinally measure recovery of bimanual coordination from one week to six months after stroke.

11 The Bimanual Coordination After Stroke Scale (BCASS) - a new Behavioural Assessment of Bimanual Coordination after Stroke

11.1 Abstract

Bimanual coordination deficits are evident at the chronic stage after stroke. Here we introduce the Bimanual Coordination After Stroke Scale (BCASS) as a behavioural assessment of bimanual coordination after stroke. The BCASS includes six categories of naturalistic bimanual tasks and is designed to be clinically feasible. Bimanual task categories differ depending on movement symmetry and the task goal(s). The aim of this study was to refine the BCASS and assess its sensitivity, validity, and reliability in people with chronic stroke. Thirty younger adults, 30 older adults, and 30 participants with chronic stroke and unilateral upper limb weakness performed four BCASS assessments across two sessions. Participants were assessed by two different raters in each session. Participants with chronic stroke also completed the Box and Block Test, the Fugl-Meyer upper-extremity assessment, and the ABILHAND assessment. Sensitivity of the BCASS to aging and stroke was evaluated by comparing scores between the three cohorts. Within-session interrater reliability, between-sessions intrarater reliability, and between-sessions interrater reliability of the BCASS were determined for participants with chronic stroke. Total BCASS scores were sensitive to the effects of stroke but not aging. All three reliability measures demonstrated excellent agreement for the BCASS, and BCASS scores correlated very highly with the unimanual

assessments and highly with the ABILHAND. Both movement symmetry and task goal(s) influenced task performance. The BCASS was found to be a sensitive, valid, and reliable assessment of bimanual coordination for people at the chronic stage after stroke. External validation of the BCASS is required.

11.2 Introduction

Between 40 – 60% of people experience unilateral upper limb weakness following a stroke (66, 68, 69). This weakness commonly persists into the chronic stage along with upper limb impairments in other domains such as function, sensation, and dexterity (82, 476). These impairments affect both unimanual and bimanual task performance. Bimanual tasks require both hands to coordinate with one another, such as tying shoelaces, opening jars, and cutting vegetables. Improving bimanual task performance after stroke is therefore critical for regaining independence in many activities of daily living (ADLs) (91). Indeed, bilateral activities make up a significant proportion of everyday tasks performed by both healthy adults and people with chronic stroke (412, 421, 474), and most of the time people with chronic stroke use their paretic limb is during bimanual activities (421, 474, 477).

Kantak et al. proposed a theory-guided taxonomy of bimanual coordination to assist the study of bimanual coordination after stroke (Figure 11.1) (151). The Kantak taxonomy can be used to identify which specific types of bimanual tasks are most challenging for patients after stroke, as well as standardise protocols for researching bimanual coordination deficits, recovery, and outcomes after stroke. The first feature in the Kantak taxonomy is whether movements are symmetric or asymmetric with respect to the midline of the body. Symmetric bimanual movements involve the simultaneous activation of homologous muscles whereas asymmetric movements activate non-homologous muscles simultaneously or homologous muscles with different timings. The second feature is how the goal to be achieved is conceptualised. Independent-goal tasks involve each upper limb acting to achieve separate goal whereas common-goal tasks involve both upper limbs acting to achieve a single goal. Common-goal tasks are further subdivided into parallel and cooperative tasks depending on whether bimanual coordination is necessary to achieve the task. These will simply be referred to as parallel and cooperative tasks. Parallel tasks do not require simultaneous bimanual movements to be successful, but coordination is desired for efficiency. An example of this is making a cup of coffee. Pouring water into a coffee cup with one hand while stirring the coffee with the other hand is more efficient than pouring the water first and then stirring it second. Cooperative tasks though do require both hands to work together simultaneously to be successful. Most ADLs are cooperative tasks such as tying shoelaces, opening jars, and peeling vegetables.

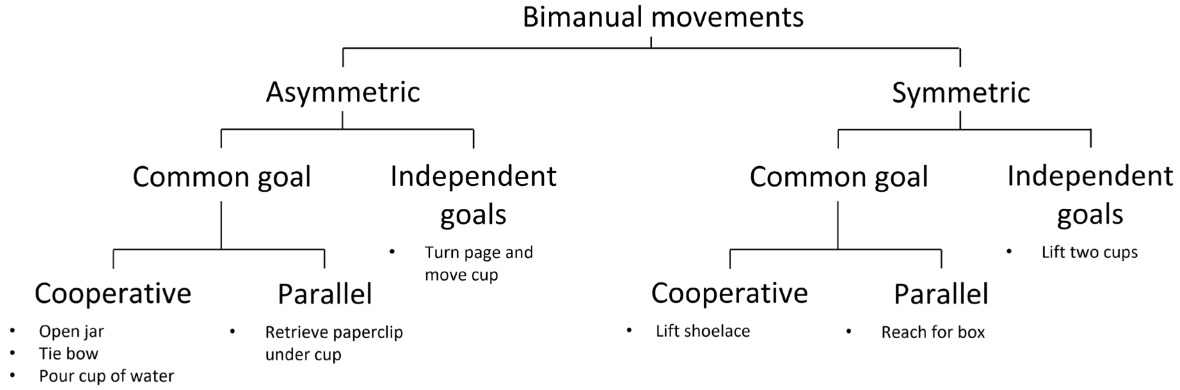


Figure 11.1. Categorisation of bimanual tasks based on the Kantak taxonomy (151). Bimanual tasks are categorised depending on movement symmetry (asymmetric or symmetric) and conceptualisation of the task goal(s) (cooperative, parallel, independent). The tasks listed under each category are included in the BCASS, and further details of each task are provided in Table 11.1.

The study of bimanual coordination in healthy adults has helped understand which specific domains of bimanual coordination are affected by stroke. It is well established that symmetric bimanual tasks are more stable and easier to perform than asymmetric tasks (221). One theory is that the activation of homologous muscles during symmetric movements leads to a functional coupling between M1s which increases task stability (221).

Studies investigating goal conceptualisation have focussed on cooperative and independent-goal tasks, while parallel tasks have been largely unstudied. Healthy adults have comparable coordination and performance during discrete reaching with independent goals compared to a cooperative goal (166, 288, 310). However, there is evidence that the neural control of bimanual movements in healthy adults differs depending on the task goal. The control of cooperative tasks appears to be more bilaterally distributed across the hemispheres and engage greater interhemispheric coupling compared to independent-goal tasks (153, 165, 166, 291, 293).

Several studies have also reported an interaction between movement symmetry and goal conceptualisation in healthy adults. Two studies reported movement symmetry affected reaction time on isometric force tasks using independent-goal conditions but not common-goal conditions (303, 395). Reaction time was longer during asymmetric independent-goal conditions than symmetric independent-goal conditions, possibly due to the greater cognitive demands of attending to two hands with different force requirements. Furthermore, a study using a bimanual reaching task found movement symmetry had a greater influence on interlimb coupling during a cooperative condition than an independent-goal condition (310).

The above studies demonstrate that movement symmetry and goal conceptualisation can influence bimanual coordination in healthy adults. It is important to note most studies examining bimanual coordination in healthy adults use laboratory tasks that have little ecological validity. Healthy younger and older adults have shown to be highly coordinated during a range of naturalistic tasks such as pouring a glass of water (316), opening a jar (317), reaching to grasp and pick up a box (168), and retrieving an item from a drawer (168, 284).

A recent meta-analysis by Kim and Kang investigated bimanual coordination deficits after stroke (156). They categorised 25 tasks comparing participants with chronic stroke and age-matched controls into the six categories used in the Kantak taxonomy. The results showed people with chronic stroke had deficits in each type of bimanual task except for symmetric independent-goal tasks, although other evidence suggests bimanual coordination may also be retained after stroke during symmetric parallel tasks (168, 322). Despite deficits after stroke being apparent on most bimanual task categories, no single study to date has investigated all six categories of bimanual tasks with the same group of participants. Furthermore, only three studies included in the meta-analysis used naturalistic tasks as most studies used lab-based tasks such as simple rhythmic movements, isometric force production, and bimanual circle drawing (156). This highlights that most research on bimanual coordination after stroke does not use tasks or environments that accurately reflect how people with stroke may use their hands in everyday life. A disparity between upper limb performance in the laboratory and in natural environments has been highlighted for both healthy adults and people with stroke (315, 413, 473).

An additional limitation of most bimanual coordination tasks is that they need to be performed in highly standardised environment. This can be problematic for people at the subacute stage after stroke who are often still in hospital or rehabilitative settings and have a wider range of deficits than people at the chronic stage. Simple assessments that can be performed in clinical settings are more useful for studying bimanual coordination at the acute and early subacute stages after stroke. Current clinical assessments using naturalistic bimanual tasks include the CAHAI, Ad-AHA Stroke, AAUT, and the ABILHAND assessment (458, 467, 468, 470). However, these assessments only contain bimanual tasks from one category of the Kantak taxonomy (ABILHAND, CAHAI), require highly standardised environments to perform (Ad-AHA Stroke, AAUT), and/or only measure performance of the paretic upper limb during bimanual tasks (Ad-AHA Stroke, CAHAI). Thus, there exists a need for a clinical assessment of bimanual coordination that covers the full range of bimanual tasks, takes bimanual task performance into account, uses naturalistic tasks, and is simple enough to be performed in a clinical setting.

The Bimanual Coordination After Stroke Scale (BCASS) assessment was developed as a behavioural assessment of coordination during bimanual task performance. The BCASS includes eight bimanual tasks that replicate real-world ADLs and cover the range of categories in the Kantak taxonomy. The BCASS was designed to be feasible for use at the patient bedside at the acute and subacute stages after stroke.

The present study had five aims. The first aim was to refine the newly developed BCASS using data obtained from participants with chronic stroke. The second aim was to determine the sensitivity of the BCASS to age and stroke using separate cohorts of healthy younger and older adults without stroke as controls. We hypothesised that healthy younger and older adults would have comparable performance and score near-full marks on the BCASS whereas participants with chronic stroke would have deficits on all task types except the symmetric independent-goal task compared to healthy older adults. The third aim was to validate the BCASS with established unimanual and bimanual assessments. The fourth aim was to investigate the reliability of the BCASS. The between-sessions interrater reliability was evaluated for all cohorts. The within-session interrater reliability and between-sessions intrarater reliability were also evaluated for participants with stroke as this is the intended cohort for the BCASS. High reliability is important for the wide-spread use of a clinical assessment to ensure it is robust to changes in raters and repeated assessments (478). The fifth aim was to investigate whether movement symmetry and/or goal conceptualisation affected task performance in participants with chronic stroke. We hypothesised that participants with stroke would perform better on symmetric tasks than asymmetric tasks and on independent-goal tasks compared to common-goal tasks based on the results of Kim and Kang's meta-analysis of bimanual coordination after stroke (156).

11.3 Methods

11.3.1 Participants

A total of 90 adults participated in this study consisting of 30 people with chronic stroke, 30 healthy older adults, and 30 healthy younger adults. Inclusion criteria for people with chronic stroke included being aged 18 years or older, at least 6 months since their most recent stroke, and still experiencing upper limb weakness or altered sensation resulting from a stroke. People with chronic stroke were excluded if their stroke occurred in the cerebellum or if they had cognitive or communication impairments precluding informed consent or the ability to follow study instructions. Healthy adults were included if they were aged between 18 – 38 years (younger cohort) or 50 – 90 years (older cohort) with no conditions that affected movement or sensation in either upper limb. All participants gave their written informed consent and this study was approved by the institutional ethics committee.

11.3.2 Procedure

All participants completed two sessions at least seven days apart and were assessed by two raters in each session. The same two raters assessed a given participant in both sessions and the order of the raters was alternated between-sessions. A total of four raters collected data: HJ (all 90 participants), BC (younger = 12, older = 16, stroke = 13), LS (younger = 13, stroke = 4), and ON (younger = 3, older = 8, stroke = 14). Two younger adults, two older adults, and three people with stroke were assessed by LS in the first session and BC in the second session for practical reasons. ON is a physiotherapist with over ten years' experience, LS is a student physiotherapist, and both HJ and BC are PhD candidates with no formal clinical training.

Healthy younger and older adults completed both sessions at the University of Auckland while participants with stroke completed the sessions either at the University of Auckland or in their own home. Participants were seated upright at a table for all assessments. In both sessions participants completed the BCASS with one rater and then completed it with the second rater, for a total of four BCASS assessments. Participants had a five-minute break between raters. The assessment in the first session by the first rater will be referred to as the initial exposure BCASS and represents participants' naïve performance on the BCASS. Participants with stroke also completed the Box and Block Test (BBT), the Fugl-Meyer upper extremity (FM-UE), and the ABILHAND assessment. The BBT was assessed once by the first rater in the first session while the FM-UE and ABILHAND were assessed once by rater HJ during either the first or second session.

Handedness for healthy participants and pre-stroke handedness for participants with stroke was determined using the short-form of the Edinburgh Handedness Inventory (146). Right- and left-handedness were determined by scores greater and lesser than zero, respectively.

11.3.3 The BCASS

The BCASS is a novel behavioural assessment of coordination during bimanual task performance after stroke. First, the participants' maximum voluntary reach (MVR) was determined by having them reach as far as they could with their hands on the table and their back against the chair. The MVR was calculated from the edge of the table to the tip of the index finger of the lesser-reaching hand. We measured MVR from the edge of the table to compensate for slight differences in how close to the table participants were sitting. Depending on the task, the objects used were placed on the table in the midline of the participant's body at 30% or 80% of their MVR to try ensure participants were able to reach the objects without requiring compensatory movements (168, 317, 479).

Participants were told before starting the BCASS that they would be completing tasks using both their hands, to perform the tasks in a naturalistic way at their normal pace, and to try keep their back against the chair while completing the task. Participants were given instructions about the goal(s) for each task, for example "open this jar and place the lid on the table", or "tie a bow around this box as if you're tying your shoelaces". No information was provided regarding how they should use their hands to complete the task. However, participants were not allowed to complete a task in a way that changed its category. For example, when asked to pick up and move a cup with each hand, participants were not allowed to stabilise the cups by holding them against each other. This would have changed the symmetric independent-goal task to a symmetric cooperative task.

Participants started and finished each task with both hands palm down the table shoulder width apart. The participant's first attempt at the task was timed, scored, and recorded. If they did not understand the task instructions or made a mistake that prevented task completion, such as dropping an item off the table, then the task was restarted. Participants were timed on each task and timing occurred from when the assessor said "go" to when both the participant's hands were back on the table.

Participants completed ten tasks as part of the BCASS in this study, and the data collection sheet is provided in Appendix 7. Two tasks were subsequently removed following refinement of the BCASS (see "BCASS refinement" section in methods). The items used in the final BCASS and examples of the set-up for several tasks are displayed in Figure 11.2. Dimensions for the BCASS items are provided in Table III of Appendix 8. The eight bimanual tasks in the final BCASS were:

1) Jar task. Participants picked up a glass jar placed at 30% MVR, opened it, and put the lid on the table. The lid was tightened to the same extent for all participants to a point where both hands were needed to open it but it could still be opened comfortably. This was an asymmetric cooperative (Asym-Coop) task as both hands needed to use counteracting forces to open the jar.
2) Water task. A plastic cup was placed at 30% MVR and a plastic jug containing 100 mL of water was placed with the handle facing away from the participant at 80%

MVR. Participants picked up the plastic cup with one hand and the plastic jug in the other hand before pouring all the water into the cup and placing the objects back on the table. This was an Asym-Coop task because both hands had to work together at the same time to successfully pour the water even though the hands were interacting with separate objects.

3) Tie Bow task. A small box was placed at 30% MVR with a shoelace positioned underneath it perpendicular to the participant. The box was elevated slightly using small plastic bumpers so the shoelace could freely move beneath it. Participants grasped the shoelace and made a half-hitch knot before tying a bow around the box as they would when tying their shoelaces. This was an Asym-Coop task as tying the bow required both hands to work together at the same time with different movements.
4) Paperclip task. This task replicated the item retrieval drawer-task used previously with participants with chronic stroke (168). Participants were shown a paperclip underneath an upside-down plastic cup placed at 30% MVR. Participants used one hand to pick up and turn the cup upright, and the other hand to pick up the paperclip and place it in the cup. This was an Asym-Parallel task as it could be completed with both hands moving concurrently or sequentially.
5) Page-Cup task. A laminated A5-size booklet opened to the middle was placed at 30% MVR with a plastic cup placed at 80% MVR. Participants used one hand to turn one page, or several pages at once, of the booklet in either direction. The other hand was used to pick up the cup, move it towards them, and place it back on the table between themselves and the booklet. This was an asymmetric independent (Asym-Indep) task as each hand had a separate task to complete involving different movements.

6) Lift Shoelace task. Participants picked up a shoelace placed at 30% MVR in both hands, held it taut, and lifted it to their shoulder height before placing it back on the table. This was a Sym-Coop task as both hands performed the same movement and needed to work together to lift the shoelace.
7) Reach Box task. An empty plastic storage box was placed at 80% MVR. Participants reached with both hands to grasp the box before pulling it towards themselves to the edge of the table. Only the reaching component of this task was scored but the task time included both the reaching and pulling components. The reaching component was a symmetric parallel (Sym-Parallel) task as both hands symmetrically reached for a single item but cooperation was not necessary.
8) Lift Cups task. An empty plastic storage box was placed at 80% MVR and two plastic cups were placed shoulder width apart at 30% MVR. Participants picked up one cup in each hand before reaching to place them on top of the box. Participants were not penalised if the cups fell over while placing them on the box. This was a symmetric independent (Sym-Indep) task as both hands moved symmetrically to complete separate tasks.

The focus of the BCASS is on coordination during bimanual task performance rather than the performance of the paretic upper limb during bimanual tasks. Therefore, each task could be made slightly easier if participants with stroke could not complete it due to paretic upper limb weakness. The amount of assistance available to participants with stroke was the same for each task but varied depending on the task characteristics. Examples include using 50mL of water instead of 100mL during the Water task, slightly loosening the lid for the Jar task, and having participants lift the shoelace to chest height rather than shoulder height during the Lift

Shoelace task. The assistance provided never made the task so easy it could be completed without involvement of the paretic upper limb. Whether or not participants required assistance from the assessor did not affect scoring for the task. Participants were also able to use their non-paretic hand to provide a small amount of help to grip or release objects in the paretic hand. This assistance from the non-paretic hand was only allowed to occur at the start or end of the task, did not affect how the objects were handled during the task, and did not affect scoring.

Participants were scored on several features of task performance, and the number of features varied depending on the task. In brief, every task was scored according to whether the participant interacted with the object(s) using both hands, whether they maintained contact between their back and the chair, whether they completed the task within a normal time, and whether they were able to successfully complete the task. The scoring for a subset of tasks also captured whether the hands moved concurrently or sequentially, whether the hands moved at the same speed, and whether the hands contributed equally to achieving the task goal. Further details for each scoring item can be found in the methods section of Appendix 8.

Table 11.1. Descriptions of the eight tasks included in the final BCASS.

	Items used	Maximum score	Time limit (s)
Asym-Coop			
Jar task	Jar with lid	5	3.77
Water task	A cup and a jug with 100mL water	5	7.26
Tie Bow task	Elevated small box and a shoelace	6	13.83
Asym-Parallel			
Paperclip task	Plastic cup and paperclip	5	4.41
Asym-Indep			
Page-Cup task	Laminated A5 booklet and plastic cup	5	5.08
Sym-Coop			
Lift Shoelace task	A shoelace	7	5.48
Sym-Parallel			
Reach Box task	An empty box	6	3.36
Sym-Indep			
Lift Cups task	2 plastic cups and a box	6	2.93

Asym, asymmetric; Coop, cooperative; Indep, independent; Sym, symmetric. Time limits were calculated as the initial exposure mean time + 2 standard deviations from the older adult cohort.

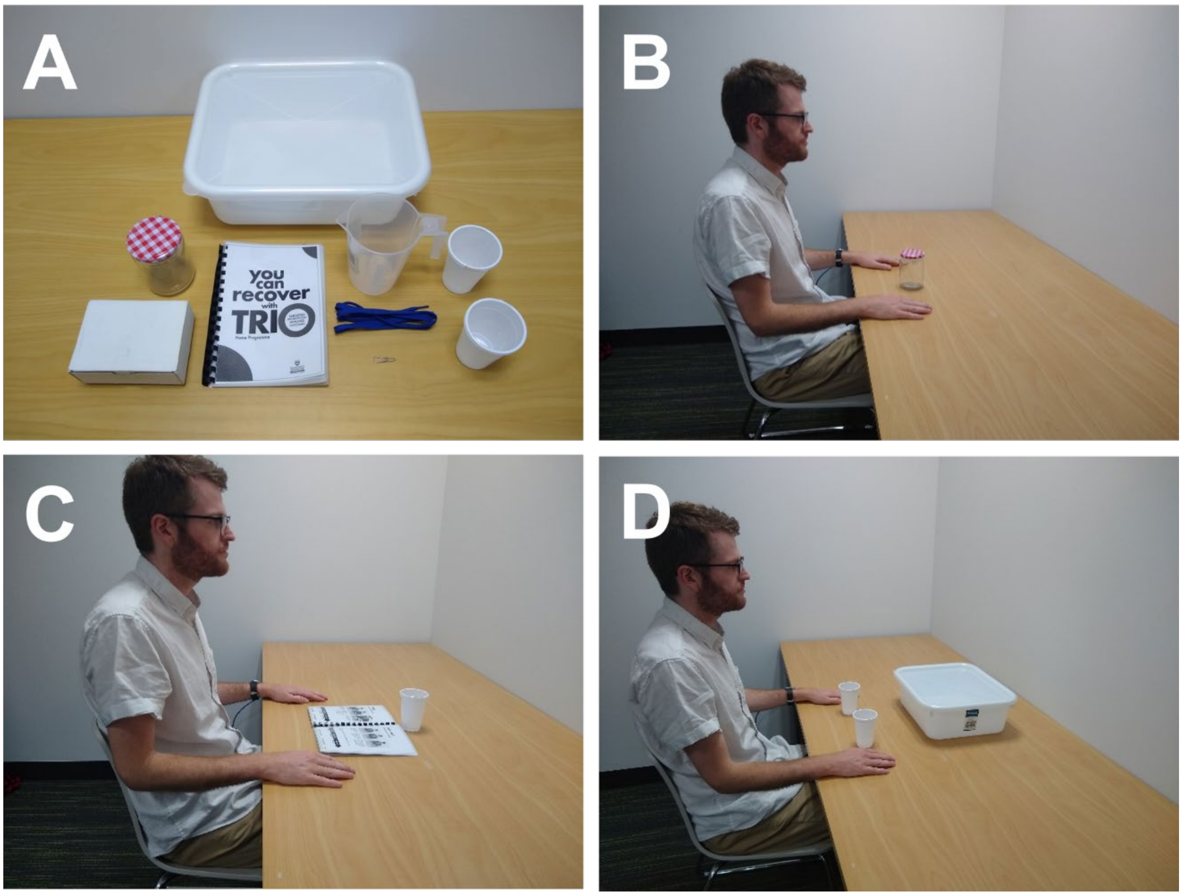


Figure 11.2. The items used for the final BCASS (A) as well as the set-up for the Jar task (B), the Page-Cup task (C), and the Lift Cups task (D).

11.3.4 Secondary Assessments

Only participants with stroke completed the BBT, FM-UE, and ABILHAND assessments. The BBT is a reliable assessment of unimanual hand dexterity that measures how many wooden blocks a participant can move one at a time across a partition in one minute (480, 481). Participants moved a few blocks with each hand prior to the timed assessment to familiarise themselves with the task and ensure they understood the instructions. Participants first completed the BBT with their non-paretic hand then their paretic hand.

The FM-UE assessment is a valid and reliable measure of unimanual upper limb impairment in people at the chronic stage after stroke (145, 482). Participants are scored ordinally from 0 – 2 on 33 items with scores of 2 indicating normal performance, 1 indicating partial performance, and 0 indicating the item cannot be performed. Participants with stroke completed the FM-UE with their paretic upper limb.

The ABILHAND is a reliable questionnaire that assesses a participant with stroke's self-reported ability to perform real-world bimanual tasks (469, 470). The rater reads out a list of 23 tasks and participants rate their performance on each task as "easy", "difficult", or "impossible". If a participant has not performed a task recently or is unsure then it is scored as N/A and excluded from analysis. All 23 tasks are categorised as Asym-Coop using the Kantak taxonomy (151).

11.3.5 BCASS Refinement

The first aim of this study was to refine the BCASS using data from the stroke cohort. The initial step for BCASS refinement was establishing time limits for each task. Time limits were calculated as the initial exposure mean time + 2 standard deviations from the older adult cohort. Times from the initial exposure BCASS were used as this was the participant's naïve performance, which is the likely scenario when using the BCASS in the future. Out of a total of 1,680 tasks performed in each cohort, only seven (0.4%) and 46 (2.7%) task completion times were slower than the time limit in younger and older adults, respectively. This confirms that the time limits classified almost all of tasks completed by healthy adults as being at normal speed. These cut-off times were used to finalise BCASS scoring for all participants and are provided in Table 11.1.

The next step in refinement was determining whether any tasks should be excluded from the BCASS due to low reliability, particularly among the Asym-Coop and Sym-Coop tasks as the BCASS includes more than one task in these categories. The between-sessions interrater reliability for each BCASS task was determined for the stroke cohort using intraclass correlation coefficients (ICCs). Between-sessions interrater reliability measures the consistency of scores between two different raters on separate days. The first assessment in each session was carried out by two different raters. Similarly, the second assessment in each session was always carried out by two different raters. This meant we were able to calculate between-sessions interrater reliability for two pairs of raters for each task. Two-way random effects models for absolute agreement with a mean of K raters, ICC (2, k), were used to calculate ICCs between the first raters in each session and between the second raters in each session. Previously defined thresholds for interpreting ICCs were used (483). Participants with stroke who scored a total of zero on the BCASS during each assessment (n = 5) were excluded to prevent inflation of reliability. Participants with stroke who did not have the same two raters for both sessions (n = 2) or did not have the raters alternate order between-sessions (n = 2) were also excluded from the analysis.

The ICC values for each task are displayed in Table I of Appendix 8. Following this initial reliability analysis, one Asym-Coop and one Sym-Coop task were removed from subsequent BCASS analysis as these were the only tasks that did not demonstrate excellent reliability between either pair of raters. Descriptions of the two excluded tasks are included in the methods section and Table II of Appendix 8.

11.3.6 Data Analysis

The final BCASS included eight tasks with a total score of 45 (Table 11.1), and a data collection sheet is provided as Figure I of Appendix 8. Higher scores indicate better coordination during bimanual task performance. The final BCASS had one bimanual task for each category of the Kantak taxonomy, except for the Asym-Coop category that had three tasks and is the most common category for ADLs.

The sensitivity analyses for our second aim compared initial exposure BCASS scores between cohorts. The validity analysis for our third aim used an online Rasch model to convert ordinal ABILHAND scores into a linear measure ranging from -6.078 (all tasks scored “impossible”) to 6.017 (all tasks scored “easy”), with higher scores representing better self-perceived ability (469).

The fourth aim of the study was to investigate the reliability of the BCASS. Between-sessions interrater reliability for the total BCASS score was determined separately for each cohort. This was done by comparing the initial exposure score with a different rater’s score in the second session, regardless of the rater order in the second assessment. The within-session interrater reliability and between-sessions intrarater reliability for the total BCASS score were also determined for the stroke cohort. Within-session interrater reliability evaluates agreement between two raters within the same session, and this was done using the raters from the first session. Between-sessions intrarater reliability evaluates agreement when a participant is assessed by the same rater in two different sessions. This was calculated for HJ, BC, and ON but not LS because LS did not assess any participants with stroke in both sessions. The only participants excluded from these reliability analyses were the five participants with stroke who scored zero on each BCASS assessment.

Our final aim was to evaluate whether movement symmetry and goal conceptualisation affected task performance in participants with chronic stroke. This was done by comparing scores between different categories of bimanual tasks from the initial exposure BCASS. The mean score from the three Asym-Coop tasks was used for this analysis and all category scores were normalised out of 100% due to the uneven number of scores for each task.

11.3.7 Statistical Analysis

All statistical analyses were performed using IBM SPSS (version 27). Shapiro-Wilk tests found the initial exposure BCASS scores for each cohort were not normally distributed (all $P < 0.001$) and so non-parametric tests were used for all statistical analysis of the BCASS unless stated otherwise. The significance level was set at $P = 0.05$ for all analyses unless stated otherwise.

Independent-samples t-tests were used to compare age, the ABILHAND, paretic hand BBT, and non-paretic hand BBT between dominant and non-dominant affected participants with stroke. All these data were normally distributed. The same comparison was performed for total BCASS and FM-UE scores using Mann-Whitney U tests (MW test) as these data were not normally distributed. A MW test was also used to compare age between the older adult and stroke cohorts.

To investigate whether the BCASS was sensitive to an effect of rater or session order, the total scores from all 90 participants were collapsed across raters and separately across sessions. Wilcoxon signed-rank tests were then used to compare total BCASS scores between raters (Rater 1, Rater 2) and sessions (Session 1, Session 2).

For the sensitivity analyses (aim 2), a MW test was used to compare total initial exposure BCASS scores between the younger and older adult cohorts to evaluate the effects of aging. The effects of stroke on BCASS performance were analysed using a MW test to compare total initial exposure BCASS scores between the older adult and stroke cohorts. MW tests were used to separately compare all six categories of bimanual tasks (Asym-Coop, Asym-Parallel, Asym-Indep, Sym-Coop, Sym-Parallel, Sym-Indep) between the older adult and stroke cohorts to evaluate whether stroke affected performance in particular task categories. The effect of concordance was evaluated using a MW test to compare total BCASS scores between dominant affected and non-dominant affected participants with stroke.

Validity of the BCASS (aim 3) was examined by investigating the relationship of the BCASS with the BBT, FM-UE, and ABILHAND in participants with stroke. This was done using Spearman rank correlation coefficients and scatterplots. Previously defined thresholds for correlation coefficients were used for interpretation (484).

Reliability (aim 4) was evaluated using ICCs for total BCASS scores. Bland-Altmann plots were also used to evaluate reliability because BCASS scores were heavily skewed towards higher scores, particularly for the control cohorts. Two-way mixed models for absolute agreement with a single rater were used to calculate separate ICCs for between-sessions intrarater reliability (483). Two-way random effects models for absolute agreement with a mean of K raters, ICC (2, k), were used to calculate ICCs for within-session interrater reliability and between-sessions interrater reliability. ICCs were interpreted with the same thresholds used during BCASS refinement (483).

The effect of movement symmetry and goal conceptualisation on task performance (aim 5) was analysed using a repeated-measures ANOVA (RM-ANOVA) because we were interested in any interaction present. The RM-ANOVA included BCASS scores with the factors Symmetry (Asym, Sym) and Goal (Coop, Parallel, Indep). Mauchly's test of sphericity confirmed the data were spherically distributed but Shapiro-Wilk tests indicated they were not normally distributed for each task. Paired-sample t-tests were used to explore any significant effects or interaction between factors, with Bonferroni corrections applied for multiple comparisons (485). The interaction effect was explored using pairwise-comparisons between all pairs of tasks in which only Symmetry or Goal differed between them.

11.4 Results

11.4.1 Participants

A total of 90 participants were recruited between April 2018 and July 2021 and their characteristics are summarised in Table 11.2. There was a mean of 20 days between sessions (range = 6 – 160 days). One older adult had 160 days between sessions due to COVID-19 restrictions. The second longest time between assessments was 83 days. There was no difference in age between the older adult and stroke cohorts (Mann-Whitney $U = 560.0$, $P = 0.10$).

Table 11.2. Participant characteristics for each cohort (N = 90).

	Stroke Participants (N = 30)	**Younger Adults (N = 30)**	**Older Adults (N = 30)**
Age			
Median (range)	70 (40 – 88)	25 (20 – 36)	67 (50 – 83)
Sex			
Male	15 (50%)	13 (43%)	16 (53%)
Female	15 (50%)	17 (57%)	14 (47%)
Handedness			
Right	29 (97%)	28 (93%)	25 (83%)
Paretic upper limb			
Dominant	19 (63%)	N/A	N/A
Months since stroke			
Median (range)	34 (8 – 252)	N/A	N/A
Non-paretic hand BBT			
Median (range)	48 (17 – 71)	N/A	N/A
Paretic hand BBT			
Median (range)	23 (0 – 64)	N/A	N/A
FM-UE score			
Median (range)	51 (8 – 66)	N/A	N/A
ABILHAND score			
Median (range)	0.81 (-2.17 – 5.86)	N/A	N/A

N/A, not applicable; BBT, Box and Block Test; FM-UE, Fugl-Meyer upper extremity; SE, standard error.

The mean FM-UE score in the stroke cohort was 45, indicating mild-moderate upper limb weakness (486). Comparisons between dominant and non-dominant affected participants with stroke revealed no differences in age ($t_{29} = 0.20$, $P = 0.84$), paretic hand BBT ($t_{29} = 1.54$, $P = 0.14$), non-paretic hand BBT scores ($t_{29} = 1.63$, $P = 0.12$), FM-UE (Mann-Whitney $U = 136.5$, $P = 0.17$), or the ABILHAND ($t_{29} = 1.30$, $P = 0.21$).

11.4.2 BCASS Practice Effects

Combining all 3 cohorts, participants scored higher on the BCASS with the second rater in each session than with the first rater ($Z = 1.99$, $P = 0.046$, mean Rater 1 = 38.6 ± 1.3, Rater 2 = 38.7 ± 1.3). Participants also scored higher in the second session than the first session ($Z = 3.52$, $P < 0.001$, mean Session 1 = 38.5 ± 1.3, Session 2 = 38.8 ± 1.3). The effects of rater and session were statistically significant, though the mean differences in scores were only 0.3 and 0.1 points, respectively.

11.4.3 BCASS Sensitivity

The distribution of initial exposure BCASS scores for the stroke cohort and the combined control cohorts are shown in Figure 11.3. Total scores for the initial exposure BCASS and the mean BCASS across the four assessments are provided in Table IV of Appendix 8. In the stroke cohort only 3 participants (10%) scored 43 or better on the initial exposure BCASS and only 2 participants (7%) had a mean score of 43 or better across the four assessments. Five participants with stroke and severe upper limb weakness scored zero on the BCASS during each assessment. There was no difference in BCASS scores between dominant- and non-dominant-affected participants with stroke (Mann-Whitney $U = 123.5$, $P = 0.42$). All 30 younger adults and 28 older adults (93%) scored at least 43 out of 45 on the initial exposure BCASS. Performance remained high with repeated assessments as all 30 younger adults and 27 older adults (90%) had a mean score of at least 43 across the four BCASS assessments.

Total initial exposure BCASS scores were compared between cohorts to determine whether the BCASS was sensitive to the effects of aging and stroke. There were no differences in BCASS scores between the younger and older adults (Mann-Whitney $U = 404.5$, $P = 0.46$)

but participants with stroke scored lower than the older adults (Mann-Whitney $U = 20.5$, $P < 0.001$, mean Older = 44.2 ± 0.2, Stroke = 26.5 ± 3.0). Participants with stroke were impaired on each bimanual task category compared to older adults (all Mann-Whitney $U > 45.0$, all P < 0.001).

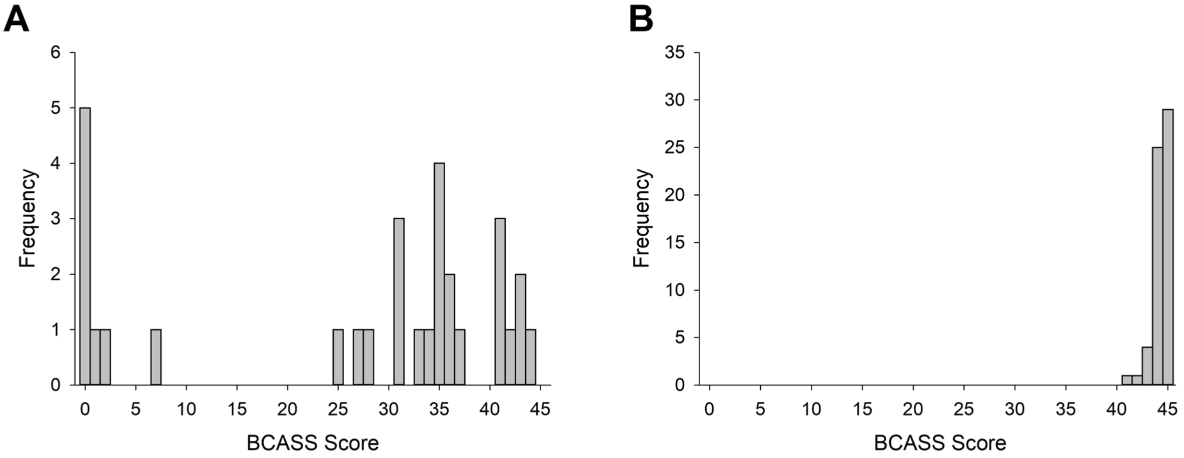


Figure 11.3. Initial exposure BCASS score distribution in participants with stroke (A, N = 30) and younger and older adults (B, N = 60). The maximum score on the BCASS was 45.

11.4.4 BCASS Validity

BCASS scores in participants with stroke correlated very highly with the paretic hand BBT ($\rho = 0.91$, $P < 0.001$) and the FM-UE ($\rho = 0.92$, $P < 0.001$), and highly with the ABILHAND ($\rho = 0.79$, $P < 0.001$) (Figure 11.4). There was no correlation between total BCASS score and the non-paretic hand BBT ($\rho = 0.54$, $P = 0.78$).

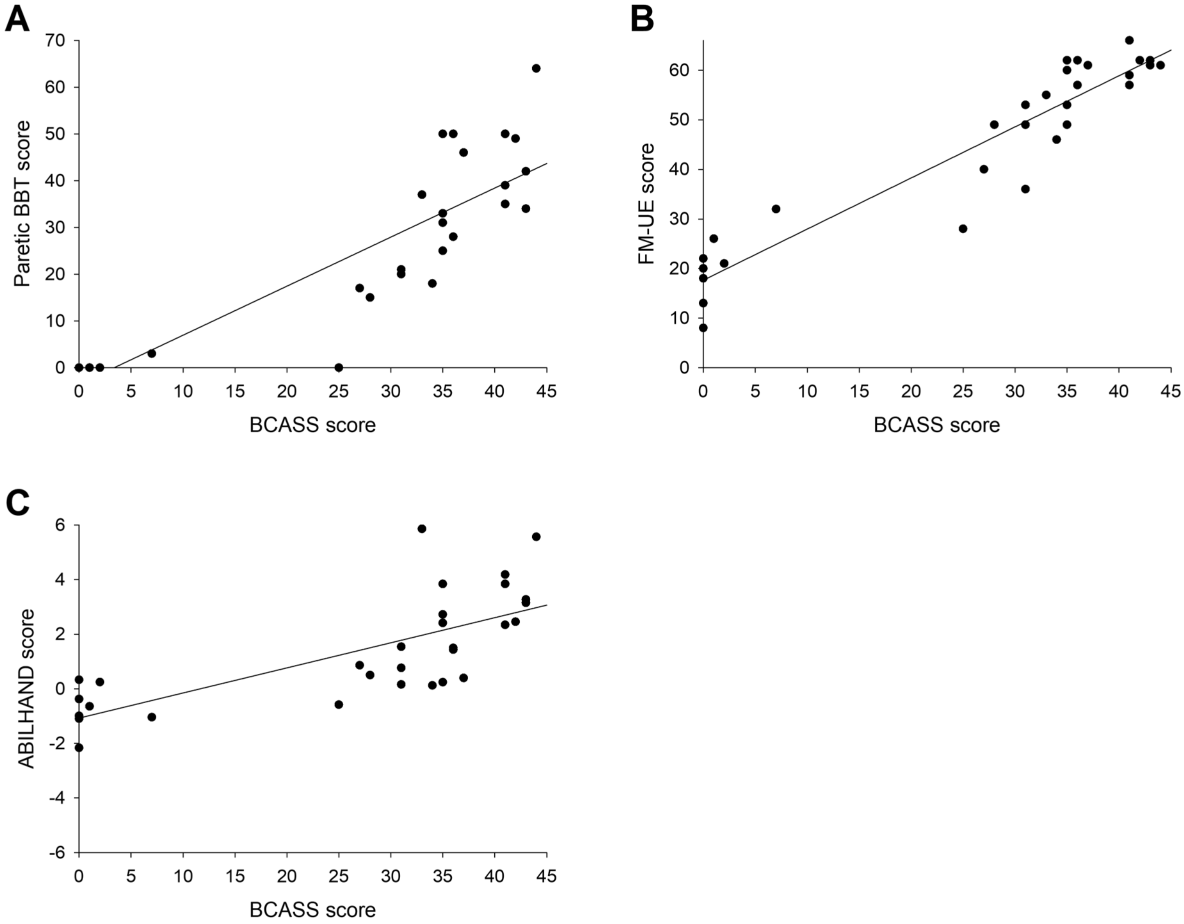


Figure 11.4. Correlations between total initial exposure BCASS score and the paretic hand BBT (A), FM-UE (B), and ABILHAND (C) assessments for participants with stroke (N = 30). Five participants scored 0 on both the BCASS and paretic hand BBT, while two participants scored 31 on the BCASS and 20 on the paretic hand BBT.

11.4.5 BCASS Reliability

For participants with stroke the BCASS demonstrated excellent between-sessions interrater reliability (ICC = 0.977, 95% CI = 0.948 – 0.990, Figure 11.5A), within-session interrater reliability (ICC = 0.980, 95% CI = 0.956 – 0.991), and between-sessions intrarater reliability for raters HJ (ICC = 0.989, 95% CI = 0.974 – 0.995), BC (ICC = 0.971, 95% CI = 0.886 – 0.992) and ON (ICC = 0.996, 95% CI = 0.987 – 0.999). Bland-Altman plots for the within-session interrater reliability and between-sessions intrarater reliability for the stroke cohort are displayed in Figures II and III, respectively, of Appendix 8.

ICCs for total BCASS scores indicated the between-sessions interrater reliability was poor for younger adults (ICC = 0.293, 95% CI = -0.480 – 0.663) and moderate for older adults (ICC = 0.726, 95% CI = 0.402 – 0.872). Inspection of the combined Bland-Altman plot for these control cohorts in Figure 11.5B shows 38 participants (63%) received the same score from both assessors while scores for a further 15 participants (25%) only differed by one point. Thus, based on the Bland-Altman plots, the BCASS shows high reliability for healthy adults and the low ICCs are likely influenced by the non-normal distribution of scores with all younger and older adults scoring full or near-full marks.

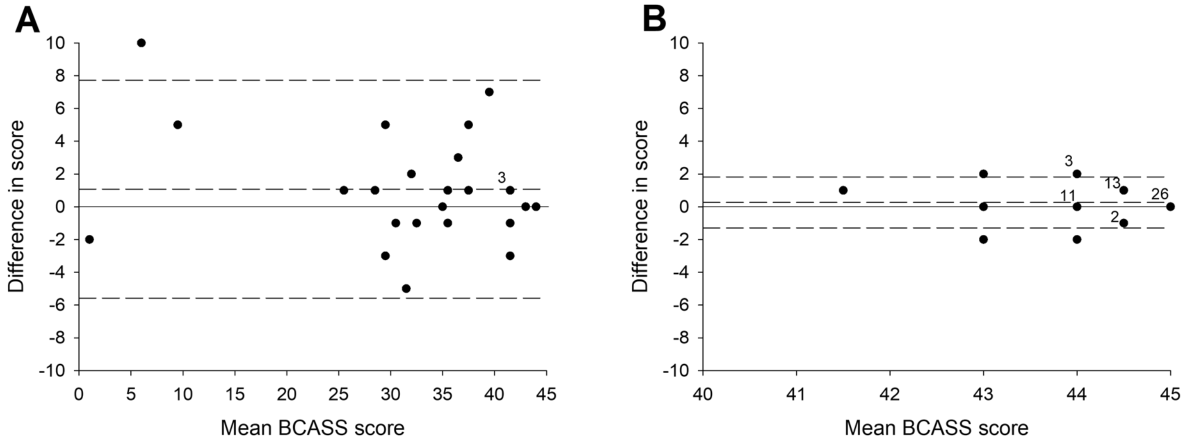


Figure 11.5. Bland-Altman plots displaying between-sessions interrater agreement for BCASS scores for participants with stroke (A, n = 25) and both younger and older adults (B, N = 60). Positive values indicate participants were scored higher by the rater in the second session than the rater in the first session. Dashed horizontal lines represent the mean (middle line) ± 2 standard deviations (top and bottom lines). Numbers on the graph indicate the number of participants at a datapoint.

11.4.6 BCASS Task Categories

The scores for each category of bimanual task in the three cohorts are displayed in Figure 11.6, and a comparison between categories for the stroke cohort is shown in Figure 11.7. An RM-ANOVA was used to evaluate whether movement symmetry and/or goal conceptualisation affected BCASS task performance in participants with stroke. There was an effect of Symmetry ($F_{1,29} = 22.40$, $P < 0.001$) because participants performed better on symmetric tasks than asymmetric tasks (mean Symmetric = 63.0 ± 6.9%, Asymmetric = 53.6 ± 6.2%). There was also an effect of Goal ($F_{1,29} = 14.28$, $P < 0.001$). Post-hoc pairwise comparisons were made using a Bonferroni-corrected significance level of $P < 0.016$. Participants with stroke performed better on cooperative tasks ($t_{29} = 5.46$, $P < 0.001$, mean Cooperative = 60.6 ± 7.0%) and parallel tasks ($t_{29} = 4.49$, $P < 0.001$, mean Parallel = 61.7 ± 6.5%), which did not differ, than on independent-goal tasks (mean Independent = 52.7 ± 6.2%).

There was an interaction between Symmetry and Goal ($F_{1,29} = 4.82$, $P = 0.012$). Post-hoc pairwise comparisons were made using a Bonferroni-corrected significance level of $P < 0.0056$. Movement symmetry affected performance of parallel tasks as participants performed better on the Sym-Parallel task than the Asym-Parallel task ($t_{29} = 5.21$, $P < 0.001$, mean Sym-Parallel = 70.0 ± 7.1%, Asym-Parallel = 53.3 ± 6.3%). Movement symmetry did not affect performance on cooperative tasks ($t_{29} = 1.15$, $P = 0.26$) or independent-goal tasks ($t_{29} = 2.54$, $P = 0.017$).

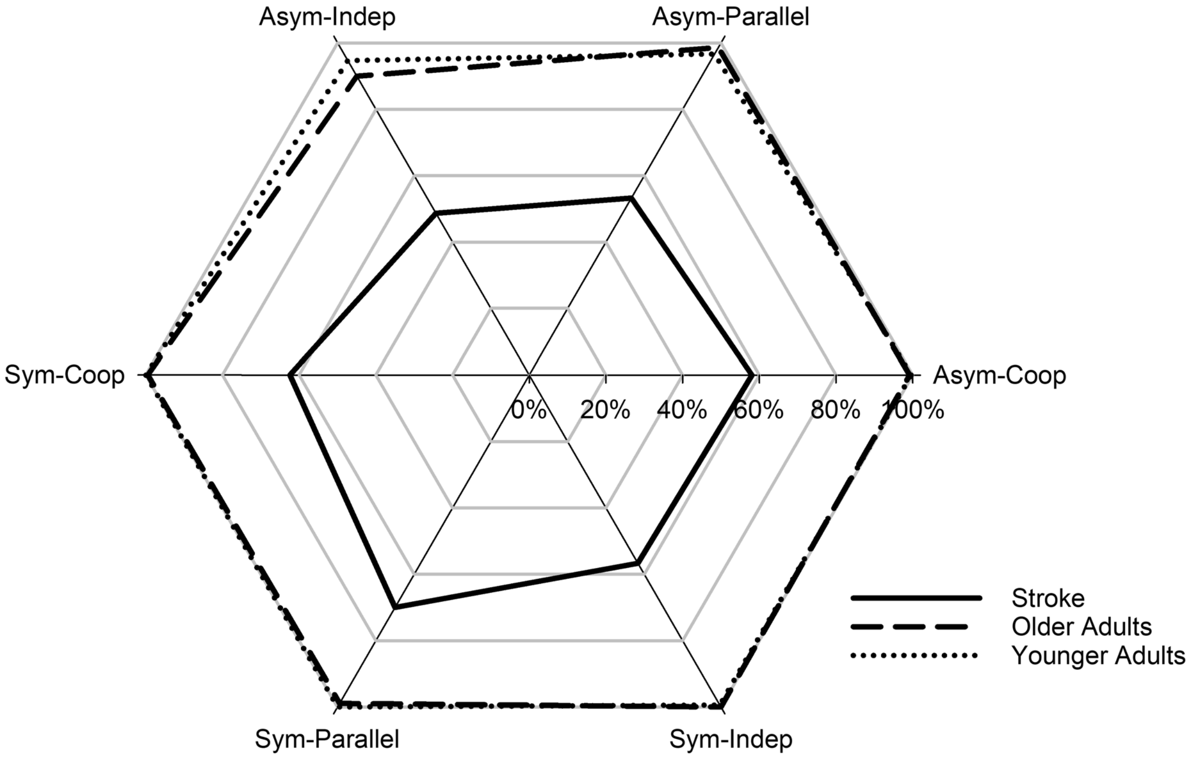


Figure 11.6. Initial exposure BCASS scores for each category of bimanual task in younger adults (N = 30), older adults (N = 30), and participants with stroke (N = 30). Scores for each category are normalised out of 100%.

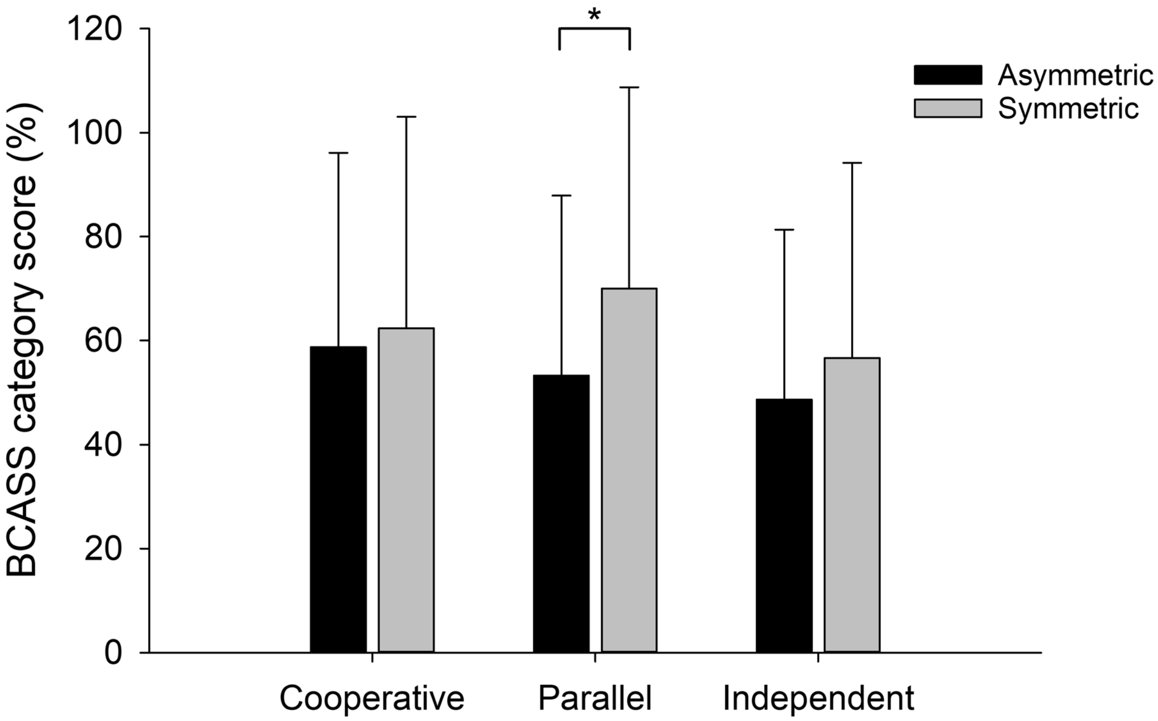


Figure 11.7. Initial exposure BCASS scores for each category of bimanual task in participants with stroke (N = 30). There was a main effect of Symmetry as participants performed better on symmetric tasks than asymmetric tasks. There was a main effect of Goal as participants performed better on cooperative and parallel tasks than independent-goal tasks. An interaction between Symmetry and Goal was present as participants performed better on the symmetric parallel task than the asymmetric parallel task. Bars represent mean normalised values of 100% and errors bars display standard error. * = $P < 0.001$.

11.5 Discussion

This study assessed the sensitivity, validity, and reliability of the BCASS. Several key findings emerged. BCASS scores were sensitive to the effects of stroke but not aging. BCASS scores correlated highly with other established upper limb assessments. The BCASS demonstrated excellent reliability between raters and between sessions for participants with chronic stroke. Lastly, task performance by participants with chronic stroke depended on the movement symmetry, the task goal(s), and an interaction between these factors. Together, these findings provide preliminary evidence the BCASS is a valid and reliable measure of coordination during bimanual task performance in participants with chronic stroke.

11.5.1 Sensitivity

As hypothesised, healthy younger and older adults scored full or near-full marks on the BCASS. This was expected because the tasks included in the BCASS replicate ADLs that adults successfully perform in everyday life, such as opening jars and retrieving items from drawers. Previous studies using laboratory and naturalistic tasks report that younger and older participants have similar performance during simple tasks, and decreased performance in older adults only becomes apparent when task demands are increased (326, 333, 334, 487-489). The naturalistic tasks in the BCASS were likely simple enough for comparable performance by younger and older adults. Therefore, as intended, the BCASS is not sensitive to the effects of aging in healthy adults.

Participants with stroke scored lower than age-matched older adults as we hypothesised, demonstrating that total BCASS scores are sensitive to the effects of stroke. We further hypothesised participants with stroke would be impaired on all categories relative to older adults except for the symmetric independent-goal task, based on a meta-analysis of bimanual coordination deficits in people with chronic stroke (156). However, we found that participants with stroke were impaired on all categories of task, including symmetric independent-goal tasks. The previous meta-analysis compared specific measures of bimanual coordination without considering task performance. For example, one of the symmetric independent-goal comparisons included in the meta-analysis came from a study in which participants symmetrically reached to grasp two small trays before transporting them onto a ledge (322). The relative phase angle, which was used as the comparison in the meta-analysis, was similar between participants with stroke and age-matched controls. However, the participants with stroke were slower than healthy controls at completing the task and were less synchronised when placing the trays on the ledge. The BCASS scores both these aspects of task performance. Thus, the BCASS may have detected impairments in symmetric independent-goal task performance in participants with stroke even if they were not impaired on kinematic measures of bimanual coordination during the task.

Only three participants with stroke scored over 95% on the total BCASS which indicates a ceiling effect was not present. Despite this, the distribution of scores was skewed with most participants scoring greater than 50%. No participants with stroke scored from eight to 24 on the initial exposure BCASS, and two properties of the BCASS likely contributed to this. Some objects are used in several BCASS tasks, for example plastic cups. This means if participants could not interact and use an object it could have affected performance of several tasks. Secondly, participants who could not complete a task were scored down on all other scoring items for that task except the "interact with object(s) bimanually" item (see method section of Appendix 8). This decision was made because it could be argued participants did not demonstrate successful bimanual coordination if they did not complete the task. Future studies could investigate revisions to the scoring items to try increase the sensitivity of the BCASS to detect bimanual task impairments in people with stroke and moderate-severe upper limb weakness.

11.5.2 Validity

Validity analyses revealed FM-UE and paretic hand BBT scores both explained approximately 90% of the variance in BCASS scores. These correlations highlight that proximal and distal paretic upper limb movement are critical for bimanual task performance. This was not surprising given that a certain degree of unimanual movement and dexterity will always be necessary to complete bimanual ADLs (421). Completing the BCASS requires a range of upper limb movements at the shoulder, elbow, and wrist joints while hand dexterity is critical for the manipulation of objects during each task. The unexplained variance beyond the FM-UE and BBT indicates the BCASS is not solely measuring paretic upper limb performance during bimanual tasks. This is illustrated by the finding that two participants who scored 36 and 53 on the FM-UE both scored 31 on the BCASS. One possibility for this unexplained variance is cognition because bimanual tasks have additional temporal and spatial coordination demands compared to unimanual tasks. The relationship between BCASS scores and cognition could be explored in a future study.

The correlation between the BCASS and the ABILHAND assessment was high, which was expected given both assess bimanual upper limb performance on naturalistic tasks. The self-reported nature of the ABILHAND may have led to the lower correlation with the BCASS in comparison to the FM-UE and BBT, which are both scored based on observed task performance. Another contributing factor may be that the ABILHAND only includes asymmetric cooperative tasks compared to the BCASS which includes six categories of bimanual tasks. Overall, these results highlight that BCASS scores correlated more strongly with unimanual motor performance than self-perceived bimanual task ability, and the BCASS is likely assessing additional aspects of bimanual task performance beyond unimanual paretic limb performance.

11.5.3 Reliability

One of the aims of the present study was to determine the reliability of the BCASS. The between-sessions interrater reliability was poor for the younger adults and moderate for the older adults using previously defined ICC thresholds (483). These low ICC values were likely due to the non-normal distribution of scores rather than truly representing low reliability. Non-normal distributions give rise to low ICC values predominantly due to differences in between-subject variability rather than rater error variability (490). All younger and older adults scored full or near-full marks which meant the variability between subjects was very low, leading to low ICC values. Visual inspection of the Bland-Altman plots shows 88% of the control participants received the same score from both raters, or the scores only differed by one point. Raters' score also did not differ by more than two points for any control participant. Therefore, we conclude the BCASS is reliable with younger and older healthy adults.

The reliability of the BCASS for participants with chronic stroke is of greater interest. We expected reliability would be lowest for the between-sessions interrater agreement as it involves different raters and different sessions compared to the within-session interrater agreement and between-sessions intrarater agreement where one of these variables remains constant. However, total BCASS scores showed excellent agreement for all reliability analyses. Moreover, each task in the final BCASS demonstrated good or excellent between-sessions interrater reliability. Clinical experience does not appear necessary to be a reliable assessor because reliability was similar for a highly experienced physiotherapist and two PhD students with no formal clinical training. However, there were a few participants with large differences in scores between raters and/or sessions. For example, a participant with stroke scored 1 on the initial exposure BCASS and scored 11 with a different rater in the second session, while another participant with stroke scored 36 on the initial exposure BCASS and scored 43 with a different rater in the second session. Ensuring assessors are well-trained with the BCASS will be important to ensure agreement between assessors, as will consciously avoiding rater biases (491). Overall, these findings indicate that the BCASS is a reliable assessment when participants with at the chronic stage after stroke are assessed by different raters and/or on different days.

11.5.4 BCASS Task Categories

Both movement symmetry and goal conceptualisation affected the performance of BCASS tasks by participants with stroke. As hypothesised, participants with stroke performed better on symmetric tasks than asymmetric tasks. To our knowledge this is the first study to directly compare performance between symmetric and asymmetric naturalistic tasks in participants with stroke. Studies using lab-based tasks have shown the preference and stability of symmetric movements is retained after stroke during rhythmic tasks (161, 427) and discrete movements (286, 429). The functional coupling that is thought to occur between M1s during symmetric movements may have helped stabilise performance on the symmetric BCASS tasks. Attempts to utilise this functional coupling has even provided the basis for many bilateral upper limb stroke interventions (126, 434, 492).

We hypothesised that participants with stroke would perform better on independent-goal tasks than cooperative and parallel tasks because a meta-analysis reported participants with stroke were impaired during all categories of bimanual tasks except for symmetric independent-goal tasks (156). Participants with stroke however scored higher on cooperative and parallel tasks, collectively known as common-goal tasks, compared to independent-goal tasks. Common-goal tasks require both hands to achieve a single goal and often require one hand to act as a manipulator while the other hand acts as a stabiliser. This means the paretic hand can take the easier stabilising role and the non-paretic hand can assume the more difficult manipulating role for most common-goal tasks in the BCASS. The mean time post-stroke for participants with chronic stroke in this study was approximately five and a half years and so they likely developed strategies for how to complete tasks in their everyday lives that they could use in the BCASS. For example, participants performing the Water task could use their non-paretic hand to bring the water jug to the paretic hand holding the plastic cup rather than needing to move both items. Compensatory strategies between the hands cannot be used during independent-goal tasks because the paretic upper limb must achieve its goal in isolation from the non-paretic upper limb's goal. The need to visually attend to two separate goals may have also impaired performance during the independent-goal tasks as attention is commonly impaired after stroke (493).

An interaction between movement symmetry and goal conceptualisation also affected task performance. Movement symmetry affected performance of parallel tasks as participants with stroke performed better during the symmetric parallel task (Reach Box task) than the asymmetric parallel task (Paperclip task). Parallel tasks are characterised by both hands having a common goal with bimanual coordination being optimal, but not required, for task efficiency. One potential explanation is that, in order to compensate for the increased cognitive demands from the asymmetric nature of the Paperclip task, other aspects of task performance may have suffered such as temporal coordination. Kantak et al. demonstrated this using an asymmetric parallel item retrieval drawer-task that the Paperclip task was modelled after (168). Healthy older adults moved their hands concurrently during the task whereas participants with chronic stroke performed it sequentially with one hand moving at a time. This impaired temporal coordination by participants with stroke did not correlate with unilateral weakness or sensory loss. The same study by Kantak et al. also found no differences in coordination between participants with stroke and healthy older adults on a near-identical task to the Reach Box task. Although this contrasts with our finding that participants with stroke were impaired on the symmetric parallel task compared to controls, it does support our finding that movement symmetry affects performance on parallel tasks by participants with chronic stroke.

Movement symmetry did not affect performance on the cooperative or independent-goal tasks in participants with stroke. Most ADLs are asymmetric cooperative tasks and so familiarity with how to use and coordinate the upper limbs together during these asymmetric tasks may have led to similar performance when compared to the symmetric cooperative task. Independent-goal tasks were performed worse than cooperative and parallel task regardless of the movement symmetry, which indicates the need to complete a separate goal with each hand was the predominant factor influencing performance during these tasks rather than movement symmetry.

11.5.5 BCASS Strengths and Limitations

The BCASS has several strengths, one being that it includes tasks covering the full range of the Kantak taxonomy in comparison to other bimanual assessments such as the ABILHAND and the CAHAI (458, 469). Including naturalistic tasks using common household objects increases the ecological validity of the BCASS, and several of them such as the Paperclip task and Reach Box task were modelled after tasks previously used with participants with stroke (168). The number of objects needed for the BCASS is minimised by using the same objects in multiple tasks, and all the objects required are inexpensive and readily available. A final strength is that the BCASS has potential to be used at the bedside at the acute stage after stroke, although this remains to be directly investigated.

The BCASS also has limitations. Each bimanual task category is only represented by one task in the BCASS, except for the asymmetric cooperative category. The decision to include one task for each category was made to decrease the assessment time of the BCASS but it may limit the sensitivity of the BCASS to assess individual task categories in participants with stroke. Differences in difficulty among tasks may also be present which could affect comparisons between task categories. Lastly, although participants completed the tasks in a natural way, they weren’t allowed to complete the task in way that changed the category of the task. This meant participants may not have been able to use compensatory strategies that changed the task category which they would normally use during ADLs.

11.5.6 Study Strengths and Limitations

One strength of the present study was having participants perform the BCASS with two assessors in each session. This meant the between-sessions interrater reliability could be evaluated, which is a very common scenario when using clinical assessments. In contrast, only the between-sessions intrarater reliability and within-session interrater reliability have been reported for other assessments such as the FM-UE and the BBT (145, 481, 482, 494). Including a younger control cohort allowed us to confirm the BCASS was not sensitive to the effects of aging. No differences in any assessment were present between dominant- and non-dominant-affected participants with stroke, indicating concordance was unlikely to have affected BCASS performance. A final strength is that our participants with stroke also covered the full range of paretic upper limb impairment based on the FM-UE.

This study also had several limitations. BCASS scores showed high agreement with unimanual clinical assessments and a bimanual task questionnaire, however it was not validated against another bimanual behavioural assessment. Furthermore, most participants with stroke only had mild-moderate unilateral upper limb weakness. Using the BCASS with more moderate-severely impaired participants with stroke could help determine whether there is a threshold of unimanual movement that needs to be met to perform at least some tasks in the BCASS. An additional potential limitation is that the recorded time for the Reach Box task included participants reaching for the box and pulling it towards themselves. Future studies using the BCASS could end the timing when both hands touch the box for the Reach Box task, although this would require collecting data from healthy older adults to determine a normative time. Instructing participants to reach for the box and pull it towards them would be useful even if the pulling box part is not timed or scored because most reaching movements for objects in everyday life are made with the intention of moving or using the object.

A final limitation to mention is that participants scored higher on the BCASS when assessed by the second rater in each session, and in the second session compared to the first. Although these differences were statistically significant, the mean difference in score between the two raters and two sessions were only 0.1 and 0.3 points, respectively. Similarly small but statistically significant differences between raters or in test-retest scenarios have been reported for other clinical assessments such as the Action Research Arm Test, Jebsen hand function test, and Wolf Motor Function Test (131, 495-497). These effects are likely due to increased familiarity with the tasks.

11.5.7 Future Directions

It should be noted this is the first iteration of the BCASS and future studies could bring further refinement. Potential improvements include simplifying how the BCASS is scored or adding another task from each category to increase the sensitivity of the BCASS for measuring impairment in individual task categories. Potential benefits of adding tasks would have to be considered against the increased time to administer the BCASS and the need for additional objects. Regardless of any potential improvements, the reliability and validity demonstrated in the present study requires replication in other settings. The feasibility of using the BCASS with people at the acute and subacute stages of stroke should also be evaluated in the future.

There are several lines of stroke research that could be explored using the BCASS. Using the BCASS with people at the acute and subacute stages after stroke could elucidate which types of bimanual tasks are most difficult immediately after a stroke because this is currently unknown. Understanding these deficits at the subacute stage after stroke could help with more targeted upper limb rehabilitation. The recovery on different types of bimanual task from the acute stage after stroke has not been investigated and could provide insight into whether the recovery trajectory of bimanual coordination differs from unimanual function. Finally, the BCASS could be used to evaluate whether upper limb stroke interventions improve bimanual coordination.

11.5.8 Conclusions

This study provided preliminary evidence that the BCASS is a valid and reliable assessment of coordination during bimanual task performance with people with chronic stroke. The BCASS needs to be evaluated in other environments but it has potential to help investigate which categories of bimanual task are most difficult for patients immediately following stroke and how bimanual coordination recovers over time.

12 Recovery of Bimanual Coordination Across the Subacute Stage after Stroke

12.1 Abstract

Bimanual coordination can be impaired at the chronic stage after stroke but has not been comprehensively studied longitudinally across the subacute stage. The aim of this study was to assess the initial impairment and subsequent recovery of bimanual coordination in the first six months after stroke, and to determine how it was influenced by movement symmetry and goal conceptualisation. We also aimed to compare the recovery of bimanual coordination with recovery of unimanual upper limb impairment and function as well as self-reported bimanual function. Fifty-six patients with stroke and unilateral upper limb weakness were recruited for this observational study. Assessments were performed within one week of stroke (Baseline) as well as one, three, and six months after stroke. Bimanual coordination was evaluated using the Bimanual Coordination After Stroke Scale (BCASS). Participants also completed the Fugl-Meyer Upper Extremity (FM-UE), Action Research Arm Test (ARAT), and ABILHAND assessments. Total BCASS, FM-UE, and ARAT scores all plateaued at three months post-stroke. BCASS and ABILHAND scores were highly correlated. Movement symmetry and goal conceptualisation influenced both the initial impairments and time course of bimanual coordination recovery. These results provide new insight into bimanual coordination early after stroke and its subsequent recovery.

12.2 Introduction

Approximately 50% of people experience upper limb impairment after stroke (66, 68, 69). Paretic upper limb motor recovery is greatest in the first three months after stroke, with smaller improvements between three and six months (67, 72, 498, 499). Subtle impairments may also be present in the ipsilesional upper limb (103, 105, 106). The impairment of both upper limbs negatively impacts ADLs (106, 426, 500).

Most ADLs such as putting on clothes or eating with a knife and fork require bimanual coordination. As a result, improving bimanual coordination is critical for people to regain independence after stroke (91). Real-world bimanual hand use early after stroke has been examined using accelerometers (78, 415, 417) and by assessing involvement of the paretic limb during bimanual tasks (418, 426). The recovery of bimanual coordination across the subacute stage after stroke has been largely unstudied as only one study has investigated bimanual coordination longitudinally during the first few months after stroke (151). Twelve participants recruited within the first month after stroke performed a symmetric parallel reach-to-grasp task that involved reaching to grasp a ball with both hands (424). Task completion time, smoothness of reaching, and between-hands synchronisation all plateaued for bimanual reaching at six weeks post-stroke. Whether a similar recovery trajectory occurs on other bimanual tasks is unknown.

The Bimanual Coordination After Stroke Scale (BCASS) is a behavioural assessment of coordination during bimanual task performance. Preliminary evidence indicates the BCASS is valid and reliable with people at the chronic stage after stroke (Chapter 11). The BCASS includes eight tasks that are categorised using the Kantak taxonomy (151). The BCASS was designed to be feasible to administer at the patient's bedside but has yet to be used at the acute and subacute stages after stroke.

The first aim of the present study was to use the BCASS to assess the recovery of bimanual coordination over the first six months post-stroke. We hypothesised that most bimanual coordination recovery would occur within the first three months post-stroke but smaller gains would be present between three and six months. The second aim was to compare the recovery of bimanual coordination with recovery of unimanual upper limb impairment and function over the first six months post-stroke. We hypothesised that unimanual upper limb recovery would plateau sooner after stroke than bimanual coordination. The third aim was to compare bimanual coordination and self-reported bimanual function outcomes, which we hypothesised would be highly correlated at three and six months post-stroke. The fourth aim was to determine if movement symmetry and goal conceptualisation affected bimanual coordination at each time point assessed post-stroke. We hypothesised participants' performance on BCASS tasks would be better for symmetric than asymmetric tasks, and better for single common-goal tasks than tasks with two independent goals. The fifth aim was to determine whether movement symmetry and/or goal conceptualisation affected the recovery of bimanual coordination. This was a hypothesis-free aim because there was no *a priori* evidence on which to base expectations.

12.3 Methods

12.3.1 Participants

This was a single-site prospective longitudinal observational study. Eligible patients admitted to Auckland City Hospital with a date of stroke between 1st May 2019 and 1st May 2021 were approached about the study within 7 days of stroke onset. Patients were eligible for the study if they were at least 18 years old, had upper limb weakness from the stroke, and received a PREP2 prediction for upper limb motor outcome as part of routine clinical care (77). Patients were excluded if they lived outside the Auckland region, or if they had cognitive impairments or pre-existing conditions precluding informed consent and compliance with study assessments. This study was approved by the regional ethics committee and all participants gave their written informed consent.

12.3.2 Procedure

Participants were assessed within one week after stroke as well as one, three, and six months after stroke (Baseline, 1M, 3M, 6M respectively). Assessments were performed either at the participant's bedside in hospital, at the University of Auckland, or in a location of the participant's choosing. Participants were seated upright in a bed or chair with a table in front of them for all assessments.

Participant demographic and stroke characteristics were obtained at Baseline. Therapy intensity was recorded for all inpatient physical therapy sessions and is reported as the median daily amount of time spent actively engaging in upper limb rehabilitation.

12.3.3 Assessments

The BCASS was performed at each time point. There are eight tasks in the BCASS and it has a maximum score of 45. Higher scores indicate better coordination during bimanual task performance. Tasks are categorised according to whether the upper limb movements are symmetric or asymmetric with respect to the midline of the body (Sym and Asym, respectively). Each task is further categorised according to its goal(s) as either cooperative, parallel, or independent-goal (Coop, Parallel, and Indep respectively). Cooperative tasks require both upper limbs to work together simultaneously to achieve a single goal. Parallel tasks do not require simultaneous bimanual movements to be successful, but coordination is desired for maximum efficiency. Cooperative and parallel tasks are collectively known as common-goal task as they each involve both hands acting together to achieve a single goal. Independent-goal tasks involve each upper limb acting to achieve a separate goal. Thus, the BCASS evaluates six categories of bimanual tasks: Asym-Coop, Asym-Parallel, Asym-Indep, Sym-Coop, Sym-Parallel, and Sym-Indep. The BCASS includes one task in each category except for Asym-Coop which includes three tasks. A detailed description of the BCASS and how it is scored has already been provided (Chapter 11). The BCASS data collection sheet used for this study is included in Appendix 7.

The Fugl-Meyer upper-extremity (FM-UE) assessment was completed with the paretic upper limb at all four time points. The FM-UE is an assessment of unimanual upper limb impairment after stroke that is reliable at the subacute stage after stroke (501). Participants are scored ordinally from 0 – 2 on 33 items and higher scores indicate better performance. The Action Research Arm Test (ARAT) was performed at 1M, 3M, and 6M. The ARAT consists of 19 tasks each scored ordinally from 0 – 3, and higher scores indicate better upper limb function (131). The ARAT data collection sheet used for this study is provided in Appendix 2. The ABILHAND assessment was performed at 3M and 6M. The ABILHAND is a reliable questionnaire that assesses a participant with stroke's self-reported ability to perform real-world bimanual tasks (469). The rater reads out a list of 23 tasks and participants rate their performance on each task as "easy", "difficult", or "impossible". An online Rasch model (http://rssandbox.iescagilly.be/) was used to convert ordinal ABILHAND scores into a linear measure ranging from -6.078 to 6.017, with higher scores representing better self-perceived ability (469).

12.3.4 Data Analysis

Only participants who completed the BCASS at all four time points were included in the statistical analyses. All BCASS data analyses were performed following BCASS refinement in participants with chronic stroke (Chapter 11). Total BCASS, FM-UE, and ARAT scores were normalised out of 100% for the second aim comparing recovery on the BCASS with other clinical measures. One participant was excluded from the comparison between BCASS and FM-UE scores for not completing the FM-UE at one time point. One participant at 3M and two participants at 6M did not complete the ABILHAND and so were excluded from comparisons between the BCASS and ABILHAND.

The fourth and fifth aims involved comparisons between the six categories of bimanual tasks included in the BCASS. The BCASS includes one task in each category except for Asym-Coop which includes three tasks, and so the mean score from the three Asym-Coop tasks was used when comparing categories. BCASS category scores were normalised out of 100% for all analyses comparing categories because the maximum score varied between categories.

12.3.5 Statistical Analysis

All statistical analyses were performed using IBM SPSS (version 27). Shapiro-Wilk tests found that BCASS scores at each time point were not normally distributed (all $P < 0.001$) but repeated-measures ANOVAs (RM-ANOVAs) were still used in the analyses as there is no widely used non-parametric test that can include multiple factors. Mauchly's Test of Sphericity was used to determine the sphericity of data for all RM-ANOVAs and the Huynh-Feldt correction was applied if the data were not spherical. Paired-sample t-tests were used to explore any significant effects or interactions between factors for all RM-ANOVAs, with sequential Bonferroni corrections applied for multiple comparisons (401). The significance level was set at $P = 0.05$ for all analyses unless stated otherwise. Values in text represent mean ± standard error (SE) unless stated otherwise.

The first aim of this study was to assess the recovery of bimanual coordination over the first six months post-stroke using the BCASS. This was done using an RM-ANOVA for total BCASS score with the factor Time (Baseline, 1M, 3M, 6M). Age (< 80 years, ≥ 80 years) and Concordance (Paretic dominant upper limb, paretic non-dominant upper limb) were added as between-subject factors to see if they influenced bimanual coordination recovery.

The second aim was to compare recovery of bimanual coordination with recovery of unimanual upper limb impairment and function over the first six months post-stroke. Separate RM-ANOVAs were run with the factors Assessment (BCASS, FM-UE) and Time (Baseline, 1M, 3M, 6M), or Assessment (BCASS, ARAT) and Time (1M, 3M, 6M).

The third aim was to compare bimanual coordination and self-reported bimanual function outcomes. Spearman rank correlation coefficients were used to compare total BCASS scores with ABILHAND scores at 3M and at 6M, and previously defined thresholds were used for interpretation (484).

The fourth aim was to determine whether movement symmetry and/or goal conceptualisation affected bimanual coordination at each time point. This was done by analysing BCASS task scores cross-sectionally using separate RM-ANOVAs for each time point with the factors Symmetry (Asym, Sym) and Goal (Coop, Parallel, Indep).

Our final aim was to investigate whether movement symmetry and/or goal conceptualisation affected the recovery of bimanual coordination. This was done using RM-ANOVAs with the factors Time (Baseline, 1M, 3M, 6M) and Symmetry (Asym, Sym) separately for Coop, Parallel, and Indep BCASS tasks.

12.4 Results

A total of 92 patients were consented to the study. Fifty-six participants completed the BCASS at each time point and were included in the data analysis. A study flowchart is presented in Figure 12.1 and characteristics for participants included in the statistical analysis are provided in Table 12.1. The mean time post-stroke for the Baseline BCASS was five days (range = 1 – 8 days). All 1M assessments were performed within one week either side of the due date and all 3M and 6M assessments were performed within two weeks either side of the due date. The only exceptions were due to COVID-19 restrictions which delayed three 1M assessments (range = 5 – 6 weeks post-stroke), three 3M assessments (range = 14 – 15 weeks post-stroke), and thirteen 6M assessments (range = 28 – 40 weeks post-stroke).

Figure 12.1. Patient study flowchart.

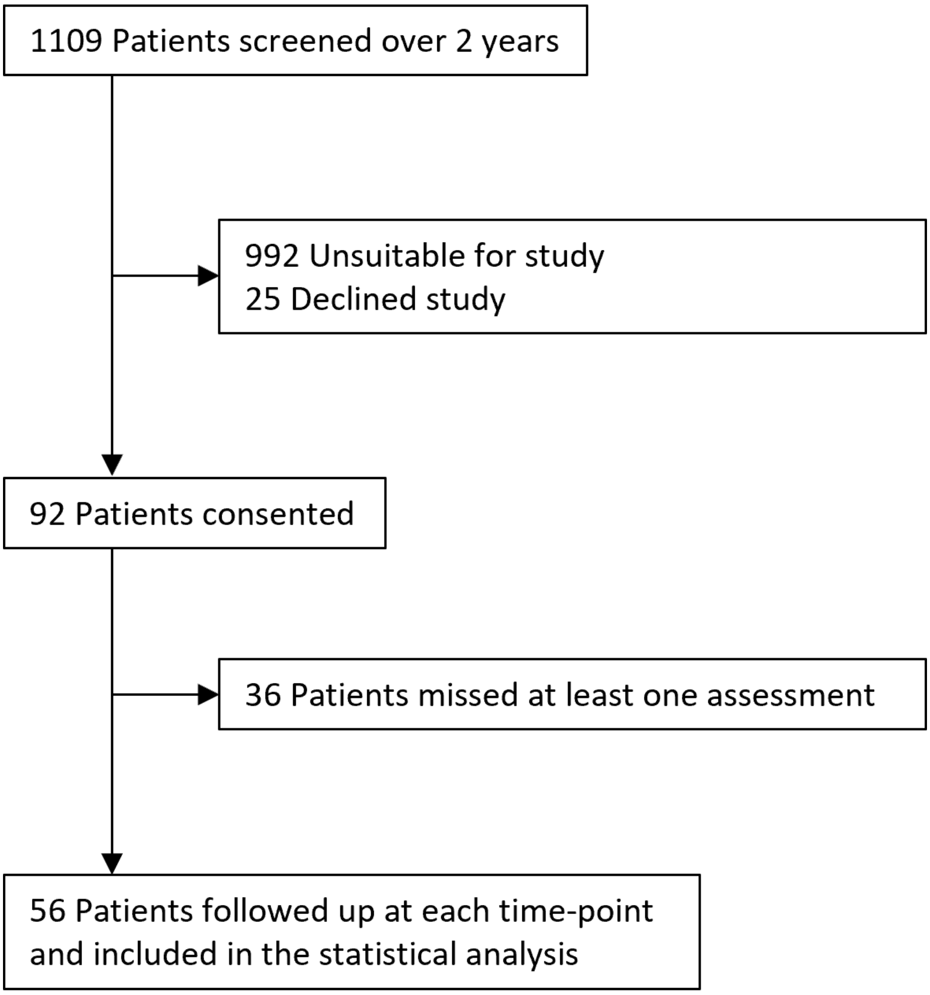


Table 12.1**.** Participant demographic and stroke characteristics (N = 56).

Demographic characteristics	
Age (years)	
Median age (range)	75 (41 – 99)
Sex	
Male	36 (64%)
Female	20 (36%)
Handedness	
Right	50 (89%)
Ethnicity	
European	41 (73%)
Pacific	7 (12%)
Asian	6 (11%)
Māori	2 (4%)
Stroke risk factors	
Smoker	6 (11%)
Ex-smoker	11 (20%)
Diabetes mellitus	7 (13%)
Hypertension	33 (59%)
Dyslipidaemia	11 (20%)
Atrial fibrillation	13 (23%)
Previous cardiac history	15 (27%)
Co-morbidities (Charlson Comorbidity Index)	
Low (Charlson score < 2)	46 (82%)
Stroke characteristics	
Previous stroke	
Yes	8 (14%)
Stroke type	
Total anterior circulation infarct	6 (11%)
Partial anterior circulation infarct	13 (23%)
Lacunar infarct	27 (48%)
Posterior circulation infarct	2 (4%)

Intracerebral haemorrhage	8 (14%)
Hemisphere	
Left	34 (61%)
Paretic upper limb	
Dominant	36 (64%)
Thrombolysis	
Yes	7 (13%)
Thrombectomy	
Yes	4 (7%)
MEP status	
MEP+	50 (89%)
PREP2 prediction	
Excellent	30 (54%)
Good	20 (36%)
Limited	2 (3%)
Poor	4 (7%)
Baseline Stroke Severity	
Median NIHSS score (range)	6 (0 – 18)
Median SAFE score (range)	7 (0 – 10)
Median FM-UE score (range)	49 (8 – 65)
Therapy intensity (minutes) (n = 55)	
Median daily upper limb therapy (range)	5 (0 – 16)

MEP, motor evoked potential; PREP2, predict recovery potential; NIHSS, National Institutes of Health Stroke Scale; SAFE, shoulder abduction, finger extension; FM-UE, Fugl-Meyer upper extremity. Stroke types categorised according to the Oxfordshire Community Stroke Project classification system (10). PREP2 predictions were based on the prediction tool developed by Stinear et al (77).

12.4.1 Aim 1: Recovery of Bimanual Task Performance

The mean BCASS score at Baseline was 21.2 ± 2.3 and the range of scores was 0 – 44. An RM-ANOVA revealed a significant effect of Time for total BCASS score ($F_{1,55} = 21.61$, $P < 0.001$, Figure 12.2). BCASS scores increased from Baseline to 1M ($t_{55} = 4.77$, $P < 0.001$, mean Baseline = 21.2 ± 2.3, 1M = 26.5 ± 2.2) and from 1M to 3M ($t_{55} = 4.23$, $P < 0.001$, mean 3M = 30.1 ± 2.0) but there was no difference between 3M and 6M ($P = 0.25$, mean 6M = 30.8 ± 2.1). There were no interactions between Time and the between-subject factors Age and Concordance (both $P > 0.45$).

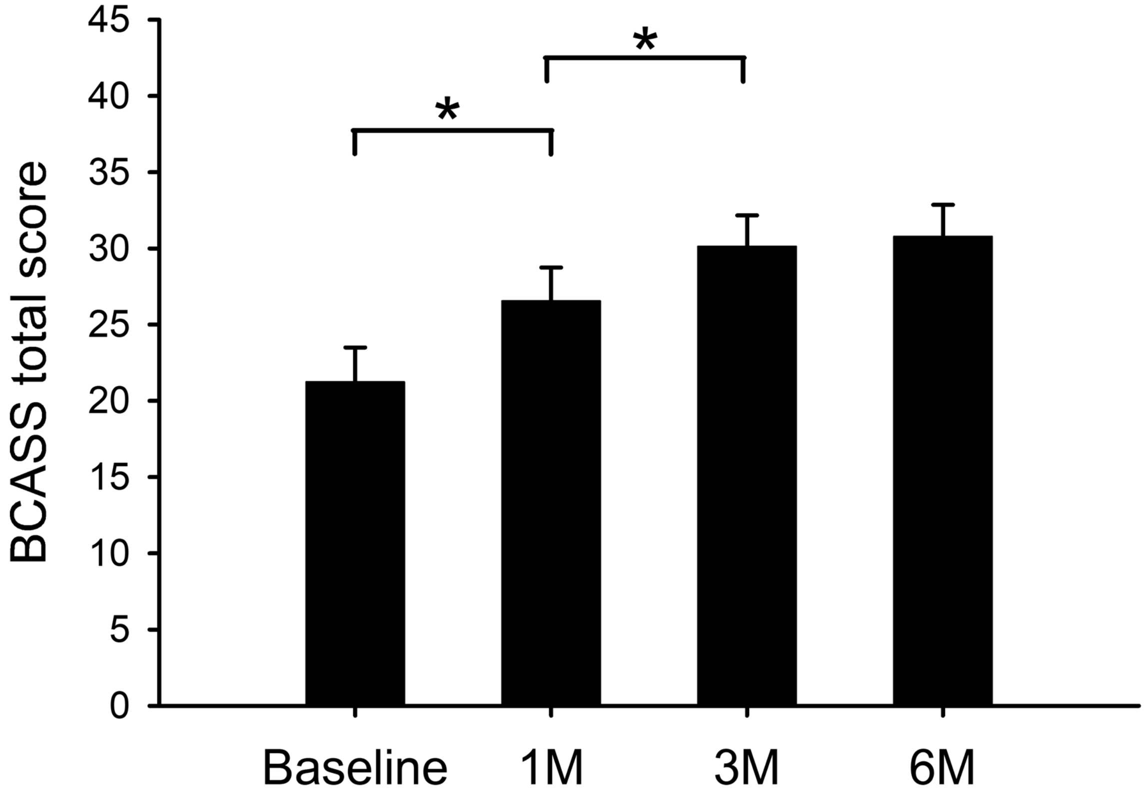


Figure 12.2. Total BCASS scores over the first six months post-stroke (N = 56). BCASS score improved from Baseline until three months post-stroke. Bars represent mean and error bars display SE. * = $P < 0.01$.

12.4.2 Aim 2: Bimanual and Unimanual Performance Comparisons

The RM-ANOVA of BCASS and FM-UE scores indicated main effects of Assessment ($F_{1,54} = 97.90$, $P < 0.001$) and Time ($F_{1,54} = 31.56$, $P < 0.001$, Figure 12.3A). Overall mean normalised FM-UE score (70.7 ± 4.0%) was higher than mean normalised BCASS score (60.6 ± 4.6%). An interaction between Assessment and Time was also present ($F_{1,54} = 7.64$, $P = 0.001$). Paired-sample t-tests comparing BCASS and FM-UE scores did not reveal how this interaction was being driven and so t-tests were used to compare delta BCASS and FM-UE scores between time points. The interaction between Assessment and Time arose because participants improved more on the BCASS than the FM-UE between Baseline and 1M ($t_{54} = 2.37$, $P = 0.021$, Mean ΔBCASS = 11.9 ± 2.5%, ΔFM-UE = 8.2 ± 1.6%) and between 1M and 3M ($t_{54} = 2.10$, $P = 0.040$, Mean ΔBCASS = 8.2 ± 1.9%, ΔFM-UE = 5.4 ± 1.3%). Neither score increased significantly between 3M and 6M (Mean ΔBCASS = 1.6 ± 1.3%, ΔFM-UE = 1.5 ± 1.1%).

The RM-ANOVA of BCASS and ARAT scores revealed main effects of Assessment ($F_{1,55} = 12.33$, $P = 0.001$) and Time ($F_{1,55} = 14.48$, $P < 0.001$, Figure 12.3B). The mean normalised ARAT score (67.2 ± 4.8%) was higher than mean normalised BCASS score (64.8 ± 4.6%). No interaction between Assessment and Time was present ($P = 0.77$).

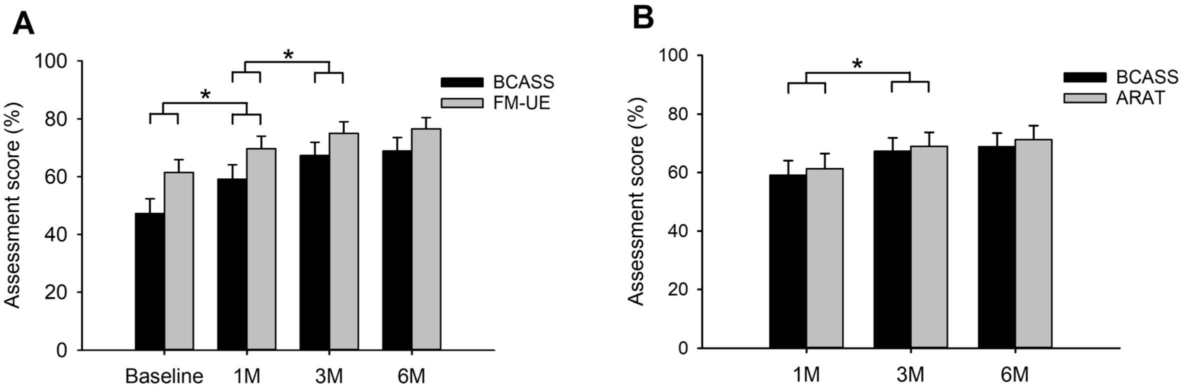


Figure 12.3. Recovery of BCASS scores compared to FM-UE scores (A, n = 55) and ARAT scores (B, N = 56). Mean FM-UE and ARAT scores were higher than mean BCASS score, and scores plateaued on each assessment at 3M. An interaction between Assessment and Time was present when comparing BCASS and FM-UE scores because BCASS scores increased more than FM-UE scores from Baseline to 1M and from 1M to 3M. Bars represent mean normalised values of 100% and error bars display SE. * = $P < 0.01$.

12.4.3 Aim 3: Assessed and Self-Reported Bimanual Performance Outcomes

BCASS scores correlated highly with the ABILHAND at 3M ($\rho = 0.79$, $P < 0.001$, mean ABILHAND = 1.8 ± 0.4, Figure 12.4A) and 6M ($\rho = 0.75$, $P < 0.001$, mean ABILHAND = 2.5 ± 0.3, Figure 12.4B).

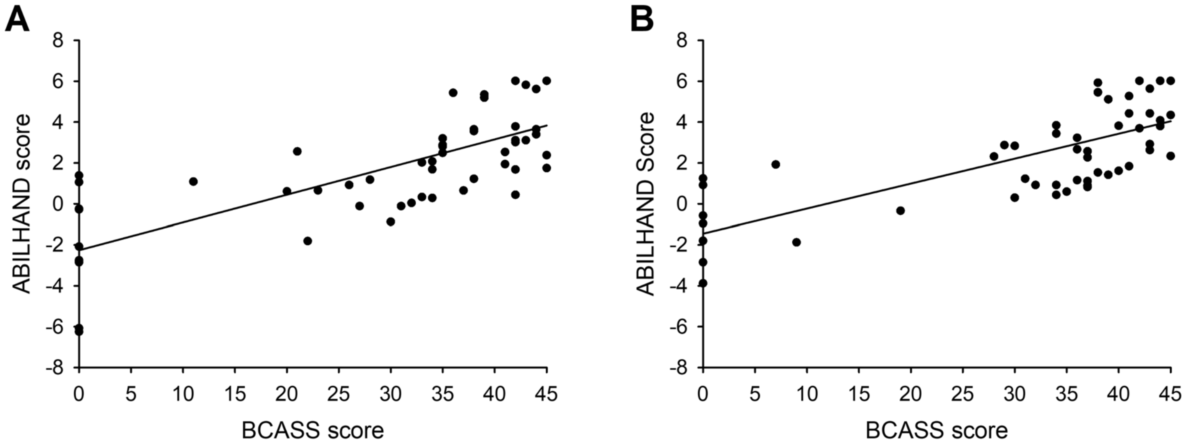


Figure 12.4. Correlations between BCASS and ABILHAND scores at 3M (A, n = 55) and 6M (B, n = 54). Four participants at 3M and two participants at 6M scored a maximum of 45 on the BCASS and 6.017 on the ABILHAND.

12.4.4 Aim 4: Cross-Sectional Analyses of Bimanual Task Categories

Mean scores for bimanual task categories at each time point grouped according to Symmetry and Goal are provided in Table 12.2. An RM-ANOVA of Baseline BCASS scores revealed a main effect of Symmetry ($F_{1,55} = 14.86$, $P < 0.001$) because participants performed better on symmetric tasks than asymmetric tasks. An effect of Goal was also present ($F_{1,55} = 9.64$, $P < 0.001$). At Baseline participants performed better on cooperative tasks ($t_{55} = 3.87$, $P < 0.001$) and parallel tasks ($t_{55} = 3.19$, $P = 0.002$), which did not differ ($P = 0.56$), than on independent-goal tasks. An interaction between Symmetry and Goal was also present at Baseline ($F_{1,55} = 5.67$, $P = 0.005$). Movement symmetry affected performance of parallel tasks as participants performed better on the Sym-Parallel task than the Asym-Parallel task ($t_{55} = 4.33$, $P < 0.001$, mean Sym-Parallel = 53.6 ± 5.6%, Asym-Parallel = 42.9 ± 5.0%, Figure 12.5). Movement symmetry did not affect performance on cooperative tasks or independent-goal tasks at Baseline (both $P > 0.10$).

Table 12.2. Normalised BCASS scores at each time point post-stroke grouped according to movement symmetry and goal conceptualisation. Values represent mean ± standard error (N = 56).

	Baseline	**1 Month**	**3 Months**	**6 Months**
Symmetry				
Asymmetric tasks	43.9 ± 4.8%	55.3 ± 4.7%	64.2 ± 4.4%	64.3 ± 4.5%
Symmetric tasks	49.5 ± 5.3%	62.5 ± 5.3%	69.8 ± 4.7%	72.5 ± 4.8%
Goal Conceptualisation				
Cooperative tasks	49.0 ± 5.2%	61.2 ± 5.1%	68.5 ± 4.7%	71.5 ± 4.7%
Parallel tasks	48.2 ± 5.2%	61.0 ± 5.1%	69.5 ± 4.7%	69.7 ± 4.8%
Independent-goal tasks	42.9 ± 4.8%	54.5 ± 4.8%	63.2 ± 4.5%	64.0 ± 4.7%

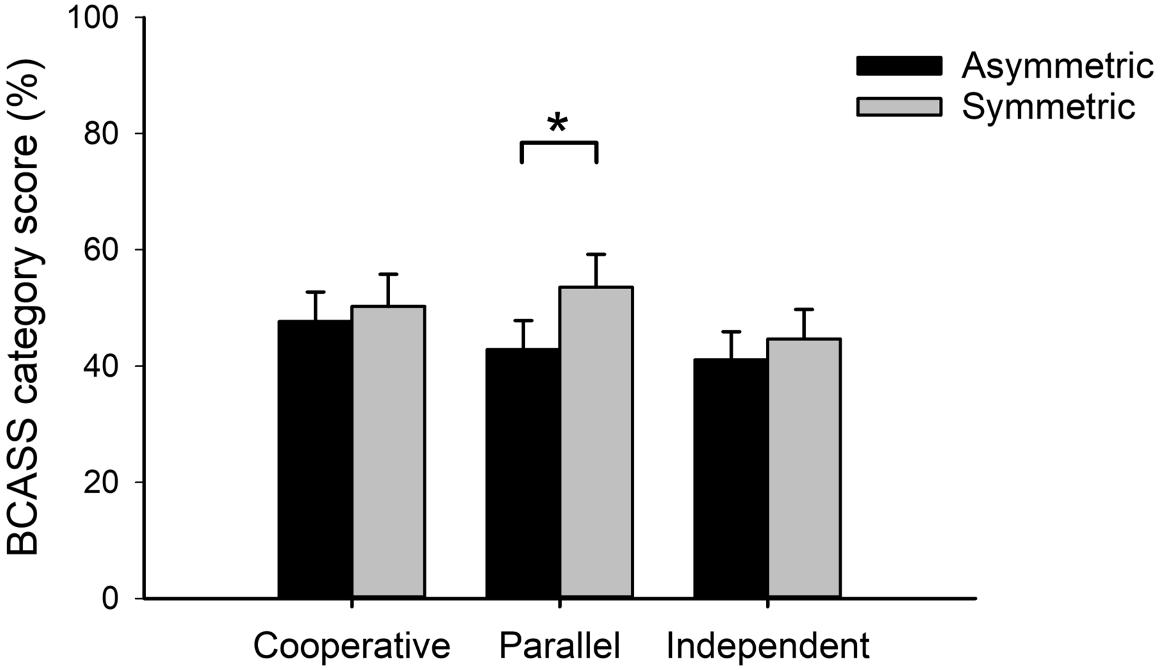


Figure 12.5. BCASS scores at Baseline for each bimanual task category (N = 56). Scores were higher for symmetric tasks than asymmetric tasks and higher for cooperative and parallel tasks than independent-goal tasks. An interaction between Symmetry and Goal was present as participants performed better on the symmetric parallel task than the asymmetric parallel task. Bars represent mean normalised values of 100% and errors bars display standard error. * = P < 0.001.

The same effects of Symmetry and Goal were present at each follow-up assessment. Participants performed better on symmetric tasks than asymmetric tasks at 1M ($F_{1,55} = 26.67$, $P < 0.001$), 3M ($F_{1,55} = 24.62$, $P < 0.001$) and 6M ($F_{1,55} = 40.00$, $P < 0.001$) after stroke. The effect of Goal was present at 1M ($F_{1,55} = 21.10$, $P < 0.001$), 3M ($F_{1,55} = 12.35$, $P < 0.001$) and 6M ($F_{1,55} = 15.31$, $P < 0.001$) as participants performed better on cooperative tasks (1M $t_{55} = 5.37$, $P < 0.001$, 3M $t_{55} = 3.56$, $P < 0.001$, 6M $t_{55} = 4.61$, $P < 0.001$) and parallel tasks (1M $t_{55} = 4.98$, $P < 0.001$, 3M $t_{55} = 4.31$, $P < 0.001$, 6M $t_{55} = 4.30$, $P < 0.001$) than on independent-goal tasks. There was no difference between Coop and Parallel tasks at 1M, 3M, or 6M (all $P > 0.15$). There was no interaction between Symmetry and Goal at 1M, 3M, or 6M (all $P > 0.25$).

12.4.5 Aim 5: Longitudinal Analyses of Bimanual Task Categories

An RM-ANOVA for Coop tasks revealed a main effect of Symmetry ($F_{1,55} = 32.27$, $P < 0.001$) because participants performed better on the Sym-Coop task than the Asym-Coop tasks. An effect of Time was also present ($F_{1,55} = 24.63$, $P < 0.001$, Figure 12.6A) because participants improved on Coop tasks from Baseline to 1M ($t_{55} = 4.67$, $P < 0.001$), from 1M to 3M ($t_{55} = 3.27$, $P = 0.002$), and from 3M to 6M ($t_{55} = 2.28$, $P = 0.026$). There was an interaction between Symmetry and Time ($F_{1,55} = 3.26$, $P = 0.023$) because participants improved on the Sym-Coop task between 3M and 6M ($t_{55} = 2.78$, $P = 0.007$, mean 3M = 71.4 ± 5.1%, 6M = 76.5 ± 5.0%) but not on the Asym-Coop tasks ($P = 0.58$).

The separate RM-ANOVAs for Parallel and Indep tasks revealed similar effects. An effect of Symmetry was present (Parallel $F_{1,55} = 36.77$, $P < 0.001$, Indep $F_{1,55} = 11.77$, $P = 0.001$) as participants' performance was better for symmetric tasks than asymmetric tasks. An effect of

Time was also present (Parallel $F_{1,55} = 27.30$, $P < 0.001$, Indep $F_{1,55} = 25.85$, $P < 0.001$, Figures 12.6B and 12.6C respectively) as participants improved from Baseline to 1M (Parallel $t_{55} = 4.76$, $P < 0.001$, Indep $t_{55} = 4.32$, $P < 0.001$) and from 1M to 3M (Parallel $t_{55} = 4.12$, $P < 0.001$, Indep $t_{55} = 4.07$, $P < 0.001$) but with no improvement between 3M and 6M (both $P > 0.65$). There was no interaction between Symmetry and Time for Parallel or Indep tasks (both $P > 0.65$).

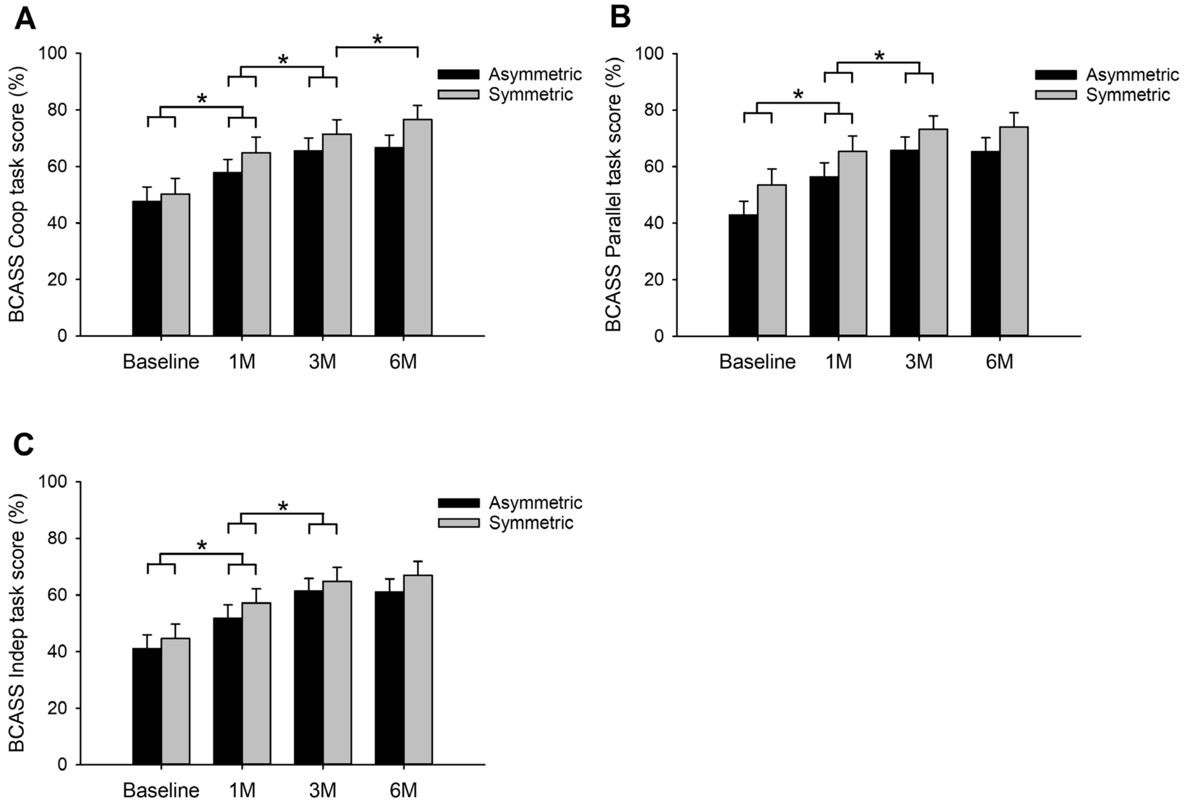


Figure 12.6. Recovery of BCASS scores for cooperative (A), parallel (B), and independent-goal (C) tasks (all N = 56). Participants performed better on symmetric tasks than asymmetric tasks overall and their performance improved from Baseline to 3M regardless of the goal. The only improvement between 3M and 6M was for the Sym-Coop task. Bars represent mean normalised values of 100% and errors bars display standard error. * = $P < 0.001$.

12.5 Discussion

The present study investigated bimanual coordination recovery in the first six months post-stroke. Bimanual coordination improved from one week post-stroke and plateaued at three months post-stroke along with unimanual upper limb motor recovery. Participants only improved between three and six months post-stroke on the symmetric cooperative BCASS task. Participants performed better on bimanual symmetric tasks than asymmetric tasks and on cooperative and parallel tasks, collectively known as common-goal tasks, than independent-goal tasks. These results indicate that bimanual and unimanual upper limb function have a similar time course of recovery and that both movement symmetry and goal conceptualisation influence bimanual coordination at the subacute stage after stroke.

12.5.1 Recovery of Bimanual Coordination

We hypothesised that most recovery of bimanual coordination would occur within the first three months after stroke and that smaller improvements would occur between three and six months post-stroke. This hypothesis was partially supported. Bimanual task performance improved up until three months post-stroke but further improvements at six months post-stroke occurred only for the symmetric cooperative task. Neither age nor concordance affected bimanual coordination recovery assessed with the BCASS, and no effect of concordance was also found for participants at the chronic stage of stroke performing the BCASS (Chapter 11).

To our knowledge this is the first longitudinal study at the subacute stage after stroke to assess coordination during naturalistic bimanual tasks with varying movement symmetry and goal conceptualisation. However, previous studies have investigated other aspects of bimanual upper limb recovery that relate to the present results. For example, participants improved on the Ad-AHA Stroke in the first six months post-stroke which assesses paretic upper limb function during bimanual tasks (426). Ad-AHA Stroke scores did improve over time but the authors did not perform post-hoc analyses to determine exactly when the recovery occurred. It is therefore uncertain how the time course of recovery for paretic upper limb function during bimanual tasks relates to the recovery of coordination during bimanual tasks assessed in the present study. The only previous study to measure bimanual coordination recovery at the subacute stage after stroke was performed by Metrot et al. and found that task performance and between-hands synchronisation plateaued on a bimanual reaching task at six weeks post-stroke (424). The authors used a task where participants reached for a ball with both hands, which was very similar to the symmetric parallel task in the BCASS. The symmetric parallel BCASS task was one of the easiest task categories for participants in the present study which may explain why bimanual coordination recovered faster in Metrot et al's study than overall BCASS scores did in the present study. It is uncertain how applicable the findings from Metrot et al's study are to the types of tasks in the current study which focused on movement symmetry and goal conceptualisation.

In line with our hypothesis, there was a high correlation between BCASS and ABILHAND scores at three and six months post-stroke. This finding indicates that participants' assessed coordination during bimanual tasks closely relates to their self-perceived ability to complete real-world bimanual tasks. A similarly strong correlation was found between the BCASS and ABILHAND in a group of 30 participants at a mean of 5.7 years since stroke (Chapter 11). This similar degree of correlation between the BCASS and ABILHAND at the subacute and chronic stages after stroke may represent a ceiling effect because the ABILHAND only includes asymmetric cooperative tasks. It is possible that the correlation between observed and perceived performance would be stronger using a questionnaire that covers all six bimanual task categories included in the BCASS.

12.5.2 Bimanual and Unimanual Task Performance Recovery

Contrary to our second hypothesis, participants plateaued on the BCASS, FM-UE, and ARAT all at three months post-stroke. Similar relationships have been found between the FM-UE and the Ad-AHA Stroke, as well as between the ARAT and CAHAI which also assesses paretic hand function during naturalistic bimanual tasks (426, 458, 459). It appears therefore that unimanual upper limb motor recovery does not precede recovery of bimanual coordination or paretic hand function during bimanual tasks.

Do BCASS scores reflect paretic arm function during bimanual tasks, rather than coordination during bimanual tasks as intended? Several factors suggest not. First, participants improved on the symmetric cooperative BCASS task between three and six months post-stroke with no improvements on the FM-UE or ARAT. Second, the rate of improvement was greater for the BCASS compared to the FM-UE between Baseline and three months post-stroke. Participants had greater potential for improvement on the BCASS because participants scored higher on the FM-UE at each time point. However, the mean FM-UE score at three months post-stroke was 75% and so the difference in recovery rate was unlikely to be due to a ceiling effect on the FM-UE. Third, a similar recovery pattern on the unimanual and bimanual assessments was not unexpected given that unimanual movement and function is necessary to have bimanual coordination and function. Indeed, people with chronic stroke with better paretic upper limb movement are more likely to spontaneously perform naturalistic tasks bimanually (422). Finally, the additional temporal and spatial coordination demands during bimanual tasks makes them more cognitively demanding than unimanual tasks. How cognition affects recovery of bimanual coordination across the subacute stage after stroke has not been examined in depth. Although both bimanual coordination and unimanual upper limb motor recovery plateau at three months post-stroke, there are likely different underlying factors for each.

12.5.3 Movement Symmetry and Goal Conceptualisation

This is the first study to examine the effects of movement symmetry and goal conceptualisation on coordination during bimanual tasks at the subacute stage after stroke. As hypothesised, participants performed better on symmetric tasks than asymmetric tasks at each time point. Previous studies have found that the preference and stability of symmetric movements is retained at the chronic stage after stroke during discrete movements (286, 429). The present results show that the superior performance of symmetric tasks is present within one week post-stroke and remains until six months post-stroke.

In agreement with our fourth hypothesis is the finding participants performed better on the common-goal tasks than independent-goal tasks at each time point. The same finding was present when using the BCASS with participants with chronic stroke (Chapter 11). Two other studies have compared performance on common-goal versus independent-goal tasks in people with chronic stroke. One study found that participants with stroke had worse temporal coordination when reaching forward to move one virtual block compared to two virtual blocks, but there were no differences in movement time or spatial coordination (286). The second study found participants with stroke were slower at reaching for two small trays compared to one large tray but there were no differences in spatial coordination between conditions (322). The results of the two previous studies in conjunction with the present study demonstrate that the effect of goal conceptualisation on bimanual coordination may vary depending on the task.

There are a few explanations for the superior performance on common-goal tasks in the present study. There is some indirect evidence that the paretic hand at the chronic stage after stroke is controlled by a greater extent from the ipsilateral hemisphere during common-goal tasks than independent-goal tasks (295). Increased control by the undamaged ipsilateral hemisphere may have improved performance of the paretic hand during the common-goal tasks. Whether the upregulation of ipsilateral control for the paretic upper limb occurs at the subacute stage after stroke remains to be investigated. Another possibility for the superior performance on common-goal tasks is that participants completed them using compensatory strategies. The paretic hand can be used to perform the easier role during asymmetric common-goal tasks whereas the paretic upper limb must achieve its goal in isolation from the non-paretic upper limb during independent-goal tasks. If compensatory strategies were used then they were spontaneous rather than learned because participants performed better on common-goal tasks as early as one week post-stroke. Examining the roles performed by the paretic and non-paretic hands during common-goal tasks of the BCASS and how they change over time may help elucidate why participants with stroke perform better on them compared to independent-goal tasks.

Task performance was affected by several interactions between movement symmetry and goal conceptualisation. At Baseline participants performed better on the symmetric parallel task than the asymmetric parallel task but symmetry did not affect performance on the cooperative and independent-goal tasks. Interestingly, the same influence of symmetry for parallel tasks was not found at one, three or six months after stroke but was present using the BCASS in a group of participants with chronic stroke (Chapter 11). The only previous study to include two parallel tasks with varying symmetry had participants with chronic stroke perform an asymmetric parallel item retrieval drawer-task as well as a symmetric parallel task where they reached for a box with both hands (168). Participants with chronic stroke displayed worse bimanual coordination than age-matched controls on the asymmetric parallel but both groups performed similarly on the symmetric parallel task. Although the two parallel tasks were not compared against each other, the results from this previous study support our finding that performance on parallel tasks also depends on movement symmetry. Future studies using different parallel tasks can further investigate how movement symmetry affects parallel task performance longitudinally after stroke.

A second interaction arose because participants continued to improve on the symmetric cooperative task between three and six months post-stroke but not on the asymmetric cooperative tasks. In fact, the symmetric cooperative task was the only measure that improved between three and six months for any assessment in the current study. Participants with chronic stroke have demonstrated bimanual coordination deficits on both lab-based and real-world symmetric cooperative tasks (168, 286) and asymmetric cooperative tasks (113, 286, 317). Given that symmetric tasks are well established to be easier than asymmetric tasks though it is possible that participants improved on the symmetric cooperative task until six months post-stroke due to a higher potential ceiling of recovery than the asymmetric cooperative tasks. This potential explanation will require further investigation. Overall, the present results demonstrate that participants with stroke perform better on symmetric and common-goal tasks compared to asymmetric and independent-goal tasks, respectively, as early as one week post-stroke and this remains until six months post-stroke.

12.5.4 Study Strengths and Limitations

This study had several limitations. COVID-19 restrictions meant that nineteen follow-up assessments were delayed while an additional ten consented participants were excluded from data analyses for having missed at least one assessment. This decreased the sample size included in the statistical analysis. Another limitation is that most participants were male, which has been identified as a general limitation of subacute stroke studies (502). Finally, the ABILHAND was the only bimanual assessment that BCASS scores were compared to. Comparing the BCASS against other bimanual behavioural assessments could provide greater evidence of its validity at the subacute stage after stroke.

There were also several strengths of this study, one being the schedule for assessments. Internal consensus recommends that studies of sensorimotor recovery perform assessments within one week and at three months post-stroke, both of which were done in the present study (122). Furthermore, the inclusion of an assessment at one-month post-stroke allowed us to determine whether upper limb improvements occurred predominantly in the first month or between one and three months post-stroke. A second strength is that the participant cohort covered the full range of upper limb impairment at Baseline based on their FM-UE scores.

12.5.5 Future Directions

The results of this study reveal several future directions. The interrater and intrarater reliability of the BCASS at the subacute stage after stroke have yet to be investigated.

External validation of the BCASS remains to be evaluated. The BCASS could be used as an outcome assessment to determine what factors early after stroke predict bimanual coordination at the chronic stage. The Ad-AHA Stroke was similarly used to predict performance of the paretic upper limb during bimanual tasks at six months post-stroke (426). Finally, numerous studies have used bilateral interventions to improve unimanual upper limb recovery post-stroke with a unimanual assessment chosen as the primary outcome measure (503, 504). Using the BCASS as an outcome assessment could help determine whether bilateral interventions provide specific benefits for recovery of performing bimanual tasks, particularly for studies comparing bilateral and unilateral interventions (505, 506).

12.5.6 Conclusion

The present study found that coordination during bimanual tasks was impaired immediately after stroke and its recovery plateaued at three months post-stroke at the same time as the recovery of unimanual impairment and function. Both movement symmetry and goal conceptualisation influenced recovery of bimanual coordination. Future studies could use the BCASS to determine what factors influence bimanual coordination deficits and recovery after stroke or as an outcome assessment for bilateral upper limb intervention studies.

13 Overall Discussion

Stroke has considerable impacts on individuals, families, and healthcare systems. These impacts are going to increase as the number of people living with stroke in New Zealand is projected to increase by 60% by 2038 (5). Upper limb weakness is one of the most common impairments after stroke and can significantly affect a person's level of functional independence (64). The first component of this thesis detailed the development and use of the FOCUS assessments for remotely categorising unimanual upper limb functional outcome after stroke (Chapters 3 and 4). Upper limb weakness after stroke can also impair bimanual coordination, and the second component of this thesis furthered our understanding of whether interhemispheric inhibition mediates different forms of bimanual coordination in healthy adults (Chapter 8). The final thesis component detailed the development and use of the BCASS for assessing coordination during bimanual task performance in people with stroke (Chapters 11 and 12).

13.1 Remote Assessment of the Paretic Upper Limb after Stroke

The COVID-19 pandemic restricted the ability to assess participants in-person and increased the need for remote upper limb assessments after stroke. The feasibility of remote assessment was helped by older adults becoming more skilled in their use of videocalls due to the COVID-19 pandemic (507). The first component of this thesis detailed the development of the FOCUS assessments for categorising upper limb outcome after stroke (Chapter 3). Each of the FOCUS assessments was highly accurate at derivation and in 10-fold cross-validation. The remote FOCUS-4 assessment demonstrated high overall accuracy when used prospectively with people at the subacute and chronic stages after stroke, particularly for people with mild or severe upper limb weakness, and good intersession reliability at the chronic stage after stroke (Chapter 4). The FOCUS assessments are the first reported assessments with potential to categorise upper limb outcome after stroke remotely during a videocall.

The FOCUS assessments have several potential clinical applications. Performing a FOCUS assessment in-person can categorise upper limb outcome faster than a full ARAT. The ARAT requires a minimum of four tasks to categorise upper limb outcome while FOCUS assessments require a maximum of three tasks, and most participants are categorised after performing one or two tasks. Reliability and accuracy of the in-person FOCUS assessment have yet to be evaluated but are unlikely to be lower than during videocalls. Being able to perform FOCUS assessments remotely could be useful in a range of scenarios where in-person assessments are not feasible or advisable, such as the participant feeling unwell or the participant moving out region. The option for remote assessment can be particularly useful for longitudinal studies that need assessments to be performed at specific time points after stroke. Using the FOCUS assessments remotely could also increase research participation as many potential participants are excluded from studies for living too far away from the study site at recruitment. For example, one longitudinal upper limb study after stroke reported that 16% of potential participants were excluded solely for living out of area (127). Finally, the ARAT score has been used as an exclusion criterion or for participant stratification in stroke studies (138-140). Although the FOCUS assessments only determine a potential range of ARAT scores, this can still be useful for quickly excluding potential participants without needing to assess them in-person.

There are several features of the FOCUS assessments that should be evaluated. Accuracy and reliability of the remote FOCUS-4 assessment needs to be evaluated in a larger sample size to confirm the findings presented in this thesis, and particularly for participants with moderate upper limb weakness. External validation needs to be carried out to test the reproducibility and generalisability of the FOCUS assessments in other settings (149). Accuracy and inter-session reliability remain to be evaluated for the FOCUS-3 and FOCUS-5 assessments while interrater reliability also needs to be evaluated for all FOCUS assessments. Finally, the feasibility of remote FOCUS assessments should be systematically investigated to optimise aspects such as the items used and how they are provided to the participant, how to minimise participant stress and effort when organising the assessment, and the most reliable way to instruct participants during the assessment. Overall, this thesis provides preliminary evidence that remote FOCUS assessments are an accurate alternative method to the in-person ARAT for categorising upper limb outcome after stroke.

13.2 Interhemispheric Mechanisms of Bimanual Coordination in Healthy Adults

Despite decades of research, many questions remain unanswered regarding the neural control of bimanual coordination. This thesis included the first experiment using transcranial magnetic stimulation (TMS) to investigate how movement symmetry and goal conceptualisation modulate corticomotor excitability (CME) as well as short and long interhemispheric inhibition (SIHI and LIHI, respectively) during bimanually coordinated movements (Chapter 8). Neither symmetry nor goal influenced SIHI or LIHI but CME was higher during asymmetric than symmetric movement patterns. These results indicate the degree of interhemispheric inhibition during bimanually coordinated movements is unaffected by movement symmetry or task goal. This provides indirect evidence that the effects of movement symmetry and goal conceptualisation on bimanual coordination in people with stroke performing the BCASS are not due to interhemispheric inhibition differing between tasks (Chapters 11 and 12). Future studies could investigate further by measuring SIHI and LIHI in people with stroke while they perform bimanual movements.

The neurophysiological mechanisms of bimanual coordination could also be further investigated using TMS protocols to probe interhemispheric connections to M1 from other motor regions known to be important for bimanual movements such as the supplementary motor area (SMA) and dorsal premotor cortex (PMd). To date, TMS protocols probing SMA-M1 facilitation and PMd-M1 inhibition have only been used with healthy adults at rest (197, 508). Establishing reliable protocols for eliciting these measures during bimanual movements is needed first, particularly if more ecologically valid tasks are used rather than the rhythmic tasks used in the TMS experiment of this thesis (Chapter 8). If reliable protocols can be established, longitudinally recording SMA-M1 facilitation and PMd-M1 inhibition after stroke, and correlating them with BCASS task performance, could provide greater understanding of whether these functional connections mediate bimanual coordination and its recovery after stroke.

13.3 Assessment and Recovery of Bimanual Coordination after Stroke

There are currently no comprehensive assessments of bimanual coordination after stroke, which has hindered the research field. This thesis presents preliminary evidence that the BCASS is a valid and reliable assessment of coordination during bimanual task performance for use after stroke.

The BCASS has several potential clinical uses. The BCASS could be used to assess initial impairments and the recovery of bimanual coordination after stroke in a larger sample than was used in this thesis. Understanding which types of bimanual tasks that people struggle to perform immediately after stroke, and which are the slowest or least likely to recover, could inform upper limb rehabilitation practices. Studying how factors such as upper limb sensory loss, inattention, and the location of the lesion affect the recovery of bimanual coordination after stroke could be achieved using the BCASS, especially as some factors may only affect certain categories of bimanual tasks such as common-goal tasks.

The BCASS could also be used as an outcome assessment for bilateral movement therapies or interventions designed to enhance paretic upper limb recovery. Bilateral therapies typically involve performing functional naturalistic tasks, robotic-assisted bimanual movements, or rhythmic symmetric movements (505). Bilateral therapies have similar effectiveness as unilateral therapies and standard upper limb therapy for recovery of paretic upper limb function (505). However, most studies of bilateral therapies only include unimanual upper limb outcomes such as the FM-UE and ARAT while potentially ignoring additional benefits to bimanual coordination or function. Indeed, there is some evidence that certain types of bilateral therapies improve bimanual coordination more than unilateral therapies (509). Bilateral therapies have even been reported to increase ipsilesional M1, SMA, and primary sensory cortex excitability as well as intra- and interhemispheric functional connectivity between these regions (510). Using the BCASS as an outcome assessment could enable studies comparing unilateral and bilateral therapies to evaluate whether the latter additionally benefit bimanual coordination. This could assist in the development of more effective bilateral therapies after stroke that benefits performance on ADLs requiring bimanual coordination.

Another potential use of the BCASS is to examine spontaneous hand role choice during naturalistic tasks by recording whether participants use their paretic upper limb as a manipulator or stabiliser during the asymmetric common-goal tasks. This could position the BCASS alongside the CAHAI, AAUT, and Ad-AHA Stroke as an assessment of spontaneous hand role choice after stroke. The BCASS is the only one of these assessments that scores bimanual coordination, and so hand choice could be correlated with BCASS scores to evaluate whether the degree of bimanual coordination impairment affects whether the paretic limb is used as a manipulator or stabiliser. The BCASS could even be used to see whether factors such as the side of stroke lesion and the extent of paretic upper limb weakness or sensory loss affect spontaneous hand role choice.

Certain psychometric properties of the BCASS have yet to be investigated, including reliability at the subacute stage after stroke. The BCASS was validated against unimanual upper limb assessments and the ABILHAND questionnaire (Chapters 11 and 12) but could also be validated against other clinical bimanual assessments that use similar tasks, such as the CAHAI. The BCASS could also be validated against kinematic measures of temporal and spatial coordination to ensure that the tasks truly reflect the intended category of bimanual coordination, for example whether the symmetric tasks involve symmetric upper limb movements. This would evaluate whether the BCASS is sensitive enough to detect bimanual coordination impairments relative to kinematic measures. Comparisons between kinematic and clinical measures have only been reported for unimanual upper limb stroke assessments but could be done bimanually with use of the BCASS (511). The combined use of kinematic and clinical measures has been advocated for to enable comprehensive and accurate evaluation of upper limb function post-stroke (511). Evaluating some or all these psychometric properties may add to the evidence presented in this thesis for using the BCASS to assess coordination during bimanual tasks after stroke.

13.4 Conclusion

In conclusion, this thesis introduced the FOCUS and BCASS assessments that address gaps in currently available assessments for the upper limbs after stroke. The novel finding that unimanual upper limb outcome after stroke can be accurately categorised remotely may increase future participation in upper limb research by providing a feasible alternative method of assessment. This thesis included the first longitudinal study of bimanual coordination recovery while considering movement symmetry and goal conceptualisation. Additionally, the studies using the BCASS at the acute stage and later stages after stroke demonstrate it has the potential to be a useful assessment for future studies of bimanual coordination after stroke. It is also important to understand the neurophysiological mechanisms of bimanual coordination in healthy adults to know how the mechanisms may be impaired after stroke, and this thesis furthered our understanding of whether interhemispheric inhibition mediates different forms of bimanual coordination**.** The original contributions from this thesis better our understanding of bimanual coordination after stroke and can facilitate future upper limb research after stroke.

14 Appendices

Appendix 1. Supplemental materials for Chapter 3

Supplemental Tables

Table I. Accuracy of the 3-CAT system decision tree produced by the CART analysis with all ARAT tasks available.

		3-CAT decision tree			
		Full	Some	None	% Correct
In-person ARAT	Full	100	0	0	100%
	Some	9	170	0	95.0%
	None	0	1	53	98.1%
	Overall				97.0%

Table II. Accuracy of the 4-CAT system decision tree produced by the CART analysis with all ARAT tasks available.

		4-CAT decision tree				
		Excellent	Good	Limited	Poor	% Correct
In-person ARAT	Excellent	169	5	0	0	97.1%
	Good	4	71	1	0	93.4%
	Limited	0	4	25	0	86.2%
	Poor	0	0	1	53	98.1%
	Overall					95.5%

Table III. Accuracy of the 5-CAT system decision tree produced by the CART analysis with all ARAT tasks available.

		5-CAT decision tree					
		Full	Notable	Limited	Poor	None	% Correct
In-person ARAT	Full	129	4	0	0	0	97.0%
	Notable	12	56	6	0	0	75.7%
	Limited	0	6	55	0	0	90.2%
	Poor	0	0	9	0	2	0%
	None	0	0	0	0	54	100%
	Overall						88.3%

Table IV. Accuracies of decision trees produced by CART analyses with all ARAT tasks available. The 5-CAT decision tree did not allocate any people to the Poor category.

	Accuracy (95% CI)	**PPV (95% CI)**	**NPV (95% CI)**
FOCUS-3			
Full (n = 100)	97.3% (94.9 – 98.8%)	91.7% (85.4 – 95.5%)	100% (100 – 100%)
Some (n = 179)	97.0% (94.6 – 98.6%)	99.4% (96.0 – 99.9%)	94.4% (90.0 – 97.0%)
None (n = 54)	99.7% (98.3 – 100%)	100% (100 – 100%)	99.6% (97.6 – 100%)
FOCUS-4			
Excellent (n = 174)	97.3% (94.9 – 98.8%)	97.7% (94.1 – 99.1%)	96.9% (92.9 – 98.7%)
Good (n = 76)	95.8% (93.1 – 97.7%)	88.8% (80.6 – 93.8%)	98% (95.5 – 99.1%)
Limited (n = 29)	98.2% (96.1 – 99.3%)	92.6% (75.7 – 98.0%)	98.7% (96.8 – 99.5%)
Poor (n = 54)	99.7% (98.3 – 100%)	100% (100 – 100%)	99.6% (97.6 – 100%)
FOCUS-5			
Full (n = 133)	95.2% (92.3 – 97.2%)	91.5% (86.1 – 94.9%)	97.9% (94.7 – 99.2%)
Notable (n = 74)	91.6% (88.1 – 94.3%)	84.9% (75.1 – 91.3%)	93.3% (90.2 – 95.4%)
Limited (n = 61)	93.7% (90.5 – 96.1%)	78.6% (69.0 – 85.8%)	97.7% (95.2 – 98.9%)
Poor (n = 11)	--	--	--
None (n = 54)	99.4% (97.9 – 99.9%)	96.4% (87.2 – 99.1%)	100% (100 – 100%)

n = number of patients in category using in-person ARAT categorisation. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value. FOCUS, Fast Outcome Categorisation of the Upper Limb after Stroke.

Table V. Accuracy of the FOCUS-3 assessment when applied to the three-month ARAT dataset from which it was derived.

		FOCUS-3 assessment			
		Full	Some	None	% Correct
In-person ARAT	Full	100	0	0	100%
	Some	9	168	2	93.9%
	None	0	0	54	100%
	Overall				96.7%

Table VI. Accuracy of the FOCUS-4 assessment when applied to the three-month ARAT dataset from which it was derived.

		FOCUS-4 assessment				
		Excellent	Good	Limited	Poor	% Correct
In-person ARAT	Excellent	169	5	0	0	97.1%
	Good	4	71	1	0	93.4%
	Limited	0	4	23	2	79.3%
	Poor	0	0	0	54	100%
	Overall					95.2%

Table VII. Accuracy of the FOCUS-5 assessment when applied to the three-month ARAT dataset from which it was derived.

		FOCUS-5 assessment					
		Full	Notable	Limited	Poor	None	% Correct
In-person ARAT	Full	127	6	0	0	0	95.5%
	Notable	4	55	15	0	0	74.3%
	Limited	0	5	56	0	0	91.8%
	Poor	0	0	9	0	2	0%
	None	0	0	0	0	54	100%
	Overall						87.7%

Table VIII. Accuracies of individual outcome categories when using the FOCUS assessments to categorise upper limb motor outcome for six-month post-stroke ARAT scores.

	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
FOCUS-3			
Full (n = 46)	93.0% (87.8 – 96.5%)	80.7% (70.5 – 88.0%)	100% (100 – 100%)
Some (n = 84)	91.1% (85.5 – 95.0%)	98.6% (91.0 – 99.8%)	84.7% (77.1 – 90.1%)
None (n = 27)	98.1% (94.5 – 99.6%)	92.9% (76.6 – 98.1%)	99.2% (94.9 – 99.9%)
FOCUS-4			
Excellent (n = 84)	95.5% (91.0 – 98.2%)	93.3% (86.5 – 96.8%)	98.5% (90.5 – 99.8%)
Good (n = 29)	94.3% (89.4 – 97.4%)	88.5% (71.2 – 96.0%)	95.4% (91.1 – 97.7%)
Limited (n = 16)	96.2% (91.9 – 98.6%)	85.7% (59.6 – 96.1%)	97.2% (93.7 – 98.8%)
Poor (n = 28)	97.5% (93.6 – 99.3%)	92.9% (76.6 – 98.1%)	98.5% (94.4 – 99.6%)
FOCUS-5			
Full (n = 67)	92.4% (87.0 – 96.0%)	96.6% (87.8 – 99.1%)	89.8% (83.2 – 94.0%)
Notable (n = 32)	87.3% (81.0 – 92.0%)	65.8% (52.7 – 76.9%)	94.1% (89.2 – 96.9%)
Limited (n = 26)	92.4% (87.0 – 96.0%)	71.9% (57.3 – 83.0%)	97.6% (93.3 – 99.2%)
Poor (n = 5)	96.8% (92.7 – 99.0%)	--	96.8% (96.8 – 96.8%)
None (n = 27)	98.1% (94.5 – 99.6%)	92.9% (76.6 – 98.1%)	99.2% (94.9 – 99.6%)

n = number of patients in category using in-person ARAT categorisation. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value. FOCUS, Fast Outcome Categorisation of the Upper Limb after Stroke.

Table IX. Accuracy of the FOCUS-3 assessment for upper limb outcome categorisation when applied to six-month post-stroke ARAT scores.

		FOCUS-3 assessment			
		Full	Some	None	% Correct
In-person ARAT	Full	46	0	0	100%
	Some	11	71	2	84.5%
	None	0	1	26	96.3%
	Overall				91.1%

Table X. Accuracy of the FOCUS-4 assessment for upper limb outcome categorisation when applied to six-month post-stroke ARAT scores.

		FOCUS-4 assessment				
		Excellent	Good	Limited	Poor	% Correct
In-person ARAT	Excellent	83	1	0	0	98.8%
	Good	6	23	0	0	79.3%
	Limited	0	2	12	2	75.0%
	Poor	0	0	2	26	92.9%
	Overall					91.7%

Table XI. Accuracy of the FOCUS-5 assessment for upper limb outcome categorisation when applied to six-month post-stroke ARAT scores.

		FOCUS-5 assessment					
		Full	Notable	Limited	Poor	None	% Correct
In-person ARAT	Full	57	10	0	--	0	85.1%
	Notable	2	25	5	--	0	78.1%
	Limited	0	3	23	--	0	88.5%
	Poor	0	0	3	--	2	0%
	None	0	0	1	--	26	96.3%
	Overall						83.4%

Supplemental Figures

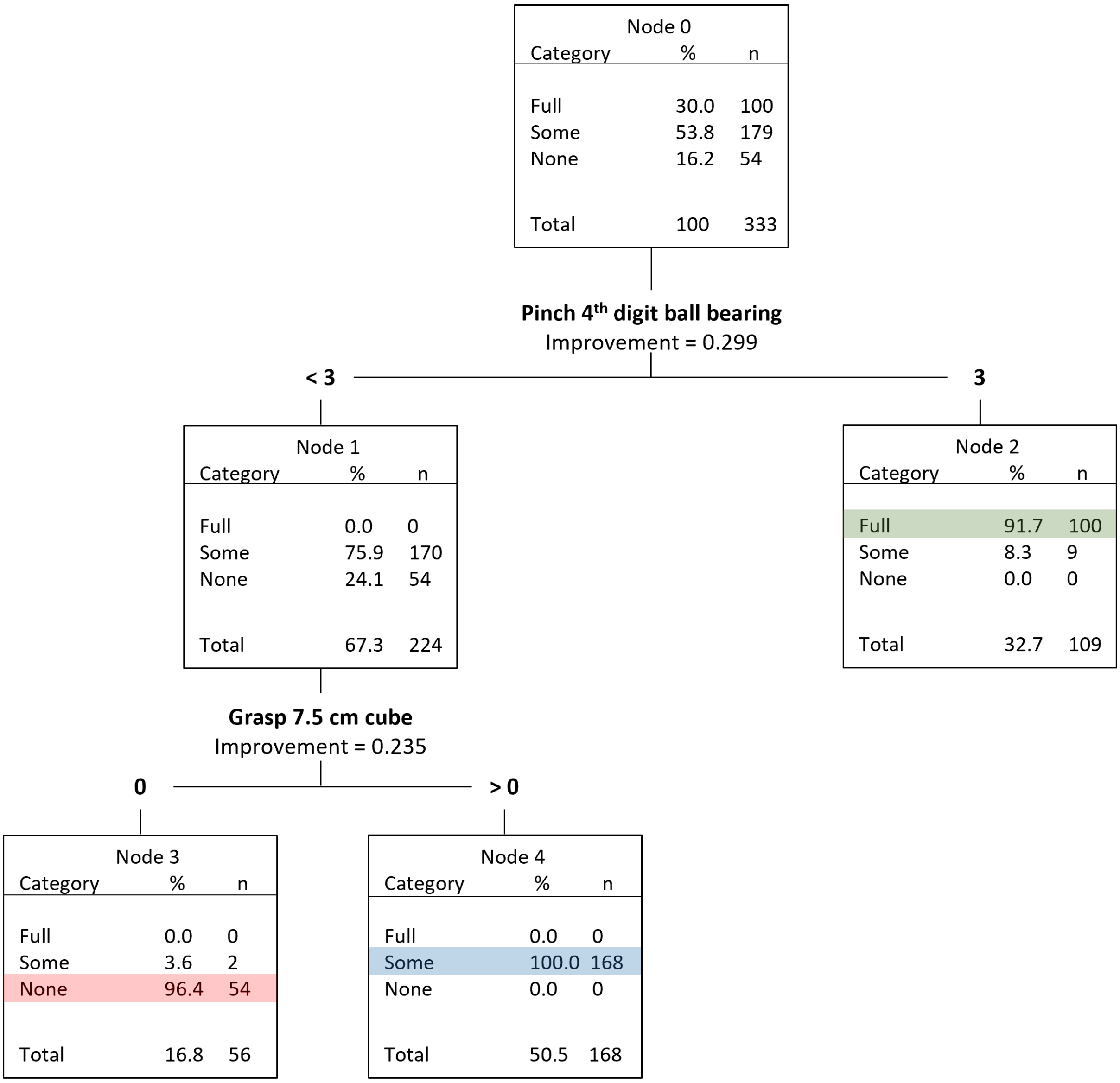


Figure I. CART analysis output for the 3-CAT system when including scores from 13 ARAT tasks.

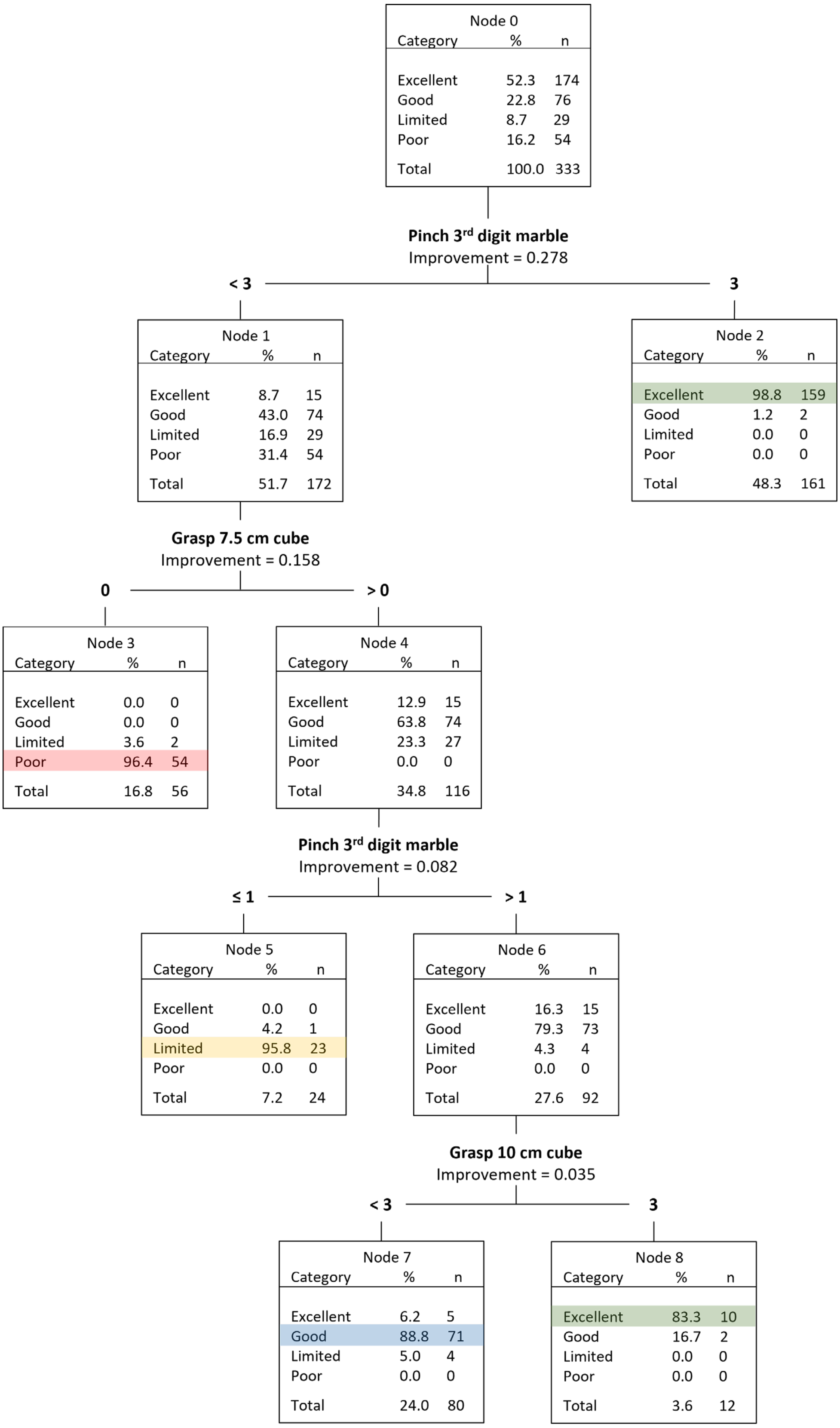


Figure II. CART analysis output for the 4-CAT system when including scores from 13 ARAT tasks.

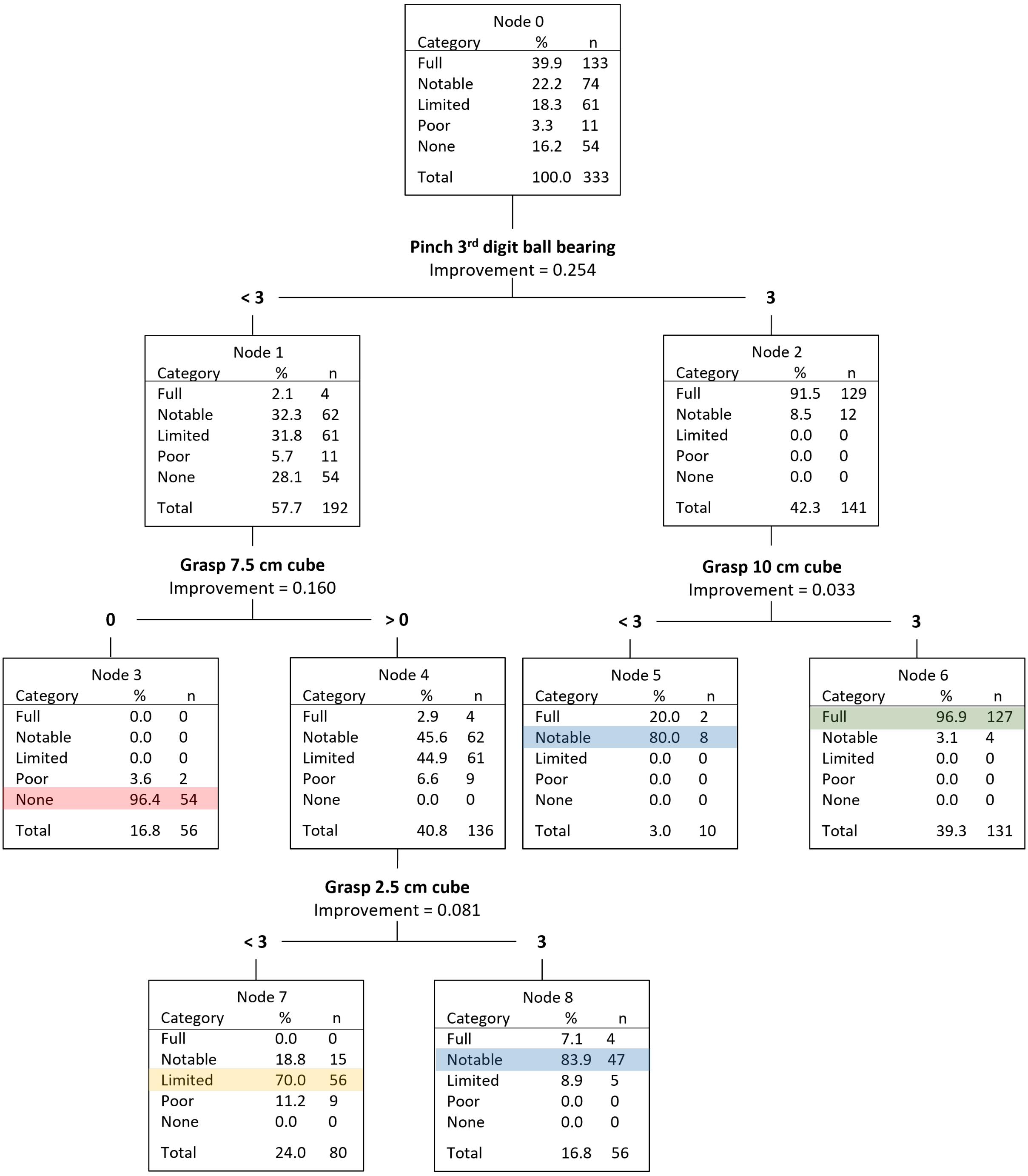
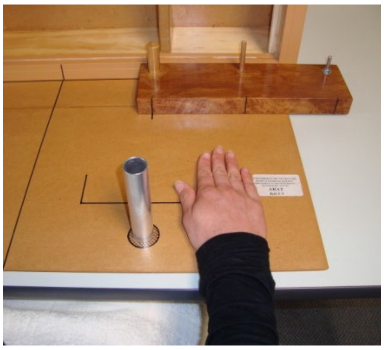


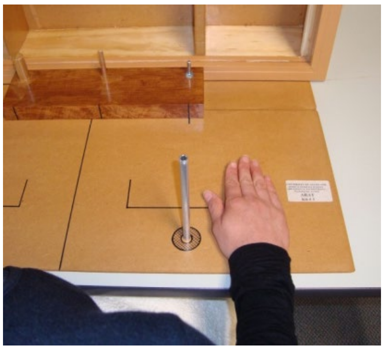
Figure III. CART analysis output for the 5-CAT system when including scores from 13 ARAT tasks.

Appendix 2. ARAT data collection sheet

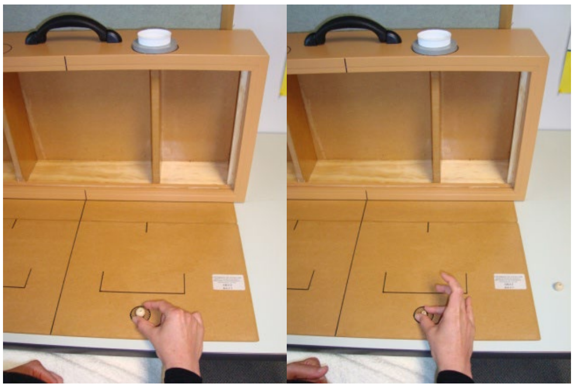
Grasp	**Time limit (sec)**	**Actual time (x.xx sec)**	**Score**	
Each item must be picked up and placed on the coaster on the shelf Hand must start and finish palm down on the table Stone is placed on its narrow long end with the narrow face towards to the patient				
10 cm block	4.2			If 3, total = 18, go to grip
2.5 cm block	3.6			If 0, total = 0, go to grip
5 cm block	3.5			
7.5 cm block	3.9			
Ball	3.8			
Stone	3.6			

Grip	**Time limit (sec)**	**Actual time (x.xx sec)**	**Score**	
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 Tall tube = start, short tube = finish Hand must start and finish palm down on the table				
Pour water cup to cup	7.9			If 3, total = 12, go to pinch
2.25 cm tube	4.2			If 0, total = 0, go to pinch
1 cm tube	4.3			
Place washer over bolt	4.0			





Pinch	**Time limit (sec)**	**Actual time (x.xx sec)**	**Score**	
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				
Small, ring and thumb	4.4			If 3, total = 18, go to gross
Large, index and thumb	3.8			If 0, total = 0, go to gross
Small, middle and thumb	4.1			
Small, index and thumb	4.0			
Large, middle and thumb	3.8			
Large, ring and thumb	4.1			



Gross	**Time limit (sec)**	**Actual time (x.xx sec)**	**Score**	
Hand must start and finish palm down on their lap				
Hand behind head	2.7			If 3, total = 9, go to grip
Hand on top of head	2.7			If 0, total = 0, go to grip
Hand to mouth	2.4			

TOTAL (/ 57) ☐

Appendix 3. Remote assessment participant instructions for Chapter 4

Videocall Assessment Instructions

- Thank you for agreeing to participate in this videocall as part of the **RAPAS** study
    - During this videocall you will be asked to perform some tasks using one of your hands
    - A friend or family member will need to be with you during the videocall to hold the video calling device
    - The videocall is expected to take approximately 10-15 minutes.
    - Please keep these items until the second videocall in a few weeks

- This postage box includes all the items you will use during the assessments.
- Leave the bags of sand inside the white cubes
- **Please do not destroy the postage box because it is used during some of the tasks.**

- **You should expect a call from the researcher Harry Jordan in the next few days to confirm the following:**
    - The time and date for the videocall
    - Which friend/family member will hold the camera during the videocall
    - Which videocall application will be used (eg. Zoom, Whatsapp, Skype)

- These items are yours to keep after you've completed the study, otherwise feel free to discard them.

The researcher will provide instructions for how to perform each task during the videocall.

At the time of the scheduled videocall, please ensure:

- You are ideally seated at a table that is a comfortable height (eg. Dining room table, work desk).
    - Sit on a straight-backed chair if possible, or use a pillow behind your back to help sit up straight
    - Please make sure you are seated close to the table
    - Have all items and the postage box itself nearby ready to use

- The friend or family member helping during the videocall should find a good position and angle to hold the phone that **shows you as well as the table area**
    - A side-on angle is best if possible.
    - Holding the camera horizontally to provide a landscape view is helpful

Good camera position

Appendix 4. Remote assessment data collection sheet for Chapter 4

RAPAS –
Remote Assessment

Session 1 **Session 2**

ID:			**Participant location:**
Date/Time:			**Participant helper:**
Affected limb:	**L**	**R**	**Assessor:**
Handedness:	**L**	**R**	**Assessor location:**
			Participant device and application used:

Comments:

GRASP	**Time Limit (s)**	**Actual Time (s)**	**Score**
10cm cube	**4.2**		
7.5cm cube	**3.9**		
2.5cm cube	**3.6**		

PINCH	**Time Limit (s)**	**Actual Time (s)**	**Score**
Small bead (ring finger)	**4.4**		
Large bead (index finger)	**3.8**		
Small bead (middle finger)	**4.1**		
Small bead (index finger)	**4.0**		
Large bead (middle finger)	**3.8**		
Large bead (ring finger)	**4.1**		

GROSS	**Time Limit (s)**	**Actual Time (s)**	**Score**
Hand to back of head	**2.7**		
Hand to top of head	**2.7**		
Hand to mouth	**2.4**		

Appendix 5. Supplemental materials for Chapter 4

Table I. Individual outcome category accuracies for the remote FOCUS-4 assessment at three months after stroke.

	Accuracy (95% CI)	**PPV (95% CI)**	**NPV (95% CI)**
Excellent (n = 13)	92.3% (74.9 – 99.1%)	86.7% (64.5 – 95.9%)	100.0% (100.0 – 100.0%)
Good (n = 4)	88.5% (69.9 – 97.6%)	66.7% (18.9 – 94.5%)	91.3% (79.7 – 96.6%)
Limited (n = 2)	88.5% (69.9 – 97.6%)	33.3% (6.8 – 77.3%)	95.7% (84.6 – 98.9%)
Poor (n = 7)	100.0% (86.8 – 100.0%)	100.0% (100.0 – 100.0%)	100.0% (100.0 – 100.0%)

n = number of patients in category using in-person ARAT categorisation. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table II. Individual outcome category accuracies for the remote FOCUS-4 assessment at six months after stroke.

	Accuracy (95% CI)	**PPV (95% CI)**	**NPV (95% CI)**
Excellent (n = 13)	96.3% (81.0 – 99.9%)	92.9% (66.3 – 98.9%)	100.0% (100.0 – 100.0%)
Good (n = 4)	96.3% (81.0 – 99.9%)	100.0% (100.0 – 100.0%)	95.8% (80.8 – 99.2%)
Limited (n = 0)	--	--	--
Poor (n = 10)	100.0% (87.2 – 100.0%)	100.0% (100.0 – 100.0%)	100.0% (100.0 – 100.0%)

n = number of patients in category using in-person ARAT categorisation. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table III. Individual outcome category accuracies for the first remote FOCUS-4 assessment at the chronic stage after stroke.

	Accuracy (95% CI)	**PPV (95% CI)**	**NPV (95% CI)**
Excellent (n = 19)	94.6% (81.8 – 99.3%)	94.7% (72.8 – 99.2%)	94.4% (71.6 – 99.1%)
Good (n = 6)	83.8% (68.0 – 93.8%)	50.0% (20.7 – 79.3%)	90.3% (80.6 – 95.4%)
Limited (n = 7)	83.8% (68.0 – 93.8%)	60.0% (23.4 – 88.0%)	87.5% (78.5 – 93.1%)
Poor (n = 5)	94.6% (81.8 – 99.3%)	71.4% (39.5 – 90.5%)	100.0% (100.0 – 100.0%)

n = number of patients in category using in-person ARAT categorisation. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Table IV. Individual outcome category accuracies for the second remote FOCUS-4 assessment at the chronic stage after stroke.

	Accuracy (95% CI)	**PPV (95% CI)**	**NPV (95% CI)**
Excellent (n = 19)	97.1% (84.7 – 99.9%)	95.0% (74.1 – 99.2%)	100.0% (100.0 – 100.0%)
Good (n = 4)	85.3% (68.9 – 95.1%)	42.9% (20.4 – 68.7%)	96.3% (82.6 – 99.3%)
Limited (n = 7)	82.4% (65.5 – 93.2%)	100.0% (100.0 – 100.0%)	81.8% (76.9 – 85.9%)
Poor (n = 4)	94.1% (80.3 – 99.3%)	66.7% (34.4 – 88.4%)	100.0% (100.0 – 100.0%)

n = number of patients in category using in-person ARAT categorisation. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Appendix 6. TMS safety checklist for Chapter 8

THE UNIVERSITY OF AUCKLAND
Te Whare Wānanga o Tāmaki Makaurau
NEW ZEALAND

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:	Your answer Yes	 No
1. Do you have epilepsy, or have you ever had an epileptic seizure?	☐	☐
2. Does anyone in your family have epilepsy?	☐	☐
3. Do you have any metal implant(s) in any part of your body or head?	☐	☐
4. (Excluding tooth fillings)		
5. Do you have any implanted electronics?	☐	☐
(Such as pacemaker, defibrillator, cochlear implant, or medication pump)		
6. Do you experience recurring headaches?	☐	☐
7. Have you ever had a skull fracture or severe head injury?	☐	☐
8. Have you ever had head or brain surgery?	☐	☐
9. Do you have any neurological or other medical conditions?	☐	☐
10. Is there any chance you could be pregnant?	☐	☐
11. Do you regularly take any medication?	☐	☐

Comments:

Participant

Name: ______________________

Signature: ___________________

Date: _______________________

Researcher

Name: ______________________

Signature: ___________________

Date: _______________________

Type of experiment:

Single Pulse TMS
Paired Pulse TMS
Repetitive TMS
TDCS
Other

Neurological condition:

Outcome

☐ Include

☐ Exclude

Supervisor

Name: ______________________

Signature: ___________________

Date: _______________________

Consultation with study physician

Name: ______________________

Signature: ___________________

Date: _______________________

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

Name: ________________________

Signature:

Date:

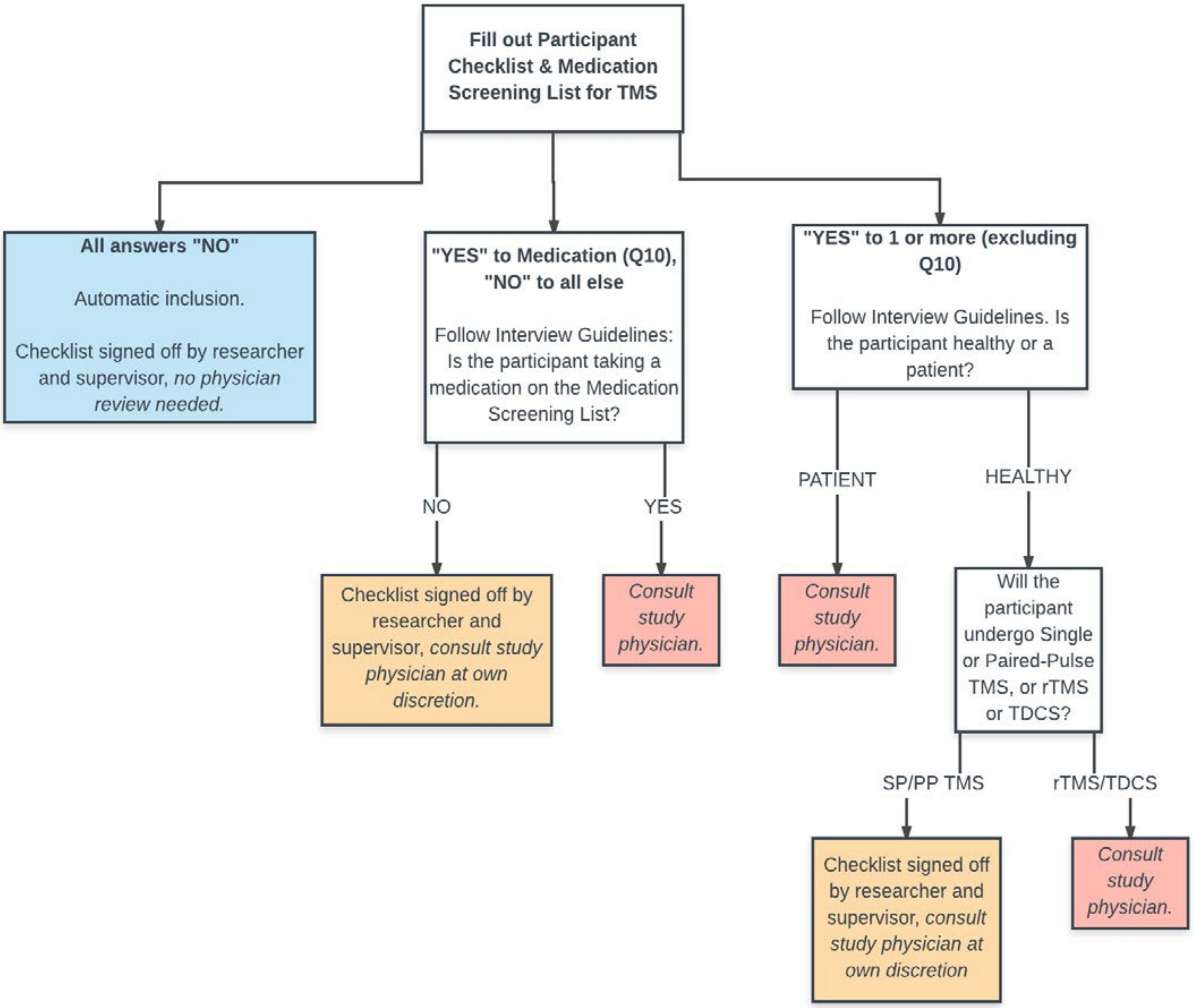
No to all	Yes		Dose
☐	☐	Alprazolam Xanax®	
	☐	Amantadine	
	☐	Amitriptyline	
	☐	Aripiprazole	
	☐	Baclofen	
	☐	Benztropine	
	☐	Bupropion Zyban®	
	☐	Carbamazepine Tegretol®	
	☐	Chlorpromazine	
	☐	Citalopram	
	☐	Clobazam Frisium®	
	☐	Clonazepam	
	☐	Clozapine Clozaril, Clopine	
	☐	Doxepin	
	☐	Duloxetine	
	☐	Fluoxetine	

No to all	Yes		Dose
☐	☐	Fluphenazine	
	☐	Fluvoxamine	
	☐	Gabapentin	
	☐	Haloperidol	
	☐	Hyoscine including Gastro-Soothe® Buscopan® tablets	
	☐	Imipramine	
	☐	Ketamine	
	☐	Lamotrigine	
	☐	Levodopa + benserazide Madopar	
	☐	Levodopa + carbidopa	
	☐	Lisuride	
	☐	Lorazepam	
	☐	Maprotiline	
	☐	Mirtazapine	
	☐	Methylphenidate Ritalin, Rubifen	
	☐	Moclobemide	

No to all	Yes		Dose
☐	☐	Nortriptyline	
	☐	Paroxetine	
	☐	Phenytoin	
	☐	Pimozide	
	☐	Quetiapine	
	☐	Reboxetine	
	☐	Risperidone	
	☐	Selegiline	
	☐	Sertraline	
	☐	Sodium valproate Epilim®	
	☐	Temazepam	
	☐	Theophylline	
	☐	Tolcapone	
	☐	Topiramate Topamax	
	☐	Triazolam	

No to all	Yes		Dose
☐	☐	Venlafaxine Efexor®	
	☐	Vigabatrin	
	☐	Ziprasidone	

TMS CHECKLIST PROTOCOL FOR RESEARCHERS



Appendix 7. BCASS data collection sheet for Chapters 11 and 12

Y/N unless stated otherwise	Peg towel Normal	Peg towel Reversed	Open jar Normal	Open jar Reversed	Place paperclip into cup Normal	Place paperclip into cup Reversed	Pour water Normal	Pour water Reversed	Turn page, move cup Normal	Turn page, move cup Reversed	Lift two cups	Reach and pull box Reach component	Reach and pull box Pull component	Lift shoelace	Tie bow
Assistance for weakness required?															
Stabilising hand (L/R)									Page	Page	▨	▨	▨	▨	▨
Manipulating hand (L/R)									Cup	Cup	▨	▨	▨	▨	▨
Time to complete task (s)															

Interact with object(s) bimanually															
Hands move concurrently													▨		
Maintains contact between back and chair															
Do the hands appear to move at the same speed?	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨			▨		
Do the hands appear to contribute equally?	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨			▨
Able to successfully complete task															
Normal task time exhibited															
Score (# Y's in T1+2):	/5	/5	/5	/5	/5	/5	/5	/5	/5	/5	/6	/5.5	/4.5	/7	/6

TOTAL SCORE: /79

Grey squares indicate that feature is not scored or recorded.

Appendix 8. Supplemental materials for Chapter 11

Methods

BCASS Scoring

Each asymmetric task except the Tie Bow task was scored out of 5. The scoring totals were more varied for the symmetric tasks. Each factor was scored as either 0 or 1. There are 4 features that participants were scored on for each task:

1) **Interacted with object(s) bimanually.** Could the participant use both hands to interact with the object(s) in some capacity? If the participant could interact with both objects they scored 1 for this feature, otherwise they were scored as 0. Examples such as moving a page of the booklet but being unable to turn it over during the Page-Cup task and grasping the cup but not being able to turn it over during the Paperclip task were scored as 1.
2) **Maintained contact between back and chair.** Could the participant complete the task without any compensatory anterior trunk flexion? If the participant's back stayed in contact with the chair during the task they were scored as 1 on this feature, but if their back left the chair then this feature was scored as 0.
3) **Normal task time exhibited.** Was the participant's task time below the designated time limit? If it was at or below the time limit this feature was scored as 1, otherwise it was scored as 0. This feature was retroactively scored for all participants following refinement of the BCASS.
4) **Able to successfully complete task.** Could the participant successfully complete the task as instructed? If the participant could complete the task this feature was scored as

1. Participants who could not complete the task were scored as 0 for this feature in addition to each other feature of that task. The only exception was the “interact with object(s) bimanually” feature as this helped differentiate participants with stroke who had no movement in their paretic hand versus those who had enough movement to attempt part of the task but not complete it.

There were several additional scoring features that were only scored for certain tasks:

1) **Hands moved concurrently.** Were the hands moving or interacting with the objects concurrently, or were they moving sequentially? This was included as a measure of temporal coordination during tasks. For example, during the Paperclip task this feature was scored as 1 if the participant used one hand to pick up the paperclip while the other hand was flipping the cup. However, if participants flipped the cup and placed it on the table with one hand before starting to pick up the paperclip with the other hand then this feature was scored as 0. For cooperative tasks such as the Jar task and the Water task this was scored depending on whether participants reached to grasp the object(s) concurrently or sequentially. The only task that did not include this scoring feature was the Pull box task because participants started with both hands already on the box and there was no way to complete the task without moving both hands concurrently.
2) **Did the hands appear to move at the same speed?** This was included as a measure of spatial coordination during tasks. If participants’ hands were moving symmetrically from the starting position and reached the object(s) at the same time this feature was scored as 1, but if one hand led the other so they reached the objects at different times

this was scored as 0. This scoring feature was only used for the Lift Cups task, the Reach Box task, the Lift Shoelace task, and the Tie Bow task because the other tasks involve reaching asymmetric distances and so were too difficult to score subjectively.

3) **Did the hands appear to contribute equally to the task goal?** This was included as a measure of whether the task was performed using both hands equally or predominantly with one hand with a lesser contribution from the other hand. Participants who used both hands equally were scored as 1 on this feature, and if they predominantly used one hand they were scored as 0. This was only scored for the two Sym-Coop tasks because different contributions from the hands during asymmetric tasks is necessary while both hands had to contribute equally during the Sym-Parallel and Sym-Indep tasks.

The hand acting as the manipulator and stabiliser was also recorded for each asymmetric task where applicable but did not contribute to the scoring.

Supplemental Tables

Table I. Between-sessions interrater reliability results for each BCASS task performed by participants with stroke (n = 21).

Task	**ICC Rater 1 (95% CI)**	**ICC Rater 2 (95% CI)**
Jar task	0.864 (0.662 – 0.945)	0.928 (0.825 – 0.971)
Water task	0.921 (0.808 – 0.968)	0.916 (0.794 – 0.966)
Tie Bow task	0.980 (0.952 – 0.992)	0.989 (0.973 – 0.995)
Paperclip task	0.912 (0.786 – 0.964)	0.931 (0.830 – 0.972)
Page-Cup task	0.878 (0.706 – 0.950)	0.927 (0.821 – 0.970)
Lift Shoelace task	0.896 (0.747 – 0.957)	0.967 (0.919 – 0.987)
Reach Box task	0.846 (0.623 – 0.937)	0.926 (0.819 – 0.970)
Lift Cups task	0.921 (0.806 – 0.968)	0.930 (0.829 – 0.972)
Tea Towel task	0.868 (0.624 – 0.949)	0.847 (0.621 – 0.938)
Pull Box task	0.837 (0.593 – 0.934)	0.880 (0.709 – 0.951)

ICC, intraclass correlation coefficient; CI, confidence interval.

Table II. Description of tasks removed from the final BCASS following refinement.

	Task requirements	**Items used**	**Maximum score**	**Time limit (s)**
Asym-Coop				
Tea towel task	Peg a tea towel to a shoelace	Peg, tea towel, and shoelace	5	3.77
Sym-Coop				
Pull box task	Pull a box towards the participant	An empty box	5	4.41

Asym, asymmetric; Coop, cooperative; Sym, symmetric.

Table III. Dimensions for items used as part of the final BCASS.

Item	Tasks used for	Dimensions
Glass screw-top jar	Jar task	Diameter = 7 cm Height = 11 cm 350mL capacity
Plastic water jug with handle	Water task	Diameter at top = 9.5 cm Diameter at bottom = 7 cm Height = 13.5 cm 650mL capacity
2x Plastic cups	Water task Paperclip task Page-Cup task Lift Cups task	Diameter at top = 7 cm Diameter at bottom = 4.4 cm Height = 9 cm 220mL capacity
Flat shoelace	Tie Bow task Lift Shoelace task	Length = 115 cm
Small box with bumpers	Tie Bow task	Length = 10 cm Width = 13.7 cm Height of box = 50 cm Height of bumpers = 0.8 cm
Paperclip	Paperclip task	Length = 3.1 cm
Laminated A5 paper booklet	Page-Cup task	Length = 15 cm Height = 21 cm 40 pages
Plastic storage container	Reach Box task Lift Cups task	Top length = 36 cm, Bottom length = 30.5 cm Height =11.5 cm Top width = 30 cm Bottom width = 25 cm 10L capacity

Table IV. Scores for each cohort during their first BCASS assessment and their mean score across the four assessments.

	Stroke Participants (N = 30)	**Younger Adults (N = 30)**	**Older Adults (N = 30)**
Mean ± SE			
Initial Exposure	26.5 ± 3.0	44.5 ± 0.1	44.2 ± 0.2
Four assessments	27.0 ± 3.0	44.6 ± 0.1	44.4 ± 0.2
Lower quartile			
Initial Exposure	5.8	44.0	44.0
Four assessments	9.1	44.3	44.3
Median			
Initial Exposure	33.5	44.5	44.0
Four assessments	32.9	44.8	44.8
Upper quartile			
Initial Exposure	38.0	45.0	45.0
Four assessments	41.1	45.0	45.0
Range			
Initial Exposure	0 – 44.0	43.0 – 45.0	41.0 – 45.0
Four assessments	0 – 44.5	43.8 – 45.0	41.8 – 45.0

SE, standard error. The four assessments row refers to participants' mean BCASS score across all four assessments.

Supplemental Figures

Y/N unless stated otherwise	Open jar	Pour water	Tie bow	Place paperclip into cup	Turn page, move cup	Lift shoelace	Reach and pull box Reach component	Lift two cups
Assistance for weakness required?								
Stabilising hand (L/R)			▨		Page	▨	▨	▨
Manipulating hand (L/R)			▨		Cup	▨	▨	▨
Time to complete task (s)								

Interact with object(s) bimanually								
Hands move concurrently								
Maintains contact between back and chair								
Do the hands appear to move at the same speed?	▨	▨		▨	▨			
Do the hands appear to contribute equally?	▨	▨	▨	▨	▨		▨	▨
Able to successfully complete task								
Normal task time exhibited	3.77	7.26	13.83	4.41	5.08	5.48	3.36	2.93
Score (# Y's):	/5	/5	/6	/5	/5	/7	/6	/6

TOTAL SCORE: /45

Figure I. Data collection sheet for the final BCASS following refinement. Grey squares indicate that item is not scored or recorded. Only items in the lower half of the collection sheet contribute towards the BCASS score. Numbers in the "normal task time exhibited" row indicate time cut-offs.

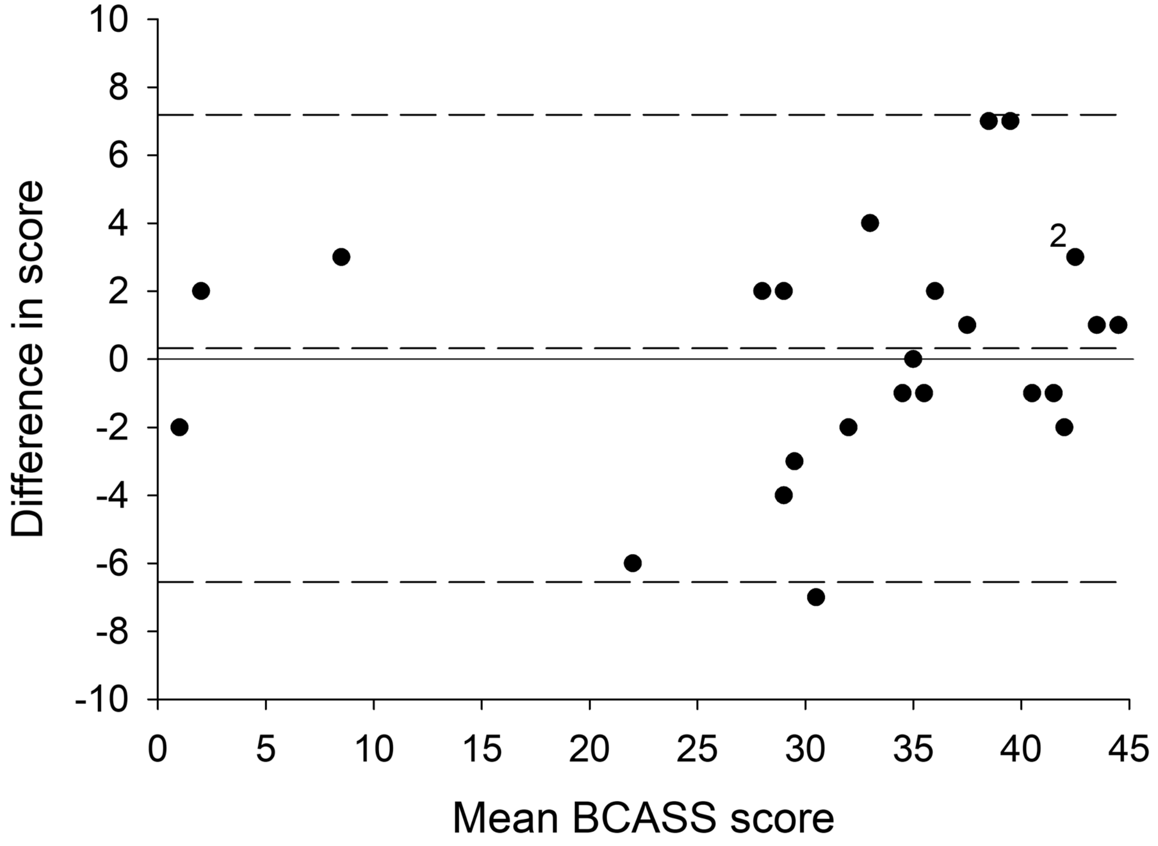


Figure II. Bland-Altman plot displaying within-session interrater agreement for total BCASS scores in participants with stroke (n = 25). Positive values indicate participants were scored higher by the second rater in the session than the first rater. Dashed horizontal lines from represent the mean (middle line) ± 2 standard deviations (top and bottom lines). The number on the graph indicates the number of participants at the datapoint.

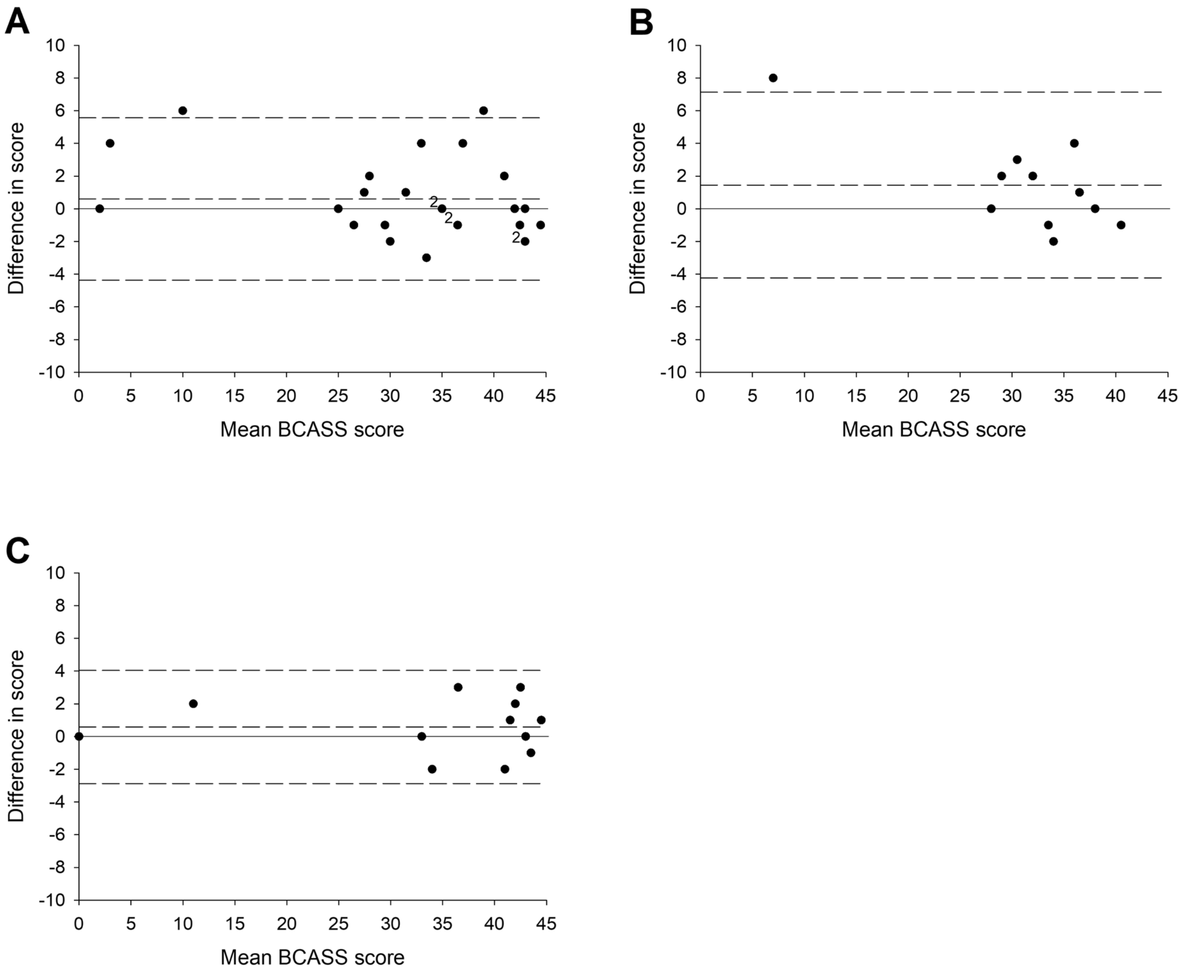


Figure III. Bland-Altman plots displaying between-sessions intrarater agreement for total BCASS scores in participants with stroke assessed by raters HJ (A, n = 25), BC (B, n = 11), and ON (C, n = 12). Positive values indicate participants scored were scored higher by the rater in the second session than in the first session. Dashed horizontal lines from represent the mean (middle line) ± 2 standard deviations (top and bottom lines). Numbers on the graph indicate the number of participants at a datapoint.

15 References

1. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet. 2008;371(9624):1612-23.

2. Collaborators GBDS. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021;20(10):795-820.

3. Feigin VL, Brainin M, Norrving B, Martins S, Sacco RL, Hacke W, et al. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. Int J Stroke. 2022;17(1):18-29.

4. Ranta A. Projected stroke volumes to provide a 10-year direction for New Zealand stroke services. N Z Med J. 2018;131(1477):15-28.

5. Hogan S, Siddharth P. The social and economic costs of stroke in New Zealand: NZIER report to the Stroke Foundation. 2020.

6. Feigin VL, Krishnamurthi RV, Barker-Collo S, McPherson KM, Barber PA, Parag V, et al. 30-Year Trends in Stroke Rates and Outcome in Auckland, New Zealand (1981-2012): A Multi-Ethnic Population-Based Series of Studies. Plos One. 2015;10(8).

7. Thompson SG, Barber PA, Gommans JH, Cadilhac DA, Davis A, Fink JN, et al. The impact of ethnicity on stroke care access and patient outcomes: a New Zealand nationwide observational study. Lancet Reg Health West Pac. 2022;20:100358.

8. Feigin V, Norrving B, Sudlow CLM, Sacco RL. Updated Criteria for Population-Based Stroke and Transient Ischemic Attack Incidence Studies for the 21st Century. Stroke. 2018;49(9):2248-55.

9. Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis. Pathophysiology. 2010;17(3):197-218.

10. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337(8756):1521-6.

11. Mead GE, Lewis SC, Wardlaw JM, Dennis MS, Warlow CP. How well does the Oxfordshire community stroke project classification predict the site and size of the infarct on brain imaging? J Neurol Neurosurg Psychiatry. 2000;68(5):558-62.

12. Asdaghi N, Jeerakathil T, Hameed B, Saini M, McCombe JA, Shuaib A, et al. Oxfordshire community stroke project classification poorly differentiates small cortical and subcortical infarcts. Stroke. 2011;42(8):2143-8.

13. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. JAMA. 2000;284(22):2901-6.

14. Amarenco P, Lavallee PC, Monteiro Tavares L, Labreuche J, Albers GW, Abboud H, et al. Five-Year Risk of Stroke after TIA or Minor Ischemic Stroke. N Engl J Med. 2018;378(23):2182-90.

15. European Stroke Organisation Executive C, Committee ESOW. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis. 2008;25(5):457-507.

16. Aronowski J, Zhao X. Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. Stroke. 2011;42(6):1781-6.

17. Prabhakaran S, Naidech AM. Ischemic brain injury after intracerebral hemorrhage: a critical review. Stroke. 2012;43(8):2258-63.

18. Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. Lancet Neurol. 2012;11(8):720-31.

19. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(7):2160-236.

20. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-67.

21. Joffres M, Falaschetti E, Gillespie C, Robitaille C, Loustalot F, Poulter N, et al. Hypertension prevalence, awareness, treatment and control in national surveys from England, the USA and Canada, and correlation with stroke and ischaemic heart disease mortality: a cross-sectional study. BMJ Open. 2013;3(8):e003423.

22. Raji YR, Abiona T, Gureje O. Awareness of hypertension and its impact on blood pressure control among elderly nigerians: report from the Ibadan study of aging. Pan Afr Med J. 2017;27:190.

23. Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet. 2017;390(10112):2549-58.

24. Yaghi S, Elkind MS. Lipids and Cerebrovascular Disease: Research and Practice. Stroke. 2015;46(11):3322-8.

25. Ivanovic B, Tadic M. Hypercholesterolemia and Hypertension: Two Sides of the Same Coin. Am J Cardiovasc Drugs. 2015;15(6):403-14.

26. Chen R, Ovbiagele B, Feng W. Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. Am J Med Sci. 2016;351(4):380-6.

27. Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S. Diabetes 2030: Insights from Yesterday, Today, and Future Trends. Popul Health Manag. 2017;20(1):6-12.

28. Fan D, Li L, Li Z, Zhang Y, Ma X, Wu L, et al. Effect of hyperlipidemia on the incidence of cardio-cerebrovascular events in patients with type 2 diabetes. Lipids Health Dis. 2018;17(1):102.

29. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. Expert Rev Cardiovasc Ther. 2010;8(7):917-32.

30. Kopin L, Lowenstein C. Dyslipidemia. Ann Intern Med. 2017;167(11):Itc81-Itc95.

31. Wu YL, Ding YP, Tanaka Y, Zhang W. Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention. Int J Med Sci. 2014;11(11):1185-200.

32. Bilano V, Gilmour S, Moffiet T, d'Espaignet ET, Stevens GA, Commar A, et al. Global trends and projections for tobacco use, 1990-2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control. Lancet. 2015;385(9972):966-76.

33. Romero JR, Morris J, Pikula A. Stroke prevention: modifying risk factors. Ther Adv Cardiovasc Dis. 2008;2(4):287-303.

34. Jiang SZ, Lu W, Zong XF, Ruan HY, Liu Y. Obesity and hypertension. Exp Ther Med. 2016;12(4):2395-9.

35. Larsson SC, Wallin A, Wolk A, Markus HS. Differing association of alcohol consumption with different stroke types: a systematic review and meta-analysis. BMC Med. 2016;14(1):178.

36. Klatsky AL, Tran HN. Alcohol and stroke: the splitters win again. BMC Med. 2016;14(1):193.

37. Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology. 2012;79(17):1781-7.

38. Li C, Baek J, Sanchez BN, Morgenstern LB, Lisabeth LD. Temporal trends in age at ischemic stroke onset by ethnicity. Ann Epidemiol. 2018;28(10):686-90 e2.

39. Jolink WM, Klijn CJ, Brouwers PJ, Kappelle LJ, Vaartjes I. Time trends in incidence, case fatality, and mortality of intracerebral hemorrhage. Neurology. 2015;85(15):1318-24.

40. Stein M, Misselwitz B, Hamann GF, Scharbrodt W, Schummer DI, Oertel MF. Intracerebral hemorrhage in the very old: future demographic trends of an aging population. Stroke. 2012;43(4):1126-8.

41. Girijala RL, Sohrabji F, Bush RL. Sex differences in stroke: Review of current knowledge and evidence. Vasc Med. 2017;22(2):135-45.

42. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018;137(12):e67-e492.

43. Ministry of Health. Mortality and Demographic Data 20112014.

44. Khan NA, McAlister FA, Pilote L, Palepu A, Quan H, Hill MD, et al. Temporal trends in stroke incidence in South Asian, Chinese and white patients: A population based analysis. PLoS One. 2017;12(5):e0175556.

45. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91(1):288-94.

46. Frangione B, Revesz T, Vidal R, Holton J, Lashley T, Houlden H, et al. Familial cerebral amyloid angiopathy related to stroke and dementia. Amyloid. 2001;8 Suppl 1:36-42.

47. Heeley EL, Wei JW, Carter K, Islam MS, Thrift AG, Hankey GJ, et al. Socioeconomic disparities in stroke rates and outcome: pooled analysis of stroke incidence studies in Australia and New Zealand. Med J Aust. 2011;195(1):10-4.

48. Ministry of Health. Tatau Kahukura: Māori Health Chart Book 2015. 3rd Edition ed. Wellington: Ministry of Health; 2015.

49. Ministry of Health. Mortality: Historical Summary 1948-2015. Wellington, New Zealand; 2018.

50. Feigin VL, Barker-Collo S, Parag V, Senior H, Lawes CM, Ratnasabapathy Y, et al. Auckland Stroke Outcomes Study. Part 1: Gender, stroke types, ethnicity, and functional outcomes 5 years poststroke. Neurology. 2010;75(18):1597-607.

51. Ministry of Health. Mātātuhi Tuawhenua: Health of Rural Māori 2012. Wellington: Ministry of Health; 2012.

52. Hammond G, Luke AA, Elson L, Towfighi A, Joynt Maddox KE. Urban-Rural Inequities in Acute Stroke Care and In-Hospital Mortality. Stroke. 2020;51(7):2131-8.

53. Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. Circ Res. 2017;120(3):439-48.

54. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. Stroke. 2014;45(1):315-53.

55. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol. 2007;6(2):182-7.

56. Yang Y, Shi YZ, Zhang N, Wang S, Ungvari GS, Ng CH, et al. The Disability Rate of 5-Year Post-Stroke and Its Correlation Factors: A National Survey in China. PLoS One. 2016;11(11):e0165341.

57. Jonsson AC, Delavaran H, Iwarsson S, Stahl A, Norrving B, Lindgren A. Functional status and patient-reported outcome 10 years after stroke: the Lund Stroke Register. Stroke. 2014;45(6):1784-90.

58. Sennfalt S, Norrving B, Petersson J, Ullberg T. Long-Term Survival and Function After Stroke. Stroke. 2018:STROKEAHA118022913.

59. Geyh S, Cieza A, Schouten J, Dickson H, Frommelt P, Omar Z, et al. ICF Core Sets for stroke. J Rehabil Med. 2004(44 Suppl):135-41.

60. Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensation" mean in patients following stroke? Neurorehabil Neural Repair. 2009;23(4):313-9.

61. Pain LM, Baker R, Richardson D, Agur AM. Effect of trunk-restraint training on function and compensatory trunk, shoulder and elbow patterns during post-stroke reach: a systematic review. Disabil Rehabil. 2015;37(7):553-62.

62. Martin JH. The corticospinal system: from development to motor control. Neuroscientist. 2005;11(2):161-73.

63. Raghavan P. Upper Limb Motor Impairment After Stroke. Phys Med Rehabil Clin N Am. 2015;26(4):599-610.

64. Veerbeek JM, Kwakkel G, van Wegen EE, Ket JC, Heymans MW. Early prediction of outcome of activities of daily living after stroke: a systematic review. Stroke. 2011;42(5):1482-8.

65. Ekstrand E, Rylander L, Lexell J, Brogardh C. Perceived ability to perform daily hand activities after stroke and associated factors: a cross-sectional study. BMC Neurol. 2016;16(1):208.

66. Simpson LA, Hayward KS, McPeake M, Field TS, Eng JJ. Challenges of Estimating Accurate Prevalence of Arm Weakness Early After Stroke. Neurorehabil Neural Repair. 2021:15459683211028240.

67. Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil. 1994;75(4):394-8.

68. Held JPO, van Duinen J, Luft AR, Veerbeek JM. Eligibility Screening for an Early Upper Limb Stroke Rehabilitation Study. Front Neurol. 2019;10:683.

69. Persson HC, Parziali M, Danielsson A, Sunnerhagen KS. Outcome and upper extremity function within 72 hours after first occasion of stroke in an unselected population at a stroke unit. A part of the SALGOT study. BMC Neurol. 2012;12:162.

70. Bernhardt J, Hayward KS, Kwakkel G, Ward NS, Wolf SL, Borschmann K, et al. Agreed Definitions and a Shared Vision for New Standards in Stroke Recovery Research: The Stroke Recovery and Rehabilitation Roundtable Taskforce. Neurorehabil Neural Repair. 2017;31(9):793-9.

71. Byblow WD, Stinear CM, Barber PA, Petoe MA, Ackerley SJ. Proportional recovery after stroke depends on corticomotor integrity. Ann Neurol. 2015;78(6):848-59.

72. Borschmann KN, Hayward KS. Recovery of upper limb function is greatest early after stroke but does continue to improve during the chronic phase: a two-year, observational study. Physiotherapy. 2020;107:216-23.

73. Ballester BR, Maier M, Duff A, Cameirao M, Bermudez S, Duarte E, et al. A critical time window for recovery extends beyond one-year post-stroke. Journal of neurophysiology. 2019;122(1):350-7.

74. Smith MC, Ackerley SJ, Barber PA, Byblow WD, Stinear CM. PREP2 Algorithm Predictions Are Correct at 2 Years Poststroke for Most Patients. Neurorehabil Neural Repair. 2019;33(8):635-42.

75. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. Nat Rev Neurosci. 2009;10(12):861-72.

76. Lin DJ, Cloutier AM, Erler KS, Cassidy JM, Snider SB, Ranford J, et al. Corticospinal Tract Injury Estimated From Acute Stroke Imaging Predicts Upper Extremity Motor Recovery After Stroke. Stroke. 2019;50(12):3569-77.

77. Stinear CM, Byblow WD, Ackerley SJ, Smith MC, Borges VM, Barber PA. PREP2: A biomarker-based algorithm for predicting upper limb function after stroke. Ann Clin Transl Neurol. 2017;4(11):811-20.

78. Waddell KJ, Strube MJ, Tabak RG, Haire-Joshu D, Lang CE. Upper Limb Performance in Daily Life Improves Over the First 12 Weeks Poststroke. Neurorehabil Neural Repair. 2019:1545968319868716.

79. Regterschot GRH, Bussmann JBJ, Fanchamps MHJ, Meskers CGM, Ribbers GM, Selles RW. Objectively measured arm use in daily life improves during the first 6 months poststroke: a longitudinal observational cohort study. J Neuroeng Rehabil. 2021;18(1):51.

80. Rand D, Eng JJ. Predicting daily use of the affected upper extremity 1 year after stroke. J Stroke Cerebrovasc Dis. 2015;24(2):274-83.

81. Lang CE, Waddell KJ, Barth J, Holleran CL, Strube MJ, Bland MD. Upper Limb Performance in Daily Life Approaches Plateau Around Three to Six Weeks Post-stroke. Neurorehabil Neural Repair. 2021;35(10):903-14.

82. Hoonhorst MH, Nijland RH, van den Berg JS, Emmelot CH, Kollen BJ, Kwakkel G. How Do Fugl-Meyer Arm Motor Scores Relate to Dexterity According to the Action Research Arm Test at 6 Months Poststroke? Arch Phys Med Rehab. 2015;96(10):1845-9.

83. Bertrand AM, Fournier K, Wick Brasey MG, Kaiser ML, Frischknecht R, Diserens K. Reliability of maximal grip strength measurements and grip strength recovery following a stroke. J Hand Ther. 2015;28(4):356-62; quiz 63.

84. Cruz EG, Waldinger HC, Kamper DG. Kinetic and kinematic workspaces of the index finger following stroke. Brain. 2005;128(Pt 5):1112-21.

85. Lang CE, Schieber MH. Reduced muscle selectivity during individuated finger movements in humans after damage to the motor cortex or corticospinal tract. Journal of neurophysiology. 2004;91(4):1722-33.

86. McMorland AJ, Runnalls KD, Byblow WD. A neuroanatomical framework for upper limb synergies after stroke. Front Hum Neurosci. 2015;9:82.

87. Yang CL, Creath RA, Magder L, Rogers MW, McCombe Waller S. Impaired posture, movement preparation, and execution during both paretic and nonparetic reaching following stroke. Journal of neurophysiology. 2019.

88. Opheim A, Danielsson A, Alt Murphy M, Persson HC, Sunnerhagen KS. Upper-limb spasticity during the first year after stroke: stroke arm longitudinal study at the University of Gothenburg. Am J Phys Med Rehabil. 2014;93(10):884-96.

89. Nijland RH, van Wegen EE, Harmeling-van der Wel BC, Kwakkel G, Early Prediction of Functional Outcome After Stroke I. Accuracy of physical therapists' early predictions of upper-limb function in hospital stroke units: the EPOS Study. Phys Ther. 2013;93(4):460-9.

90. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. Stroke. 2003;34(9):2181-6.

91. Haaland KY, Mutha PK, Rinehart JK, Daniels M, Cushnyr B, Adair JC. Relationship between arm usage and instrumental activities of daily living after unilateral stroke. Arch Phys Med Rehabil. 2012;93(11):1957-62.

92. Vega-Gonzalez A, Granat MH. Continuous monitoring of upper-limb activity in a free-living environment. Arch Phys Med Rehabil. 2005;86(3):541-8.

93. van der Pas SC, Verbunt JA, Breukelaar DE, van Woerden R, Seelen HA. Assessment of arm activity using triaxial accelerometry in patients with a stroke. Arch Phys Med Rehabil. 2011;92(9):1437-42.

94. Lum PS, Shu LQ, Bochniewicz EM, Tran T, Chang LC, Barth J, et al. Improving Accelerometry-Based Measurement of Functional Use of the Upper Extremity After Stroke: Machine Learning Versus Counts Threshold Method. Neurorehab Neural Re. 2020;34(12):1078-87.

95. Yang CL, Liu J, Simpson LA, Menon C, Eng JJ. Real-World Functional Grasping Activity in Individuals With Stroke and Healthy Controls Using a Novel Wearable Wrist Sensor. Neurorehabil Neural Repair. 2021;35(10):929-37.

96. Mani S, Przybyla A, Good DC, Haaland KY, Sainburg RL. Contralesional Arm Preference Depends on Hemisphere of Damage and Target Location in Unilateral Stroke Patients. Neurorehabil Neural Repair. 2014;28(6):584-93.

97. Tyryshkin K, Coderre AM, Glasgow JI, Herter TM, Bagg SD, Dukelow SP, et al. A robotic object hitting task to quantify sensorimotor impairments in participants with stroke. J Neuroeng Rehabil. 2014;11:47.

98. Buxbaum LJ, Varghese R, Stoll H, Winstein CJ. Predictors of Arm Nonuse in Chronic Stroke: A Preliminary Investigation. Neurorehabil Neural Repair. 2020;34(6):512-22.

99. Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys. 2006;42(3):241-56.

100. Leuenberger K, Gonzenbach R, Wachter S, Luft A, Gassert R. A method to qualitatively assess arm use in stroke survivors in the home environment. Med Biol Eng Comput. 2017;55(1):141-50.

101. Bhatnagar K, Bever CT, Tian J, Zhan M, Conroy SS. Comparing Home Upper Extremity Activity with Clinical Evaluations of Arm Function in Chronic Stroke. Arch Rehabil Res Clin Transl. 2020;2(2).

102. Noskin O, Krakauer JW, Lazar RM, Festa JR, Handy C, O'Brien KA, et al. Ipsilateral motor dysfunction from unilateral stroke: implications for the functional neuroanatomy of hemiparesis. J Neurol Neurosurg Psychiatry. 2008;79(4):401-6.

103. Semrau JA, Herter TM, Kenzie JM, Findlater SE, Scott SH, Dukelow SP. Robotic Characterization of Ipsilesional Motor Function in Subacute Stroke. Neurorehabil Neural Repair. 2017;31(6):571-82.

104. Morris JH, Van Wijck F. Responses of the less affected arm to bilateral upper limb task training in early rehabilitation after stroke: a randomized controlled trial. Arch Phys Med Rehabil. 2012;93(7):1129-37.

105. Metrot J, Froger J, Hauret I, Mottet D, van Dokkum L, Laffont I. Motor recovery of the ipsilesional upper limb in subacute stroke. Arch Phys Med Rehabil. 2013;94(11):2283-90.

106. Hmaied Assadi S, Barel H, Dudkiewicz I, Gross-Nevo RF, Rand D. Less-Affected Hand Function Is Associated With Independence in Daily Living: A Longitudinal Study Poststroke. Stroke. 2021:STROKEAHA121034478.

107. Jung HY, Yoon JS, Park BS. Recovery of proximal and distal arm weakness in the ipsilateral upper limb after stroke. NeuroRehabilitation. 2002;17(2):153-9.

108. Bustren EL, Sunnerhagen KS, Alt Murphy M. Movement Kinematics of the Ipsilesional Upper Extremity in Persons With Moderate or Mild Stroke. Neurorehabil Neural Repair. 2017;31(4):376-86.

109. Maenza C, Good DC, Winstein CJ, Wagstaff DA, Sainburg RL. Functional Deficits in the Less-Impaired Arm of Stroke Survivors Depend on Hemisphere of Damage and Extent of Paretic Arm Impairment. Neurorehabil Neural Repair. 2020;34(1):39-50.

110. Pandian S, Arya KN. Motor impairment of the ipsilesional body side in poststroke subjects. J Bodyw Mov Ther. 2013;17(4):495-503.

111. Johnson BP, Westlake KP. Chronic Poststroke Deficits in Gross and Fine Motor Control of the Ipsilesional Upper Limb. Am J Phys Med Rehabil. 2021;100(4):345-8.

112. Schaefer SY, Haaland KY, Sainburg RL. Ipsilesional motor deficits following stroke reflect hemispheric specializations for movement control. Brain. 2007;130(Pt 8):2146-58.

113. Jayasinghe SAL, Good D, Wagstaff DA, Winstein C, Sainburg RL. Motor Deficits in the Ipsilesional Arm of Severely Paretic Stroke Survivors Correlate With Functional Independence in Left, but Not Right Hemisphere Damage. Front Hum Neurosci. 2020;14:599220.

114. de Kovel CGF, Carrion-Castillo A, Francks C. A large-scale population study of early life factors influencing left-handedness. Sci Rep. 2019;9(1):584.

115. Sainburg RL. Handedness: differential specializations for control of trajectory and position. Exerc Sport Sci Rev. 2005;33(4):206-13.

116. Varghese R, Winstein CJ. Relationship Between Motor Capacity of the Contralesional and Ipsilesional Hand Depends on the Side of Stroke in Chronic Stroke Survivors With Mild-to-Moderate Impairment. Front Neurol. 2019;10:1340.

117. Lee YM, Lee S, Uhm KE, Kurillo G, Han JJ, Lee J. Upper Limb Three-Dimensional Reachable Workspace Analysis Using the Kinect Sensor in Hemiplegic Stroke Patients: A Cross-Sectional Observational Study. Am J Phys Med Rehabil. 2020;99(5):397-403.

118. Kim J, Sin M, Kim WS, Min YS, Kim W, Park D, et al. Remote Assessment of Post-Stroke Elbow Function Using Internet-Based Telerobotics: A Proof-of-Concept Study. Front Neurol. 2020;11:583101.

119. Kim WS, Cho S, Baek D, Bang H, Paik NJ. Upper Extremity Functional Evaluation by Fugl-Meyer Assessment Scoring Using Depth-Sensing Camera in Hemiplegic Stroke Patients. PLoS One. 2016;11(7):e0158640.

120. Song X, Chen S, Jia J, Shull PB. Cellphone-Based Automated Fugl-Meyer Assessment to Evaluate Upper Extremity Motor Function After Stroke. IEEE Trans Neural Syst Rehabil Eng. 2019;27(10):2186-95.

121. Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurol. 2009;8(8):741-54.

122. Kwakkel G, Lannin NA, Borschmann K, English C, Ali M, Churilov L, et al. Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. Int J Stroke. 2017;12(5):451-61.

123. Garcia Alvarez A, Roby-Brami A, Robertson J, Roche N. Functional classification of grasp strategies used by hemiplegic patients. PLoS One. 2017;12(11):e0187608.

124. Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. Brain. 2012;135(Pt 8):2527-35.

125. Lundquist CB, Nielsen JF, Arguissain FG, Brunner IC. Accuracy of the Upper Limb Prediction Algorithm PREP2 Applied 2 Weeks Poststroke: A Prospective Longitudinal Study. Neurorehabil Neural Repair. 2021;35(1):68-78.

126. Stinear CM, Petoe MA, Anwar S, Barber PA, Byblow WD. Bilateral priming accelerates recovery of upper limb function after stroke: a randomized controlled trial. Stroke. 2014;45(1):205-10.

127. Stinear CM, Byblow WD, Ackerley SJ, Barber PA, Smith MC. Predicting Recovery Potential for Individual Stroke Patients Increases Rehabilitation Efficiency. Stroke. 2017;48(4):1011-9.

128. Cirillo J, Mooney RA, Ackerley SJ, Barber PA, Borges VM, Clarkson AN, et al. Neurochemical balance and inhibition at the sub-acute stage after stroke. Journal of neurophysiology. 2020.

129. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. 2016;6(11):e012799.

130. Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the action research arm test. Neurorehabil Neural Repair. 2008;22(1):78-90.

131. Van der Lee JH, De Groot V, Beckerman H, Wagenaar RC, Lankhorst GJ, Bouter LM. The intra- and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke. Arch Phys Med Rehabil. 2001;82(1):14-9.

132. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int J Rehabil Res. 1981;4(4):483-92.

133. Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012;98(9):683-90.

134. Koh CL, Hsueh IP, Wang WC, Sheu CF, Yu TY, Wang CH, et al. Validation of the action research arm test using item response theory in patients after stroke. J Rehabil Med. 2006;38(6):375-80.

135. Chen H-F, Lin K-C, Wu C-Y, Chen C-L. Rasch Validation and Predictive Validity of the Action Research Arm Test in Patients Receiving Stroke Rehabilitation. Arch Phys Med Rehab. 2012;93(6):1039-45.

136. Kwakkel G, Winters C, van Wegen EE, Nijland RH, van Kuijk AA, Visser-Meily A, et al. Effects of Unilateral Upper Limb Training in Two Distinct Prognostic Groups Early After Stroke: The EXPLICIT-Stroke Randomized Clinical Trial. Neurorehabil Neural Repair. 2016;30(9):804-16.

137. Brunner I, Skouen JS, Hofstad H, Assmus J, Becker F, Sanders AM, et al. Virtual Reality Training for Upper Extremity in Subacute Stroke (VIRTUES): A multicenter RCT. Neurology. 2017;89(24):2413-21.

138. van Delden AL, Peper CL, Nienhuys KN, Zijp NI, Beek PJ, Kwakkel G. Unilateral versus bilateral upper limb training after stroke: the Upper Limb Training After Stroke clinical trial. Stroke. 2013;44(9):2613-6.

139. Rodgers H, Bosomworth H, Krebs HI, van Wijck F, Howel D, Wilson N, et al. Robot assisted training for the upper limb after stroke (RATULS): a multicentre randomised controlled trial. Lancet. 2019;394(10192):51-62.

140. Remsik AB, Dodd K, Williams L, Jr., Thoma J, Jacobson T, Allen JD, et al. Behavioral Outcomes Following Brain-Computer Interface Intervention for Upper Extremity Rehabilitation in Stroke: A Randomized Controlled Trial. Front Neurosci. 2018;12:752.

141. Remsik AB, Williams L, Gjini K, Dodd K, Thomats J, Jacobson T, et al. Ipsilesional Mu Rhythm Desynchronization and Changes in Motor Behavior Following Post Stroke BCI Intervention for Motor Rehabilitation. Front Neurosci-Switz. 2019;13.

142. Moons KG, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart. 2012;98(9):691-8.

143. Barth J, Waddell KJ, Bland MD, Lang CE. Accuracy of an Algorithm in Predicting Upper Limb Functional Capacity in a United States Population. Arch Phys Med Rehabil. 2022;103(1):44-51.

144. Duncan PW, Bernhardt J. Telerehabilitation: Has Its Time Come? Stroke. 2021;52(8):2694-6.

145. Sullivan KJ, Tilson JK, Cen SY, Rose DK, Hershberg J, Correa A, et al. Fugl-Meyer assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. Stroke. 2011;42(2):427-32.

146. Veale JF. Edinburgh Handedness Inventory - Short Form: a revised version based on confirmatory factor analysis. Laterality. 2014;19(2):164-77.

147. Jordan HT, Che J, Byblow WD, Stinear CM. Fast Outcome Categorization of the Upper Limb After Stroke. Stroke. 2021:STROKEAHA121035170.

148. Zonjee VJ, Selles RW, Roorda LD, Nijland RH, van der Oest MJW, Bosomworth HJ, et al. Reducing the number of test items of the Action Research Arm Test post stroke: A decision tree analysis. Arch Phys Med Rehabil. 2022.

149. Ramspek CL, Jager KJ, Dekker FW, Zoccali C, van Diepen M. External validation of prognostic models: what, why, how, when and where? Clin Kidney J. 2021;14(1):49-58.

150. Yao K, Sternad D, Billard A. Hand Pose Selection in a Bimanual Fine-Manipulation Task. Journal of neurophysiology. 2021.

151. Kantak S, Jax S, Wittenberg G. Bimanual coordination: A missing piece of arm rehabilitation after stroke. Restor Neurol Neurosci. 2017;35(4):347-64.

152. Woytowicz E, Whitall J, Westlake KP. Age-related changes in bilateral upper extremity coordination. Curr Geriatr Rep. 2016;5(3):191-9.

153. Duque J, Davare M, Delaunay L, Jacob B, Saur R, Hummel F, et al. Monitoring coordination during bimanual movements: where is the mastermind? J Cogn Neurosci. 2010;22(3):526-42.

154. Liao WW, Whitall J, Barton JE, McCombe Waller S. Neural motor control differs between bimanual common-goal vs. bimanual dual-goal tasks. Exp Brain Res. 2018;236(6):1789-800.

155. Wolf A, Scheiderer R, Napolitan N, Belden C, Shaub L, Whitford M. Efficacy and task structure of bimanual training post stroke: a systematic review. Top Stroke Rehabil. 2014;21(3):181-96.

156. Kim RK, Kang N. Bimanual Coordination Functions between Paretic and Nonparetic Arms: A Systematic Review and Meta-analysis. J Stroke Cerebrovasc Dis. 2020;29(2):104544.

157. Schrafl-Altermatt M, Dietz V. Cooperative hand movements in post-stroke subjects: Neural reorganization. Clin Neurophysiol. 2016;127(1):748-54.

158. Stone KD, Bryant DC, Gonzalez CLR. Hand use for grasping in a bimanual task: evidence for different roles? Experimental Brain Research. 2013;224(3):455-67.

159. Aramaki Y, Osu R, Sadato N. Resource-demanding versus cost-effective bimanual interaction in the brain. Exp Brain Res. 2010;203(2):407-18.

160. Perez MA, Butler JE, Taylor JL. Modulation of transcallosal inhibition by bilateral activation of agonist and antagonist proximal arm muscles. Journal of neurophysiology. 2014;111(2):405-14.

161. Lewis GN, Byblow WD. Bimanual coordination dynamics in poststroke hemiparetics. J Mot Behav. 2004;36(2):174-88.

162. David A, ReethaJanetSureka S, Gayathri S, Annamalai SJ, Samuelkamleshkumar S, Kuruvilla A, et al. Quantification of the relative arm use in patients with hemiparesis using inertial measurement units. J Rehabil Assist Technol Eng. 2021;8:20556683211019694.

163. Blinch J, de Cellio Martins G, Chua R. Effects of integrated feedback on discrete bimanual movements in choice reaction time. Exp Brain Res. 2017;235(1):247-57.

164. Blinch J, Cameron BD, Franks IM, Carpenter MG, Chua R. Facilitation and interference during the preparation of bimanual movements: contributions from starting locations, movement amplitudes, and target locations. Psychol Res. 2015;79(6):978-88.

165. Diedrichsen J. Optimal task-dependent changes of bimanual feedback control and adaptation. Current biology : CB. 2007;17(19):1675-9.

166. Mutha PK, Sainburg RL. Shared bimanual tasks elicit bimanual reflexes during movement. Journal of neurophysiology. 2009;102(6):3142-55.

167. Schaffer JE, Sainburg RL. Interlimb Responses to Perturbations of Bilateral Movements are Asymmetric. J Mot Behav. 2021;53(2):217-33.

168. Kantak S, Zahedi N, McGrath RL. Task-Dependent Bimanual Coordination After Stroke: Relationship With Sensorimotor Impairments. Arch Phys Med Rehabil. 2016;97(5):798-806.

169. Swinnen SP, Gooijers J. Bimanual Coordination. In: Brain Mapping: An Encyclopedic Reference Vol. 2: Academic Press: Elsevier; 2015.

170. Kermadi I, Liu Y, Tempini A, Calciati E, Rouiller EM. Neuronal activity in the primate supplementary motor area and the primary motor cortex in relation to spatio-temporal bimanual coordination. Somatosens Mot Res. 1998;15(4):287-308.

171. Donchin O, Gribova A, Steinberg O, Bergman H, Vaadia E. Primary motor cortex is involved in bimanual coordination. Nature. 1998;395(6699):274-8.

172. Schott GD. Penfield's homunculus: a note on cerebral cartography. J Neurol Neurosurg Psychiatry. 1993;56(4):329-33.

173. Luppino G, Matelli M, Camarda R, Rizzolatti G. Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. J Comp Neurol. 1993;338(1):114-40.

174. Cona G, Semenza C. Supplementary motor area as key structure for domain-general sequence processing: A unified account. Neurosci Biobehav Rev. 2017;72:28-42.

175. Chan JL, Ross ED. Left-handed mirror writing following right anterior cerebral artery infarction: evidence for nonmirror transformation of motor programs by right supplementary motor area. Neurology. 1988;38(1):59-63.

176. Laplane D, Talairach J, Meininger V, Bancaud J, Orgogozo JM. Clinical consequences of corticectomies involving the supplementary motor area in man. J Neurol Sci. 1977;34(3):301-14.

177. Kraft E, Chen AW, Flaherty AW, Blood AJ, Kwong KK, Jenkins BG. The role of the basal ganglia in bimanual coordination. Brain Res. 2007;1151:62-73.

178. Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP. Cerebellar and premotor function in bimanual coordination: parametric neural responses to spatiotemporal complexity and cycling frequency. Neuroimage. 2004;21(4):1416-27.

179. Luppino G, Rozzi S, Calzavara R, Matelli M. Prefrontal and agranular cingulate projections to the dorsal premotor areas F2 and F7 in the macaque monkey. Eur J Neurosci. 2003;17(3):559-78.

180. Burman KJ, Bakola S, Richardson KE, Reser DH, Rosa MG. Patterns of afferent input to the caudal and rostral areas of the dorsal premotor cortex (6DC and 6DR) in the marmoset monkey. J Comp Neurol. 2014;522(16):3683-716.

181. Verstraelen S, van Dun K, Depestele S, Van Hoornweder S, Jamil A, Ghasemian-Shirvan E, et al. Dissociating the causal role of left and right dorsal premotor cortices in planning and executing bimanual movements - A neuro-navigated rTMS study. Brain Stimul. 2021;14(2):423-34.

182. van den Berg FE, Swinnen SP, Wenderoth N. Hemispheric asymmetries of the premotor cortex are task specific as revealed by disruptive TMS during bimanual versus unimanual movements. Cereb Cortex. 2010;20(12):2842-51.

183. Fujiyama H, Van Soom J, Rens G, Cuypers K, Heise KF, Levin O, et al. Performing two different actions simultaneously: The critical role of interhemispheric interactions during the preparation of bimanual movement. Cortex. 2016;77:141-54.

184. Manto M, Bower JM, Conforto AB, Delgado-Garcia JM, da Guarda SN, Gerwig M, et al. Consensus paper: roles of the cerebellum in motor control--the diversity of ideas on cerebellar involvement in movement. Cerebellum. 2012;11(2):457-87.

185. Welniarz Q, Worbe Y, Gallea C. The Forward Model: A Unifying Theory for the Role of the Cerebellum in Motor Control and Sense of Agency. Front Syst Neurosci. 2021;15:644059.

186. Palesi F, De Rinaldis A, Castellazzi G, Calamante F, Muhlert N, Chard D, et al. Contralateral cortico-ponto-cerebellar pathways reconstruction in humans in vivo: implications for reciprocal cerebro-cerebellar structural connectivity in motor and non-motor areas. Sci Rep. 2017;7(1):12841.

187. Palesi F, Tournier JD, Calamante F, Muhlert N, Castellazzi G, Chard D, et al. Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo. Brain Struct Funct. 2015;220(6):3369-84.

188. Goldstein A, Covington BP, Mahabadi N, Mesfin FB. Neuroanatomy, Corpus Callosum. In: StatPearls. Treasure Island (FL)2021.

189. Bonzano L, Tacchino A, Roccatagliata L, Abbruzzese G, Mancardi GL, Bove M. Callosal contributions to simultaneous bimanual finger movements. J Neurosci. 2008;28(12):3227-33.

190. Serrien DJ, Nirkko AC, Wiesendanger M. Role of the corpus callosum in bimanual coordination: a comparison of patients with congenital and acquired callosal damage. Eur J Neurosci. 2001;14(11):1897-905.

191. Kennerley SW, Diedrichsen J, Hazeltine E, Semjen A, Ivry RB. Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. Nature neuroscience. 2002;5(4):376-81.

192. Wolff PH, Kotwica K, Obregon M. The development of interlimb coordination during bimanual finger tapping. Int J Neurosci. 1998;93(1-2):7-27.

193. Muetzel RL, Collins PF, Mueller BA, A MS, Lim KO, Luciana M. The development of corpus callosum microstructure and associations with bimanual task performance in healthy adolescents. Neuroimage. 2008;39(4):1918-25.

194. Fagard J, Hardy-Leger I, Kervella C, Marks A. Changes in interhemispheric transfer rate and the development of bimanual coordination during childhood. J Exp Child Psychol. 2001;80(1):1-22.

195. Ruddy KL, Leemans A, Carson RG. Transcallosal connectivity of the human cortical motor network. Brain Struct Funct. 2017;222(3):1243-52.

196. Carson RG. Inter-hemispheric inhibition sculpts the output of neural circuits by co-opting the two cerebral hemispheres. J Physiol. 2020.

197. Calvert GHM, McMackin R, Carson RG. Probing interhemispheric dorsal premotor-primary motor cortex interactions with threshold hunting transcranial magnetic stimulation. Clin Neurophysiol. 2020;131(11):2551-60.

198. Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR. Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. Neuroimage. 2008;41(4):1382-94.

199. Seo JP, Jang SH. Different characteristics of the corticospinal tract according to the cerebral origin: DTI study. AJNR Am J Neuroradiol. 2013;34(7):1359-63.

200. Welniarz Q, Dusart I, Roze E. The corticospinal tract: Evolution, development, and human disorders. Dev Neurobiol. 2017;77(7):810-29.

201. Lemon RN, Griffiths J. Comparing the function of the corticospinal system in different species: organizational differences for motor specialization? Muscle Nerve. 2005;32(3):261-79.

202. Bradnam LV, Stinear CM, Byblow WD. Ipsilateral motor pathways after stroke: implications for non-invasive brain stimulation. Front Hum Neurosci. 2013;7:184.

203. Bawa P, Hamm JD, Dhillon P, Gross PA. Bilateral responses of upper limb muscles to transcranial magnetic stimulation in human subjects. Exp Brain Res. 2004;158(3):385-90.

204. Uehara K, Morishita T, Funase K. Excitability changes in the ipsilateral primary motor cortex during rhythmic contraction of finger muscles. Neurosci Lett. 2011;488(1):22-5.

205. Carson RG, Riek S, Mackey DC, Meichenbaum DP, Willms K, Forner M, et al. Excitability changes in human forearm corticospinal projections and spinal reflex pathways during rhythmic voluntary movement of the opposite limb. J Physiol. 2004;560(Pt 3):929-40.

206. Stinear CM, Walker KS, Byblow WD. Symmetric facilitation between motor cortices during contraction of ipsilateral hand muscles. Exp Brain Res. 2001;139(1):101-5.

207. Muellbacher W, Facchini S, Boroojerdi B, Hallett M. Changes in motor cortex excitability during ipsilateral hand muscle activation in humans. Clin Neurophysiol. 2000;111(2):344-9.

208. Ames KC, Churchland MM. Motor cortex signals for each arm are mixed across hemispheres and neurons yet partitioned within the population response. Elife. 2019;8.

209. Lemon RN. Descending Pathways in Motor Control. Annual Review of Neuroscience. 2008;31(1):195-218.

210. Brownstone RM, Chopek JW. Reticulospinal Systems for Tuning Motor Commands. Front Neural Circuits. 2018;12:30.

211. Honeycutt CF, Kharouta M, Perreault EJ. Evidence for reticulospinal contributions to coordinated finger movements in humans. Journal of neurophysiology. 2013;110(7):1476-83.

212. Maslovat D, Teku F, Smith V, Drummond NM, Carlsen AN. Bimanual but not unimanual finger movements are triggered by a startling acoustic stimulus: evidence for increased reticulospinal drive for bimanual responses. Journal of neurophysiology. 2020;124(6):1832-8.

213. Davidson AG, Schieber MH, Buford JA. Bilateral spike-triggered average effects in arm and shoulder muscles from the monkey pontomedullary reticular formation. J Neurosci. 2007;27(30):8053-8.

214. Davidson AG, Buford JA. Bilateral actions of the reticulospinal tract on arm and shoulder muscles in the monkey: stimulus triggered averaging. Exp Brain Res. 2006;173(1):25-39.

215. Bruton M, O'Dwyer N. Synergies in coordination: a comprehensive overview of neural, computational, and behavioral approaches. Journal of neurophysiology. 2018;120(6):2761-74.

216. Profeta VLS, Turvey MT. Bernstein's levels of movement construction: A contemporary perspective. Hum Mov Sci. 2018;57:111-33.

217. Shea CH, Boyle J, Kovacs AJ. Bimanual Fitts' tasks: Kelso, Southard, and Goodman, 1979 revisited. Exp Brain Res. 2012;216(1):113-21.

218. Haken H, Kelso JA, Bunz H. A theoretical model of phase transitions in human hand movements. Biol Cybern. 1985;51(5):347-56.

219. Zanone PG, Kelso JA. Evolution of behavioral attractors with learning: nonequilibrium phase transitions. J Exp Psychol Hum Percept Perform. 1992;18(2):403-21.

220. Fontaine RJ, Lee TD, Swinnen SP. Learning a new bimanual coordination pattern: Reciprocal influences of intrinsic and to-be-learned patterns. Can J Exp Psychol. 1997;51(1):1-9.

221. Swinnen SP. Intermanual coordination: from behavioural principles to neural-network interactions. Nat Rev Neurosci. 2002;3(5):348-59.

222. Cardoso de Oliveira S. The neuronal basis of bimanual coordination: recent neurophysiological evidence and functional models. Acta Psychol (Amst). 2002;110(2-3):139-59.

223. Cattaert D, Semjen A, Summers JJ. Simulating a neural cross-talk model for between-hand interference during bimanual circle drawing. Biol Cybern. 1999;81(4):343-58.

224. Aramaki Y, Honda M, Okada T, Sadato N. Neural correlates of the spontaneous phase transition during bimanual coordination. Cereb Cortex. 2006;16(9):1338-48.

225. Houweling S, Beek PJ, Daffertshofer A. Spectral changes of interhemispheric crosstalk during movement instabilities. Cereb Cortex. 2010;20(11):2605-13.

226. Hughes CM, Seegelke C, Reissig P. Problems in planning bimanually incongruent grasp postures relate to simultaneous response specification processes. Brain Cogn. 2014;87:22-9.

227. Maki Y, Wong KF, Sugiura M, Ozaki T, Sadato N. Asymmetric control mechanisms of bimanual coordination: an application of directed connectivity analysis to kinematic and functional MRI data. Neuroimage. 2008;42(4):1295-304.

228. Diedrichsen J, Shadmehr R, Ivry RB. The coordination of movement: optimal feedback control and beyond. Trends in cognitive sciences. 2010;14(1):31-9.

229. Scott SH. Optimal feedback control and the neural basis of volitional motor control. Nat Rev Neurosci. 2004;5(7):532-46.

230. van Dun K, Brinkmann P, Depestele S, Verstraelen S, Meesen R. Cerebellar Activation During Simple and Complex Bimanual Coordination: an Activation Likelihood Estimation (ALE) Meta-analysis. Cerebellum. 2021.

231. Serrien DJ, Ivry RB, Swinnen SP. Dynamics of hemispheric specialization and integration in the context of motor control. Nat Rev Neurosci. 2006;7(2):160-6.

232. Vuoksimaa E, Koskenvuo M, Rose RJ, Kaprio J. Origins of handedness: a nationwide study of 30,161 adults. Neuropsychologia. 2009;47(5):1294-301.

233. Peters M, Reimers S, Manning JT. Hand preference for writing and associations with selected demographic and behavioral variables in 255,100 subjects: the BBC internet study. Brain Cogn. 2006;62(2):177-89.

234. Gonzalez CL, Flindall JW, Stone KD. Hand preference across the lifespan: effects of end-goal, task nature, and object location. Frontiers in psychology. 2014;5:1579.

235. de Bruin N, Bryant DC, MacLean JN, Gonzalez CL. Assessing Visuospatial Abilities in Healthy Aging: A Novel Visuomotor Task. Front Aging Neurosci. 2016;8:7.

236. Gonzalez CL, Goodale MA. Hand preference for precision grasping predicts language lateralization. Neuropsychologia. 2009;47(14):3182-9.

237. Liang J, Wilkinson KM, Sainburg RL. Cognitive-perceptual load modulates hand selection in left-handers to a greater extent than in right-handers. Exp Brain Res. 2019;237(2):389-99.

238. Scharoun SM, Scanlan KA, Bryden PJ. Hand and Grasp Selection in a Preferential Reaching Task: The Effects of Object Location, Orientation, and Task Intention. Frontiers in psychology. 2016;7:360.

239. Pearce JM. Hugo Karl Liepmann and apraxia. Clin Med (Lond). 2009;9(5):466-70.

240. Amunts K, Schlaug G, Schleicher A, Steinmetz H, Dabringhaus A, Roland PE, et al. Asymmetry in the human motor cortex and handedness. Neuroimage. 1996;4(3 Pt 1):216-22.

241. Volkmann J, Schnitzler A, Witte OW, Freund H. Handedness and asymmetry of hand representation in human motor cortex. Journal of neurophysiology. 1998;79(4):2149-54.

242. Stinear JW, Byblow WD. An interhemispheric asymmetry in motor cortex disinhibition during bimanual movement. Brain Res. 2004;1022(1-2):81-7.

243. Serrien DJ, Cassidy MJ, Brown P. The importance of the dominant hemisphere in the organization of bimanual movements. Hum Brain Mapp. 2003;18(4):296-305.

244. Bagesteiro LB, Sainburg RL. Nondominant arm advantages in load compensation during rapid elbow joint movements. Journal of neurophysiology. 2003;90(3):1503-13.

245. Woytowicz EJ, Westlake KP, Whitall J, Sainburg RL. Handedness results from complementary hemispheric dominance, not global hemispheric dominance: evidence from mechanically coupled bilateral movements. Journal of neurophysiology. 2018;120(2):729-40.

246. Woytowicz EJ, Sainburg RL, Westlake KP, Whitall J. Competition for limited neural resources in older adults leads to greater asymmetry of bilateral movements than in young adults. Journal of neurophysiology. 2020;123(4):1295-304.

247. Sainburg RL, Duff SV. Does motor lateralization have implications for stroke rehabilitation? J Rehabil Res Dev. 2006;43(3):311-22.

248. Branco MP, De Boer LM, Ramsey NF, Vansteensel MJ. Encoding of kinetic and kinematic movement parameters in the sensorimotor cortex: A Brain-Computer Interface perspective. European Journal of Neuroscience. 2019;50(5):2755-72.

249. Carson RG, Thomas J, Summers JJ, Walters MR, Semjen A. The dynamics of bimanual circle drawing. Q J Exp Psychol-A. 1997;50(3):664-83.

250. Kelso JA. Phase transitions and critical behavior in human bimanual coordination. Am J Physiol. 1984;246(6 Pt 2):R1000-4.

251. Kelso JAS, Buchanan JJ, Deguzman GC, Ding M. Spontaneous Recruitment and Annihilation of Degrees of Freedom in Biological Coordination. Phys Lett A. 1993;179(4-5):364-71.

252. Byblow WD, Carson RG, Goodman D. Expressions of Asymmetries and Anchoring in Bimanual Coordination. Hum Movement Sci. 1994;13(1):3-28.

253. Byblow WD, Goodman D. Performance Asymmetries in Multifrequency Coordination. Hum Movement Sci. 1994;13(2):147-74.

254. Byblow WD, Bysouth-Young D, Summers JJ, Carson RG. Performance asymmetries and coupling dynamics in the acquisition of multifrequency bimanual coordination. Psychol Res-Psych Fo. 1998;61(1):56-70.

255. Peper CE, Beek PJ, Vanwieringen PCW. Multifrequency Coordination in Bimanual Tapping - Asymmetrical Coupling and Signs of Supercriticality. J Exp Psychol Human. 1995;21(5):1117-38.

256. Summers JJ, Ford SK, Todd JA. Practice Effects on the Coordination of the 2 Hands in a Bimanual Tapping Task. Hum Movement Sci. 1993;12(1-2):111-33.

257. Summers JJ, Rosenbaum DA, Burns BD, Ford SK. Production of Polyrhythms. J Exp Psychol Human. 1993;19(2):416-28.

258. Nomura Y, Jono Y, Tani K, Chujo Y, Hiraoka K. Corticospinal Modulations during Bimanual Movement with Different Relative Phases. Front Hum Neurosci. 2016;10:95.

259. Kovacs AJ, Wang Y, Kennedy DM. Accessing interpersonal and intrapersonal coordination dynamics. Experimental Brain Research. 2020;238(1):17-27.

260. Longo A, Meulenbroek R. Precision-Dependent Changes in Motor Variability During Sustained Bimanual Reaching. Motor Control. 2018;22(1):28-44.

261. Marteniuk RG, Mackenzie CL, Baba DM. Bimanual Movement Control - Information-Processing and Interaction Effects. Q J Exp Psychol-A. 1984;36(2):335-65.

262. Mason AH, Bruyn JL. Manual asymmetries in bimanual prehension tasks: manipulation of object size and object distance. Hum Mov Sci. 2009;28(1):48-73.

263. Miller KA, Smyth MM. Asynchrony in discrete bimanual aiming: evidence for visual strategies of coordination. Q J Exp Psychol (Hove). 2012;65(10):1911-26.

264. Wenderoth N, Bock O. Learning of a new bimanual coordination pattern is governed by three distinct processes. Motor Control. 2001;5(1):23-35.

265. Herth RA, Zhu Q, Bingham GP. The role of intentionality in the performance of a learned 90 degrees bimanual rhythmic coordination during frequency scaling: data and model. Exp Brain Res. 2021.

266. Howard IS, Ingram JN, Wolpert DM. Separate representations of dynamics in rhythmic and discrete movements: evidence from motor learning. Journal of neurophysiology. 2011;105(4):1722-31.

267. Levy-Tzedek S, Krebs HI, Song D, Hogan N, Poizner H. Non-monotonicity on a spatio-temporally defined cyclic task: evidence of two movement types? Exp Brain Res. 2010;202(4):733-46.

268. Kelso JA, Southard DL, Goodman D. On the coordination of two-handed movements. J Exp Psychol Hum Percept Perform. 1979;5(2):229-38.

269. Fitts PM. The information capacity of the human motor system in controlling the amplitude of movement. J Exp Psychol. 1954;47(6):381-91.

270. Riek S, Tresilian JR, Mon-Williams M, Coppard VL, Carson RG. Bimanual aiming and overt attention: one law for two hands. Exp Brain Res. 2003;153(1):59-75.

271. Sleimen-Malkoun R, Temprado J-J, Thefenne L, Berton E. Bimanual training in stroke: How do coupling and symmetry-breaking matter? BMC Neurology. 2011;11(1):11.

272. Byblow WD, Stinear CM, Smith MC, Bjerre L, Flaskager BK, McCambridge AB. Mirror symmetric bimanual movement priming can increase corticomotor excitability and enhance motor learning. PLoS One. 2012;7(3):e33882.

273. Matsuda T, Watanabe S, Kuruma H, Murakami Y, Watanabe R, Senou A. A Comparison of Three Bimanual Coordinations: An fMRI Study. J Phys Ther Sci. 2009;21(1):85-92.

274. Zehr EP, Collins DF, Frigon A, Hoogenboom N. Neural control of rhythmic human arm movement: phase dependence and task modulation of hoffmann reflexes in forearm muscles. Journal of neurophysiology. 2003;89(1):12-21.

275. Cunningham DA, Roelle SM, Allexandre D, Potter-Baker KA, Sankarasubramanian V, Knutson JS, et al. The effect of motor overflow on bimanual asymmetric force coordination. Experimental Brain Research. 2017;235(4):1097-105.

276. Kagerer FA, Summers JJ, Semjen A. Instabilities during antiphase bimanual movements: are ipsilateral pathways involved? Exp Brain Res. 2003;151(4):489-500.

277. Desrochers PC, Brunfeldt AT, Kagerer FA. Neurophysiological Correlates of Adaptation and Interference during Asymmetrical Bimanual Movements. Neuroscience. 2020;432:30-43.

278. Rokni U, Steinberg O, Vaadia E, Sompolinsky H. Cortical representation of bimanual movements. J Neurosci. 2003;23(37):11577-86.

279. Liuzzi G, Horniss V, Zimerman M, Gerloff C, Hummel FC. Coordination of uncoupled bimanual movements by strictly timed interhemispheric connectivity. J Neurosci. 2011;31(25):9111-7.

280. Diedrichsen J, Hazeltine E, Nurss WK, Ivry RB. The role of the corpus callosum in the coupling of bimanual isometric force pulses. Journal of neurophysiology. 2003;90(4):2409-18.

281. Halsband U, Ito N, Tanji J, Freund HJ. The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. Brain. 1993;116 (Pt 1):243-66.

282. Obhi SS, Haggard P, Taylor J, Pascual-Leone A. rTMS to the supplementary motor area disrupts bimanual coordination. Motor Control. 2002;6(4):319-32.

283. Steyvers M, Etoh S, Sauner D, Levin O, Siebner HR, Swinnen SP, et al. High-frequency transcranial magnetic stimulation of the supplementary motor area reduces bimanual coupling during anti-phase but not in-phase movements. Exp Brain Res. 2003;151(3):309-17.

284. Kazennikov O, Perrig S, Wiesendanger M. Kinematics of a coordinated goal-directed bimanual task. Behav Brain Res. 2002;134(1-2):83-91.

285. Perrig S, Kazennikov O, Wiesendanger M. Time structure of a goal-directed bimanual skill and its dependence on task constraints. Behav Brain Res. 1999;103(1):95-104.

286. Kantak S, McGrath R, Zahedi N. Goal conceptualization and symmetry of arm movements affect bimanual coordination in individuals after stroke. Neurosci Lett. 2016;626:86-93.

287. Diedrichsen J, Dowling N. Bimanual coordination as task-dependent linear control policies. Hum Movement Sci. 2009;28(3):334-47.

288. Howard IS, Ingram JN, Wolpert DM. Composition and Decomposition in Bimanual Dynamic Learning. Journal of Neuroscience. 2008;28(42):10531-40.

289. Abdollahi F, Kenyon RV, Patton JL. Mirror versus parallel bimanual reaching. J Neuroeng Rehabil. 2013;10:71.

290. Dimitriou M, Franklin DW, Wolpert DM. Task-dependent coordination of rapid bimanual motor responses. Journal of neurophysiology. 2012;107(3):890-901.

291. Dietz V, Macauda G, Schrafl-Altermatt M, Wirz M, Kloter E, Michels L. Neural coupling of cooperative hand movements: a reflex and fMRI study. Cereb Cortex. 2015;25(4):948-58.

292. Schrafl-Altermatt M, Easthope CS. Cooperative hand movements: task-dependent modulation of ipsi- and contralateral cortical control. Physiol Rep. 2018;6(10):e13581.

293. Schrafl-Altermatt M, Dietz V. Task-specific role of ipsilateral pathways: somatosensory evoked potentials during cooperative hand movements. Neuroreport. 2014;25(18):1429-32.

294. Dietz V, Schrafl-Altermatt M. Control of functional movements in healthy and post-stroke subjects: Role of neural interlimb coupling. Clin Neurophysiol. 2016;127(5):2286-93.

295. Schrafl-Altermatt M, Dietz V. Neural coupling of cooperative hand movements after stroke: role of ipsilateral afference. Ann Clin Transl Neurol. 2016;3(11):884-8.

296. Schrafl-Altermatt M, Jordan HT, Ho K, Byblow W. Cooperative hand movements up-regulate bilateral input to the upper limb - an ipsilateral MEP study. 29th NCM Annual Meeting; Toyama, Japan: Poster presentation; 2019.

297. Michels L, Dietz V, Schattin A, Schrafl-Altermatt M. Neuroplastic Changes in Older Adults Performing Cooperative Hand Movements. Front Hum Neurosci. 2018;12:488.

298. Bretas RV, Taoka M, Suzuki H, Iriki A. Secondary somatosensory cortex of primates: beyond body maps, toward conscious self-in-the-world maps. Exp Brain Res. 2020;238(2):259-72.

299. Disbrow E, Roberts T, Poeppel D, Krubitzer L. Evidence for interhemispheric processing of inputs from the hands in human S2 and PV. Journal of neurophysiology. 2001;85(5):2236-44.

300. Singh-Curry V, Husain M. The functional role of the inferior parietal lobe in the dorsal and ventral stream dichotomy. Neuropsychologia. 2009;47(6):1434-48.

301. Palejwala AH, O'Connor KP, Milton CK, Anderson C, Pelargos P, Briggs RG, et al. Anatomy and white matter connections of the fusiform gyrus. Sci Rep. 2020;10(1):13489.

302. Hoyer EH, Bastian AJ. The effects of task demands on bimanual skill acquisition. Experimental Brain Research. 2013;226(2):193-208.

303. Franz EA, McCormick R. Conceptual unifying constraints override sensorimotor interference during anticipatory control of bimanual actions. Experimental Brain Research. 2010;205(2):273-82.

304. Shea CH, Buchanan JJ, Kennedy DM. Perception and action influences on discrete and reciprocal bimanual coordination. Psychon Bull Rev. 2016;23(2):361-86.

305. Kovacs AJ, Buchanan JJ, Shea CH. Bimanual 1:1 with 90 degrees continuous relative phase: difficult or easy! Exp Brain Res. 2009;193(1):129-36.

306. Kovacs AJ, Buchanan JJ, Shea CH. Using scanning trials to assess intrinsic coordination dynamics. J Sport Exercise Psy. 2009;31:S80-S.

307. Kovacs AJ, Shea CH. Amplitude differences, spatial assimilation, and integrated feedback in bimanual coordination. Exp Brain Res. 2010;202(2):519-25.

308. Kovacs AJ, Buchanan JJ, Shea CH. Perceptual and attentional influences on continuous 2:1 and 3:2 multi-frequency bimanual coordination. J Exp Psychol Hum Percept Perform. 2010;36(4):936-54.

309. Kovacs AJ, Buchanan JJ, Shea CH. Impossible is nothing: 5:3 and 4:3 multi-frequency bimanual coordination. Exp Brain Res. 2010;201(2):249-59.

310. Hughes CM, Haddad JM, Franz EA, Zelaznik HN, Ryu JH. Physically coupling two objects in a bimanual task alters kinematics but not end-state comfort. Exp Brain Res. 2011;211(2):219-29.

311. Columb MO, Atkinson MS. Statistical analysis: sample size and power estimations. Bja Educ. 2016;16(5):159-61.

312. Panzer S, Kennedy D, Leinen P, Pfeifer C, Shea C. Bimanual coordination associated with left- and right-hand dominance: testing the limb assignment and limb dominance hypothesis. Experimental Brain Research. 2021.

313. Pan Z, Van Gemmert AWA. The control of amplitude and direction in a bimanual coordination task. Hum Mov Sci. 2019;65.

314. Jin Y, Kim M, Oh S, Yoon B. Motor control strategies during bimanual isometric force control among healthy individuals. Adapt Behav. 2019;27(2):127-36.

315. Ingram JN, Wolpert DM. Naturalistic approaches to sensorimotor control. Prog Brain Res. 2011;191:3-29.

316. Weiss PH, Jeannerod M, Paulignan Y, Freund HJ. Is the organisation of goal-directed action modality specific? A common temporal structure. Neuropsychologia. 2000;38(8):1136-47.

317. Wu CY, Chou SH, Chen CL, Kuo MY, Lu TW, Fu YC. Kinematic analysis of a functional and sequential bimanual task in patients with left hemiparesis: intra-limb and interlimb coordination. Disabil Rehabil. 2009;31(12):958-66.

318. Itaguchi Y, Fukuzawa K. Hand-use and tool-use in grasping control. Experimental Brain Research. 2014;232(11):3613-22.

319. Itaguchi Y. Toward natural grasping with a tool: effects of practice and required accuracy on the kinematics of tool-use grasping. Journal of neurophysiology. 2020;123(5):2024-36.

320. Bock O, Zull A. Characteristics of grasping movements in a laboratory and in an everyday-like context. Hum Mov Sci. 2013;32(1):249-56.

321. Baak B, Bock O, Dovern A, Saliger J, Karbe H, Weiss PH. Deficits of reach-to-grasp coordination following stroke: Comparison of instructed and natural movements. Neuropsychologia. 2015;77:1-9.

322. Kilbreath SL, Crosbie J, Canning CG, Lee MJ. Inter-limb coordination in bimanual reach-to-grasp following stroke. Disabil Rehabil. 2006;28(23):1435-43.

323. Schmidle S, Gulde P, Herdegen S, Bohme GE, Hermsdorfer J. Kinematic analysis of activities of daily living performance in frail elderly. BMC Geriatr. 2022;22(1):244.

324. Kang N, Ko DK, Cauraugh JH. Bimanual Motor Impairments in Older Adults: An Updated Systematic Review and Meta-Analysis. Excli J. 2022;21:1068-83.

325. Bangert AS, Reuter-Lorenz PA, Walsh CM, Schachter AB, Seidler RD. Bimanual coordination and aging: neurobehavioral implications. Neuropsychologia. 2010;48(4):1165-70.

326. Summers JJ, Lewis J, Fujiyama H. Aging effects on event and emergent timing in bimanual coordination. Hum Mov Sci. 2010;29(5):820-30.

327. Fujiyama H, Van Soom J, Rens G, Gooijers J, Leunissen I, Levin O, et al. Age-Related Changes in Frontal Network Structural and Functional Connectivity in Relation to Bimanual Movement Control. Journal of Neuroscience. 2016;36(6):1808-22.

328. Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, Seidler RD. Differential callosal contributions to bimanual control in young and older adults. J Cogn Neurosci. 2011;23(9):2171-85.

329. Kiyama S, Kunimi M, Iidaka T, Nakai T. Distant functional connectivity for bimanual finger coordination declines with aging: an fMRI and SEM exploration. Front Hum Neurosci. 2014;8:251.

330. Coats RO, Wann JP. Reaching a better understanding of the control of bimanual movements in older adults. PLoS One. 2012;7(10):e47222.

331. Hughes CM, Tommasino P, Budhota A, Campolo D. Upper extremity proprioception in healthy aging and stroke populations, and the effects of therapist- and robot-based rehabilitation therapies on proprioceptive function. Front Hum Neurosci. 2015;9:120.

332. Coats RO, Fath AJ, Astill SL, Wann JP. Eye and hand movement strategies in older adults during a complex reaching task. Exp Brain Res. 2016;234(2):533-47.

333. Gulde P, Schmidle S, Aumuller A, Hermsdorfer J. The effects of speed of execution on upper-limb kinematics in activities of daily living with respect to age. Exp Brain Res. 2019;237(6):1383-95.

334. Gulde P, Hermsdorfer J. Both hands at work: the effect of aging on upper-limb kinematics in a multi-step activity of daily living. Exp Brain Res. 2017;235(5):1337-48.

335. Giorgio A, Santelli L, Tomassini V, Bosnell R, Smith S, De Stefano N, et al. Age-related changes in grey and white matter structure throughout adulthood. Neuroimage. 2010;51(3):943-51.

336. Fling BW, Peltier SJ, Bo J, Welsh RC, Seidler RD. Age differences in interhemispheric interactions: callosal structure, physiological function, and behavior. Front Neurosci. 2011;5:38.

337. Fling BW, Seidler RD. Task-dependent effects of interhemispheric inhibition on motor control. Behav Brain Res. 2012;226(1):211-7.

338. Goble DJ, Coxon JP, Van Impe A, De Vos J, Wenderoth N, Swinnen SP. The neural control of bimanual movements in the elderly: Brain regions exhibiting age-related increases in activity, frequency-induced neural modulation, and task-specific compensatory recruitment. Hum Brain Mapp. 2010;31(8):1281-95.

339. Ni Z, Isayama R, Castillo G, Gunraj C, Saha U, Chen R. Reduced dorsal premotor cortex and primary motor cortex connectivity in older adults. Neurobiol Aging. 2015;36(1):301-3.

340. Hinder MR, Fujiyama H, Summers JJ. Premotor-Motor Interhemispheric Inhibition Is Released during Movement Initiation in Older but Not Young Adults. Plos One. 2012;7(12).

341. Green PE, Ridding MC, Hill KD, Semmler JG, Drummond PD, Vallence AM. Supplementary motor area-primary motor cortex facilitation in younger but not older adults. Neurobiol Aging. 2018;64:85-91.

342. Rurak BK, Rodrigues JP, Power BD, Drummond PD, Vallence AM. Reduced SMA-M1 connectivity in older than younger adults measured using dual-site TMS. Eur J Neurosci. 2021;54(7):6533-52.

343. Hallett M, Di Iorio R, Rossini PM, Park JE, Chen R, Celnik P, et al. Contribution of transcranial magnetic stimulation to assessment of brain connectivity and networks. Clin Neurophysiol. 2017;128(11):2125-39.

344. Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. Nature. 1980;285(5762):227.

345. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1(8437):1106-7.

346. Terao Y, Ugawa Y. Basic mechanisms of TMS. J Clin Neurophysiol. 2002;19(4):322-43.

347. Di Lazzaro V, Rothwell JC. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. J Physiol. 2014;592(19):4115-28.

348. Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I. Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. Exp Brain Res. 1997;113(1):24-32.

349. Di Lazzaro V, Profice P, Ranieri F, Capone F, Dileone M, Oliviero A, et al. I-wave origin and modulation. Brain Stimul. 2012;5(4):512-25.

350. Rusu CV, Murakami M, Ziemann U, Triesch J. A model of TMS-induced I-waves in motor cortex. Brain Stimul. 2014;7(3):401-14.

351. Ni Z, Charab S, Gunraj C, Nelson AJ, Udupa K, Yeh IJ, et al. Transcranial magnetic stimulation in different current directions activates separate cortical circuits. Journal of neurophysiology. 2011;105(2):749-56.

352. Di Lazzaro V, Oliviero A, Saturno E, Pilato F, Insola A, Mazzone P, et al. The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. Exp Brain Res. 2001;138(2):268-73.

353. Di Lazzaro V, Oliviero A, Pilato F, Mazzone P, Insola A, Ranieri F, et al. Corticospinal volleys evoked by transcranial stimulation of the brain in conscious humans. Neurol Res. 2003;25(2):143-50.

354. Sale MV, Lavender AP, Opie GM, Nordstrom MA, Semmler JG. Increased intracortical inhibition in elderly adults with anterior-posterior current flow: A TMS study. Clin Neurophysiol. 2016;127(1):635-40.

355. Day BL, Dressler D, Maertens de Noordhout A, Marsden CD, Nakashima K, Rothwell JC, et al. Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. J Physiol. 1989;412:449-73.

356. Janssen AM, Oostendorp TF, Stegeman DF. The coil orientation dependency of the electric field induced by TMS for M1 and other brain areas. J Neuroeng Rehabil. 2015;12:47.

357. Laakso I, Hirata A, Ugawa Y. Effects of coil orientation on the electric field induced by TMS over the hand motor area. Phys Med Biol. 2014;59(1):203-18.

358. Mills KR, Boniface SJ, Schubert M. Magnetic brain stimulation with a double coil: the importance of coil orientation. Electroencephalogr Clin Neurophysiol. 1992;85(1):17-21.

359. Brasil-Neto JP, Cohen LG, Panizza M, Nilsson J, Roth BJ, Hallett M. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. J Clin Neurophysiol. 1992;9(1):132-6.

360. Hallett M. Transcranial magnetic stimulation: a primer. Neuron. 2007;55(2):187-99.

361. Ziemann U, Reis J, Schwenkreis P, Rosanova M, Strafella A, Badawy R, et al. TMS and drugs revisited 2014. Clin Neurophysiol. 2015;126(10):1847-68.

362. Valls-Sole J, Pascual-Leone A, Brasil-Neto JP, Cammarota A, McShane L, Hallett M. Abnormal facilitation of the response to transcranial magnetic stimulation in patients with Parkinson's disease. Neurology. 1994;44(4):735-41.

363. Cantello R, Gianelli M, Bettucci D, Civardi C, De Angelis MS, Mutani R. Parkinson's disease rigidity: magnetic motor evoked potentials in a small hand muscle. Neurology. 1991;41(9):1449-56.

364. Goldsworthy MR, Hordacre B, Ridding MC. Minimum number of trials required for within- and between-session reliability of TMS measures of corticospinal excitability. Neuroscience. 2016;320:205-9.

365. Biabani M, Farrell M, Zoghi M, Egan G, Jaberzadeh S. The minimal number of TMS trials required for the reliable assessment of corticospinal excitability, short interval intracortical inhibition, and intracortical facilitation. Neurosci Lett. 2018;674:94-100.

366. Ni Z, Gunraj C, Nelson AJ, Yeh IJ, Castillo G, Hoque T, et al. Two phases of interhemispheric inhibition between motor related cortical areas and the primary motor cortex in human. Cereb Cortex. 2009;19(7):1654-65.

367. Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric Inhibition of the Human Motor Cortex. J Physiol-London. 1992;453:525-46.

368. Hanajima R, Ugawa Y, Machii K, Mochizuki H, Terao Y, Enomoto H, et al. Interhemispheric facilitation of the hand motor area in humans. J Physiol-London. 2001;531(3):849-59.

369. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R. The mechanisms of interhemispheric inhibition in the human motor cortex. J Physiol. 2002;543(Pt 1):317-26.

370. Chen R, Yung D, Li JY. Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. Journal of neurophysiology. 2003;89(3):1256-64.

371. Hinder MR, Puri R, Kemp S, Waitzer S, Reissig P, Stockel T, et al. Distinct modulation of interhemispheric inhibitory mechanisms during movement preparation reveals the influence of cognition on action control. Cortex. 2018;99:13-29.

372. Morishita T, Kubota S, Hirano M, Funase K. Different modulation of short- and long-latency interhemispheric inhibition from active to resting primary motor cortex during a fine-motor manipulation task. Physiol Rep. 2014;2(10).

373. Butefisch CM, Wessling M, Netz J, Seitz RJ, Homberg V. Relationship between interhemispheric inhibition and motor cortex excitability in subacute stroke patients. Neurorehabil Neural Repair. 2008;22(1):4-21.

374. Mooney RA, Cirillo J, Byblow WD. Adaptive threshold hunting reveals differences in interhemispheric inhibition between young and older adults. European Journal of Neuroscience. 2018;48(5):2247-58.

375. Turco CV, Fassett HJ, Locke MB, El-Sayes J, Nelson AJ. Parallel modulation of interhemispheric inhibition and the size of a cortical hand muscle representation during active contraction. Journal of neurophysiology. 2019;122(1):368-77.

376. Irlbacher K, Brocke J, Mechow JV, Brandt SA. Effects of GABA(A) and GABA(B) agonists on interhemispheric inhibition in man. Clin Neurophysiol. 2007;118(2):308-16.

377. Udupa K, Ni Z, Gunraj C, Chen R. Effect of long interval interhemispheric inhibition on intracortical inhibitory and facilitatory circuits. J Physiol-London. 2010;588(14):2633-41.

378. Perez MA, Cohen LG. Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. J Neurosci. 2008;28(22):5631-40.

379. Hubers A, Orekhov Y, Ziemann U. Interhemispheric motor inhibition: its role in controlling electromyographic mirror activity. Eur J Neurosci. 2008;28(2):364-71.

380. Florian J, Muller-Dahlhaus M, Liu Y, Ziemann U. Inhibitory circuits and the nature of their interactions in the human motor cortex a pharmacological TMS study. J Physiol. 2008;586(2):495-514.

381. Talelli P, Waddingham W, Ewas A, Rothwell JC, Ward NS. The effect of age on task-related modulation of interhemispheric balance. Experimental Brain Research. 2008;186(1):59-66.

382. Hinder MR, Schmidt MW, Garry MI, Summers JJ. Unilateral contractions modulate interhemispheric inhibition most strongly and most adaptively in the homologous muscle of the contralateral limb. Exp Brain Res. 2010;205(3):423-33.

383. Uehara K, Morishita T, Kubota S, Hirano M, Funase K. Functional difference in short- and long-latency interhemispheric inhibitions from active to resting hemisphere during a unilateral muscle contraction. Journal of neurophysiology. 2014;111(1):17-25.

384. Liang N, Funase K, Takahashi M, Matsukawa K, Kasai T. Unilateral imagined movement increases interhemispheric inhibition from the contralateral to ipsilateral motor cortex. Exp Brain Res. 2014;232(6):1823-32.

385. Nelson AJ, Hoque T, Gunraj C, Ni Z, Chen R. Bi-directional interhemispheric inhibition during unimanual sustained contractions. Bmc Neuroscience. 2009;10.

386. Morishita T, Uehara K, Funase K. Changes in interhemispheric inhibition from active to resting primary motor cortex during a fine-motor manipulation task. Journal of neurophysiology. 2012;107(11):3086-94.

387. Lewis GN, Perreault EJ. Side of lesion influences interhemispheric inhibition in subjects with post-stroke hemiparesis. Clin Neurophysiol. 2007;118(12):2656-63.

388. Asanuma H, Okuda O. Effects of transcallosal volleys on pyramidal tract cell activity of cat. Journal of neurophysiology. 1962;25:198-208.

389. Georgopoulos AP, Carpenter AF. Coding of movements in the motor cortex. Curr Opin Neurobiol. 2015;33:34-9.

390. Opitz A, Zafar N, Bockermann V, Rohde V, Paulus W. Validating computationally predicted TMS stimulation areas using direct electrical stimulation in patients with brain tumors near precentral regions. Neuroimage Clin. 2014;4:500-7.

391. Bestmann S, Krakauer JW. The uses and interpretations of the motor-evoked potential for understanding behaviour. Exp Brain Res. 2015;233(3):679-89.

392. Bailey RR, Klaesner JW, Lang CE. Quantifying Real-World Upper-Limb Activity in Nondisabled Adults and Adults With Chronic Stroke. Neurorehabil Neural Repair. 2015;29(10):969-78.

393. Ruddy KL, Carson RG. Neural pathways mediating cross education of motor function. Front Hum Neurosci. 2013;7:397.

394. Oliveira FT, Ivry RB. The Representation of Action: Insights From Bimanual Coordination. Curr Dir Psychol Sci. 2008;17(2):130-5.

395. Hoyer EH, Bastian AJ. The effects of task demands on bimanual skill acquisition. Exp Brain Res. 2013;226(2):193-208.

396. Khong KYW, Galan F, Soteropoulos DS. Rapid crossed responses in an intrinsic hand muscle during perturbed bimanual movements. Journal of neurophysiology. 2020;123(2):630-44.

397. Soteropoulos DS, Perez MA. Physiological changes underlying bilateral isometric arm voluntary contractions in healthy humans. Journal of neurophysiology. 2011;105(4):1594-602.

398. Hiraoka K, Ae M, Ogura N, Sano C, Shiomi K, Morita Y, et al. Bimanual coordination of force enhances interhemispheric inhibition between the primary motor cortices. Neuroreport. 2014;25(15):1203-7.

399. Awiszus F, Borckdardt JJ. TMS motor threshold assessment tool (MTAT 2.0). 2011.

400. Sattler V, Dickler M, Michaud M, Simonetta-Moreau M. Interhemispheric inhibition in human wrist muscles. Exp Brain Res. 2012;221(4):449-58.

401. Rom DM. A sequentially rejective test procedure based on a modified Bonferroni inequality. Biometrika. 1990;77(3):663-5.

402. Carson RG, Riek S, Bawa P. Electromyographic activity, H-reflex modulation and corticospinal input to forearm motoneurones during active and passive rhythmic movements. Hum Movement Sci. 1999;18(2-3):307-43.

403. Tazoe T, Komiyama T. Interlimb neural interactions in the corticospinal pathways. Journal of Sports Medicine and Physical Fitness. 2014;3(2):181-90.

404. Stinear JW, Byblow WD. Disinhibition in the human motor cortex is enhanced by synchronous upper limb movements. J Physiol. 2002;543(Pt 1):307-16.

405. Chiou SY, Wang RY, Liao KK, Wu YT, Lu CF, Yang YR. Co-activation of primary motor cortex ipsilateral to muscles contracting in a unilateral motor task. Clin Neurophysiol. 2013;124(7):1353-63.

406. Yedimenko JA, Perez MA. The Effect of Bilateral Isometric Forces in Different Directions on Motor Cortical Function in Humans. Journal of neurophysiology. 2010;104(6):2922-31.

407. Wu T, Wang L, Hallett M, Li K, Chan P. Neural correlates of bimanual anti-phase and in-phase movements in Parkinson's disease. Brain. 2010;133(Pt 8):2394-409.

408. Wiegel P, Kurz A, Leukel C. Evidence that distinct human primary motor cortex circuits control discrete and rhythmic movements. J Physiol-London. 2020;598(6):1235-51.

409. Patel P, Lodha N. Functional implications of impaired bimanual force coordination in chronic stroke. Neurosci Lett. 2020;738:135387.

410. Arai N, Lu MK, Ugawa Y, Ziemann U. Effective connectivity between human supplementary motor area and primary motor cortex: a paired-coil TMS study. Exp Brain Res. 2012;220(1):79-87.

411. Vier C, Mochizuki L, Gomes RP, Rodrigues LC, Demartino AM, Michaelsen SM. Bilateral capacity is related to bilateral upper limb use after stroke: a study by behavioral maps, accelerometers and perceived amount of use. Disabil Rehabil. 2020:1-9.

412. Kilbreath SL, Heard RC. Frequency of hand use in healthy older persons. Aust J Physiother. 2005;51(2):119-22.

413. Waddell KJ, Strube MJ, Bailey RR, Klaesner JW, Birkenmeier RL, Dromerick AW, et al. Does Task-Specific Training Improve Upper Limb Performance in Daily Life Poststroke? Neurorehabil Neural Repair. 2017;31(3):290-300.

414. McLeod A, Bochniewicz EM, Lum PS, Holley RJ, Emmer G, Dromerick AW. Using Wearable Sensors and Machine Learning Models to Separate Functional Upper Extremity Use From Walking-Associated Arm Movements. Arch Phys Med Rehabil. 2016;97(2):224-31.

415. Lang CE, Wagner JM, Edwards DF, Dromerick AW. Upper extremity use in people with hemiparesis in the first few weeks after stroke. J Neurol Phys Ther. 2007;31(2):56-63.

416. Thrane G, Emaus N, Askim T, Anke A. Arm use in patients with subacute stroke monitored by accelerometry: association with motor impairment and influence on self-dependence. J Rehabil Med. 2011;43(4):299-304.

417. Chin LF, Hayward KS, Brauer S. Upper limb use differs among people with varied upper limb impairment levels early post-stroke: a single-site, cross-sectional, observational study. Top Stroke Rehabil. 2020;27(3):224-35.

418. McLaren R, Signal N, Lord S, Taylor S, Henderson J, Taylor D. The volume and timing of upper limb movement in acute stroke rehabilitation: still room for improvement. Disabil Rehabil. 2020;42(22):3237-42.

419. de Niet M, Bussmann JB, Ribbers GM, Stam HJ. The stroke upper-limb activity monitor: its sensitivity to measure hemiplegic upper-limb activity during daily life. Arch Phys Med Rehabil. 2007;88(9):1121-6.

420. Lee SI, Liu X, Rajan S, Ramasarma N, Choe EK, Bonato P. A novel upper-limb function measure derived from finger-worn sensor data collected in a free-living setting. PLoS One. 2019;14(3):e0212484.

421. Demartino AM, Rodrigues LC, Gomes RP, Michaelsen SM. Hand function and type of grasp used by chronic stroke individuals in actual environment. Top Stroke Rehabil. 2019;26(4):247-54.

422. Varghese R, Kutch JJ, Schweighofer N, Winstein CJ. The probability of choosing both hands depends on an interaction between motor capacity and limb-specific control in chronic stroke. Exp Brain Res. 2020;238(11):2569-79.

423. Bui Q, Kaufman KJ, Pham V, Lenze EJ, Lee JM, Mohr DC, et al. Ecological Momentary Assessment of Real-World Functional Behaviors in Individuals with Stroke: A Longitudinal Observational Study. Arch Phys Med Rehabil. 2022.

424. Metrot J, Mottet D, Hauret I, van Dokkum L, Bonnin-Koang HY, Torre K, et al. Changes in bimanual coordination during the first 6 weeks after moderate hemiparetic stroke. Neurorehabil Neural Repair. 2013;27(3):251-9.

425. Lowrey C, Jackson C, Bagg S, Dukelow S, Scott SH. A Novel Robotic Task for Assessing Impairments in Bimanual Coordination Post-Stroke. International Journal of Physical Medicine and Rehabilitation. 2014;S3:002.

426. Plantin J, Verneau M, Godbolt AK, Pennati GV, Laurencikas E, Johansson B, et al. Recovery and Prediction of Bimanual Hand Use After Stroke. Neurology. 2021;97(7):e706-e19.

427. Rice MS, Newell KM. Upper-extremity interlimb coupling in persons with left hemiplegia due to stroke. Arch Phys Med Rehabil. 2004;85(4):629-34.

428. Johnson MJ, Wang S, Bai P, Strachota E, Tchekanov G, Melbye J, et al. Bilateral assessment of functional tasks for robot-assisted therapy applications. Med Biol Eng Comput. 2011;49(10):1157-71.

429. Rose DK, Winstein CJ. The co-ordination of bimanual rapid aiming movements following stroke. Clin Rehabil. 2005;19(4):452-62.

430. Gosser SM, Rice MS. Efficiency of unimanual and bimanual reach in persons with and without stroke. Top Stroke Rehabil. 2015;22(1):56-62.

431. McCombe Waller S, Whitall J. Fine motor control in adults with and without chronic hemiparesis: baseline comparison to nondisabled adults and effects of bilateral arm training. Arch Phys Med Rehabil. 2004;85(7):1076-83.

432. van Delden AL, Beek PJ, Roerdink M, Kwakkel G, Peper CL. Unilateral and bilateral upper-limb training interventions after stroke have similar effects on bimanual coupling strength. Neurorehabil Neural Repair. 2015;29(3):255-67.

433. Rose DK, Winstein CJ. Temporal coupling is more robust than spatial coupling: an investigation of interlimb coordination after stroke. J Mot Behav. 2013;45(4):313-24.

434. Harris-Love ML, McCombe Waller S, Whitall J. Exploiting interlimb coupling to improve paretic arm reaching performance in people with chronic stroke. Arch Phys Med Rehabil. 2005;86(11):2131-7.

435. Jayasinghe SAL, Maenza C, Good DC, Sainburg RL. Deficits in Performance on a Mechanically Coupled Asymmetrical Bilateral Task in Chronic Stroke Survivors with Mild Unilateral Paresis. Symmetry. 2021;13(8):1366.

436. Schaffer JE, Maenza C, Good DC, Przybyla A, Sainburg RL. Left hemisphere damage produces deficits in predictive control of bilateral coordination. Exp Brain Res. 2020;238(12):2733-44.

437. Schaefer SY, Haaland KY, Sainburg RL. Hemispheric specialization and functional impact of ipsilesional deficits in movement coordination and accuracy. Neuropsychologia. 2009;47(13):2953-66.

438. Sainburg R, Good D, Przybyla A. Bilateral Synergy: A Framework for Post-Stroke Rehabilitation. J Neurol Transl Neurosci. 2013;1(3).

439. Lench DH, Hutchinson S, Woodbury ML, Hanlon CA. Kinematic Measures of Bimanual Performance are Associated With Callosum White Matter Change in People With Chronic Stroke. Arch Rehabil Res Clin Transl. 2020;2(4):100075.

440. Wang LE, Tittgemeyer M, Imperati D, Diekhoff S, Ameli M, Fink GR, et al. Degeneration of corpus callosum and recovery of motor function after stroke: a multimodal magnetic resonance imaging study. Hum Brain Mapp. 2012;33(12):2941-56.

441. Li Y, Wu P, Liang F, Huang W. The microstructural status of the corpus callosum is associated with the degree of motor function and neurological deficit in stroke patients. PLoS One. 2015;10(4):e0122615.

442. Ivry RB, Hazeltine E. Subcortical locus of temporal coupling in the bimanual movements of a callosotomy patient. Hum Movement Sci. 1999;18(2-3):345-75.

443. Ivry RB, Franz EA, Kingstone A, Johnston JC. The psychological refractory period effect following callosotomy: uncoupling of lateralized response codes. J Exp Psychol Hum Percept Perform. 1998;24(2):463-80.

444. Franz EA, Eliassen JC, Ivry RB, Gazzaniga MS. Dissociation of Spatial and Temporal Coupling in the Bimanual Movements of Callosotomy Patients. Psychological Science. 1996;7(5):306-10.

445. Hammerbeck U, Hoad D, Greenwood R, Rothwell JC. The unsolved role of heightened connectivity from the unaffected hemisphere to paretic arm muscles in chronic stroke. Clin Neurophysiol. 2019;130(5):781-8.

446. Arya KN, Pandian S, Sharma A, Kumar V, Kashyap VK. Interlimb coupling in poststroke rehabilitation: a pilot randomized controlled trial. Top Stroke Rehabil. 2020;27(4):272-89.

447. Amengual JL, Munte TF, Marco-Pallares J, Rojo N, Grau-Sanchez J, Rubio F, et al. Overactivation of the supplementary motor area in chronic stroke patients. Journal of neurophysiology. 2014;112(9):2251-63.

448. Zhang Y, Liu H, Wang L, Yang J, Yan R, Zhang J, et al. Relationship between functional connectivity and motor function assessment in stroke patients with hemiplegia: a resting-state functional MRI study. Neuroradiology. 2016;58(5):503-11.

449. Yin D, Song F, Xu D, Peterson BS, Sun L, Men W, et al. Patterns in cortical connectivity for determining outcomes in hand function after subcortical stroke. PLoS One. 2012;7(12):e52727.

450. Bestmann S, Swayne O, Blankenburg F, Ruff CC, Teo J, Weiskopf N, et al. The role of contralesional dorsal premotor cortex after stroke as studied with concurrent TMS-fMRI. J Neurosci. 2010;30(36):11926-37.

451. Bruyn JL, Mason AH. Temporal coordination during bimanual reach-to-grasp movements: the role of vision. Q J Exp Psychol (Hove). 2009;62(7):1328-42.

452. Choudhury S, Shobhana A, Singh R, Sen D, Anand SS, Shubham S, et al. The Relationship Between Enhanced Reticulospinal Outflow and Upper Limb Function in Chronic Stroke Patients. Neurorehabil Neural Repair. 2019;33(5):375-83.

453. Owen M, Ingo C, Dewald JPA. Upper Extremity Motor Impairments and Microstructural Changes in Bulbospinal Pathways in Chronic Hemiparetic Stroke. Front Neurol. 2017;8:257.

454. Santisteban L, Teremetz M, Bleton JP, Baron JC, Maier MA, Lindberg PG. Upper Limb Outcome Measures Used in Stroke Rehabilitation Studies: A Systematic Literature Review. PLoS One. 2016;11(5):e0154792.

455. Stewart JC, Cramer SC. Patient-reported measures provide unique insights into motor function after stroke. Stroke. 2013;44(4):1111-6.

456. Essers B, Van Gils A, Lafosse C, Michielsen M, Beyens H, Schillebeeckx F, et al. Evolution and prediction of mismatch between observed and perceived upper limb function after stroke: a prospective, longitudinal, observational cohort study. BMC Neurol. 2021;21(1):488.

457. Barreca S, Gowland CK, Stratford P, Huijbregts M, Griffiths J, Torresin W, et al. Development of the Chedoke Arm and Hand Activity Inventory: theoretical constructs, item generation, and selection. Top Stroke Rehabil. 2004;11(4):31-42.

458. Barreca SR, Stratford PW, Lambert CL, Masters LM, Streiner DL. Test-retest reliability, validity, and sensitivity of the Chedoke arm and hand activity inventory: a new measure of upper-limb function for survivors of stroke. Arch Phys Med Rehabil. 2005;86(8):1616-22.

459. Barreca SR, Stratford PW, Masters LM, Lambert CL, Griffiths J. Comparing 2 versions of the Chedoke Arm and Hand Activity Inventory with the Action Research Arm Test. Phys Ther. 2006;86(2):245-53.

460. Alt Murphy M, Resteghini C, Feys P, Lamers I. An overview of systematic reviews on upper extremity outcome measures after stroke. BMC Neurol. 2015;15:29.

461. Rowland TJ, Turpin M, Gustafsson L, Henderson RD, Read SJ. Chedoke Arm and Hand Activity Inventory-9 (CAHAI-9): perceived clinical utility within 14 days of stroke. Top Stroke Rehabil. 2011;18(4):382-93.

462. Gustafsson LA, Turpin MJ, Dorman CM. Clinical utility of the Chedoke Arm and Hand Activity Inventory for stroke rehabilitation. Can J Occup Ther. 2010;77(3):167-73.

463. Molad R, Levin MF. Construct Validity of the Upper-Limb Interlimb Coordination Test in Stroke. Neurorehab Neural Re. 2021:154596832110580.

464. Johnson B, Waller SM, Whitall J, Westlake K. Bimanual Assessment Measure (BAM): Development of a Measure of Bimanual Function for Use After Stroke. The American Journal of Occupational Therapy. 2015;69(Supplement_1):6911500004p1.

465. Johnson BP, Waller SM, J. W, Westlake KP, editors. Development of the bimanual assessment measure (BAM) to assess function after stroke. World Congress for Neurorehabilitation; 2016; Philadelphia, PA, USA.

466. Krumlinde-Sundholm L, Lindkvist B, Plantin J, Hoare B. Development of the assisting hand assessment for adults following stroke: a Rasch-built bimanual performance measure. Disabil Rehabil. 2017:1-9.

467. Van Gils A, Meyer S, Van Dijk M, Thijs L, Michielsen M, Lafosse C, et al. The Adult Assisting Hand Assessment Stroke: Psychometric properties of an observation-based bimanual upper-limb performance measurement. Arch Phys Med Rehabil. 2018.

468. Chen S, Wolf SL, Zhang Q, Thompson PA, Winstein CJ. Minimal detectable change of the actual amount of use test and the motor activity log: the EXCITE Trial. Neurorehabil Neural Repair. 2012;26(5):507-14.

469. Penta M, Tesio L, Arnould C, Zancan A, Thonnard JL. The ABILHAND questionnaire as a measure of manual ability in chronic stroke patients: Rasch-based validation and relationship to upper limb impairment. Stroke. 2001;32(7):1627-34.

470. Ekstrand E, Lindgren I, Lexell J, Brogardh C. Test-retest reliability of the ABILHAND questionnaire in persons with chronic stroke. PM R. 2014;6(4):324-31.

471. Meyer S, De Bruyn N, Krumlinde-Sundholm L, Peeters A, Feys H, Thijs V, et al. Associations Between Sensorimotor Impairments in the Upper Limb at 1 Week and 6 Months After Stroke. J Neurol Phys Ther. 2016;40(3):186-95.

472. Ekstrand E, Alt Murphy M, Sunnerhagen KS. Clinical interpretation and cutoff scores for manual ability measured by the ABILHAND questionnaire in people with stroke. Topics in Stroke Rehabilitation. 2021:1-11.

473. Demers M, Winstein CJ. A perspective on the use of ecological momentary assessment and intervention to promote stroke recovery and rehabilitation. Top Stroke Rehabil. 2020:1-12.

474. Chen YA, Demers M, Lewthwaite R, Schweighofer N, Monterosso JR, Fisher BE, et al. A Novel Combination of Accelerometry and Ecological Momentary Assessment for Post-Stroke Paretic Arm/Hand Use: Feasibility and Validity. J Clin Med. 2021;10(6).

475. Torriani-Pasin C, Demers M, Polese JC, Bishop L, Wade E, Hempel S, et al. mHealth technologies used to capture walking and arm use behavior in adult stroke survivors: a scoping review beyond measurement properties. Disability and Rehabilitation. 2021.

476. Ingram LA, Butler AA, Brodie MA, Lord SR, Gandevia SC. Quantifying upper limb motor impairment in chronic stroke: a physiological profiling approach. J Appl Physiol (1985). 2021;131(3):949-65.

477. Michielsen ME, Selles RW, Stam HJ, Ribbers GM, Bussmann JB. Quantifying nonuse in chronic stroke patients: a study into paretic, nonparetic, and bimanual upper-limb use in daily life. Arch Phys Med Rehabil. 2012;93(11):1975-81.

478. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res. 2010;19(4):539-49.

479. Wu CY, Chou SH, Kuo MY, Chen CL, Lu TW, Fu YC. Effects of object size on intralimb and interlimb coordination during a bimanual prehension task in patients with left cerebral vascular accidents. Motor Control. 2008;12(4):296-310.

480. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block Test of manual dexterity. Am J Occup Ther. 1985;39(6):386-91.

481. Chen HM, Chen CC, Hsueh IP, Huang SL, Hsieh CL. Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. Neurorehabil Neural Repair. 2009;23(5):435-40.

482. See J, Dodakian L, Chou C, Chan V, McKenzie A, Reinkensmeyer DJ, et al. A standardized approach to the Fugl-Meyer assessment and its implications for clinical trials. Neurorehabil Neural Repair. 2013;27(8):732-41.

483. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15(2):155-63.

484. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J. 2012;24(3):69-71.

485. Andrade C. Multiple Testing and Protection Against a Type 1 (False Positive) Error Using the Bonferroni and Hochberg Corrections. Indian J Psychol Med. 2019;41(1):99-100.

486. Woytowicz EJ, Rietschel JC, Goodman RN, Conroy SS, Sorkin JD, Whitall J, et al. Determining Levels of Upper Extremity Movement Impairment by Applying a Cluster Analysis to the Fugl-Meyer Assessment of the Upper Extremity in Chronic Stroke. Arch Phys Med Rehabil. 2017;98(3):456-62.

487. Danuta RL, Tokarski T. Age-related differences in bimanual coordination performance. Int J Occup Saf Ergon. 2021;27(2):620-32.

488. Boisgontier MP, Swinnen SP. Age-related deficit in a bimanual joint position matching task is amplitude dependent. Front Aging Neurosci. 2015;7:162.

489. Wishart LR, Lee TD, Murdoch JE, Hodges NJ. Effects of aging on automatic and effortful processes in bimanual coordination. J Gerontol B Psychol Sci Soc Sci. 2000;55(2):P85-94.

490. Mehta S, Bastero-Caballero RF, Sun Y, Zhu R, Murphy DK, Hardas B, et al. Performance of intraclass correlation coefficient (ICC) as a reliability index under various distributions in scale reliability studies. Stat Med. 2018;37(18):2734-52.

491. Wood TJ. Exploring the role of first impressions in rater-based assessments. Adv Health Sci Educ Theory Pract. 2014;19(3):409-27.

492. Lin KC, Chen YA, Chen CL, Wu CY, Chang YF. The effects of bilateral arm training on motor control and functional performance in chronic stroke: a randomized controlled study. Neurorehabil Neural Repair. 2010;24(1):42-51.

493. Hyndman D, Pickering RM, Ashburn A. The influence of attention deficits on functional recovery post stroke during the first 12 months after discharge from hospital. J Neurol Neurosurg Psychiatry. 2008;79(6):656-63.

494. Desrosiers J, Bravo G, Hebert R, Dutil E, Mercier L. Validation of the Box and Block Test as a measure of dexterity of elderly people: reliability, validity, and norms studies. Arch Phys Med Rehabil. 1994;75(7):751-5.

495. Hsieh CL, Hsueh IP, Chiang FM, Lin PH. Inter-rater reliability and validity of the action research arm test in stroke patients. Age Ageing. 1998;27(2):107-13.

496. Schaefer SY, Saba A, Baird JF, Kolar MB, Duff K, Stewart JC. Within-Session Practice Effects in the Jebsen Hand Function Test (JHFT). Am J Occup Ther. 2018;72(6):7206345010p1-p5.

497. Morris DM, Uswatte G, Crago JE, Cook EW, 3rd, Taub E. The reliability of the wolf motor function test for assessing upper extremity function after stroke. Arch Phys Med Rehabil. 2001;82(6):750-5.

498. Lee KB, Lim SH, Kim KH, Kim KJ, Kim YR, Chang WN, et al. Six-month functional recovery of stroke patients: a multi-time-point study. Int J Rehabil Res. 2015;38(2):173-80.

499. Kwakkel G, Kollen B, Twisk J. Impact of time on improvement of outcome after stroke. Stroke. 2006;37(9):2348-53.

500. Harris JE, Eng JJ. Paretic upper-limb strength best explains arm activity in people with stroke. Phys Ther. 2007;87(1):88-97.

501. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. Phys Ther. 1993;73(7):447-54.

502. Strong B, Pudar J, Thrift AG, Howard VJ, Hussain M, Carcel C, et al. Sex Disparities in Enrollment in Recent Randomized Clinical Trials of Acute Stroke: A Meta-analysis. JAMA Neurol. 2021;78(6):666-77.

503. Cauraugh JH, Lodha N, Naik SK, Summers JJ. Bilateral movement training and stroke motor recovery progress: a structured review and meta-analysis. Hum Mov Sci. 2010;29(5):853-70.

504. Sheng B, Zhang Y, Meng W, Deng C, Xie S. Bilateral robots for upper-limb stroke rehabilitation: State of the art and future prospects. Med Eng Phys. 2016;38(7):587-606.

505. Chen PM, Kwong PWH, Lai CKY, Ng SSM. Comparison of bilateral and unilateral upper limb training in people with stroke: A systematic review and meta-analysis. PLoS One. 2019;14(5):e0216357.

506. Richardson MC, Tears C, Morris A, Alexanders J. The Effects of Unilateral Versus Bilateral Motor Training on Upper Limb Function in Adults with Chronic Stroke: A Systematic Review. J Stroke Cerebrovasc Dis. 2021;30(4):105617.

507. Van Orden KA, Bower E, Lutz J, Silva C, Gallegos AM, Podgorski CA, et al. Strategies to Promote Social Connections Among Older Adults During "Social Distancing" Restrictions. Am J Geriatr Psychiatry. 2021;29(8):816-27.

508. Rurak BK, Rodrigues JP, Power BD, Drummond PD, Vallence AM. Test Re-test Reliability of Dual-site TMS Measures of SMA-M1 Connectivity Differs Across Inter-stimulus Intervals in Younger and Older Adults. Neuroscience. 2021;472:11-24.

509. McCombe Waller S, Liu W, Whitall J. Temporal and spatial control following bilateral versus unilateral training. Hum Mov Sci. 2008;27(5):749-58.

510. Wu J, Cheng H, Zhang J, Bai Z, Cai S. The modulatory effects of bilateral arm training (BAT) on the brain in stroke patients: a systematic review. Neurol Sci. 2021;42(2):501-11.

511. Villepinte C, Verma A, Dimeglio C, De Boissezon X, Gasq D. Responsiveness of kinematic and clinical measures of upper-limb motor function after stroke: A systematic review and meta-analysis. Ann Phys Rehabil Med. 2021;64(2):101366.