Kinematic assessment of upper limb function in progressive multiple sclerosis

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Abstract

Upper limb dysfunction is common in multiple sclerosis (MS) with current evaluation methods relying on capacity assessments and a subjective evaluation of impairment. Kinematic techniques allow the quantification of upper limb dysfunction and may provide a useful marker in the prognosis of those affected. The aim of this thesis was to develop and use kinematic assessment techniques to characterise the extent and progression of upper limb dysfunction in people with MS (pwMS). Forty-two patients with progressive MS and 15 healthy controls reached-and-grasped objects while movement trajectories were captured with a kinematic assessment system. Clinical measures including the nine hole peg test (9HPT), Expanded Disability Status Scale (EDSS), and patient reported outcomes were administered at baseline and six months. PwMS had longer reaction and reach times, took longer to pick-up objects and move them between pre-defined positions, and spent more time placing objects, compared to controls. PwMS had lower peak wrist velocities when reaching towards and moving objects. Kinematic assessment demonstrated consistent differences between the mildly and severely affected patients, driven by object grasp dimensions, which weren't captured by 9HPT. There was no correlation between upper limb performance and EDSS, with wide variation in upper limb performance as measured by the kinematic assessment across a narrow EDSS range. There was moderate correlation between kinematic assessment and 9HPT. There was a significant change in some kinematic parameters at 6 months follow-up capturing predicted change in function. This study developed and evaluated a novel upper limb function assessment tool and found better sensitivity and behaviour capture than the EDSS and 9HPT. For the first time, we have quantified the spatiotemporal patterns of hand function impairment in people with progressive MS.

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Abbreviations used in this thesis

9HPT	Nine hole peg test
AMSQ	Arm function multiple sclerosis questionnaire
AMSQ-SF	Arm function multiple sclerosis questionnaire - short form
ANOVA	Analysis of variance
ARAT	Action research arm tests
BBT	Box and block test
BIGKAT	Boxed infra-red gross kinematic assessment tool
CI	Confidence interval
CNS	Central nervous system
CRF	Case report form
CSF	Cerebrospinal fluid
DASH	Disabilities of the arm, shoulder and hand scale
DMT	Disease modifying treatment
EDK	Event detection kit
EDSS	Expanded disability status scale
EMG	Electromyography
EXPAND	Exploring the efficacy and safety of siponimod in patients with secondary progressive multiple sclerosis trial
FS	Functional system
GA	Grip aperture
GUI	Graphical user interface
HRA	Health research authority
IPS	Intraparietal sulcus
IR	Infra-red
IRED	Infra-red emitting diode
KAIMS	Kinematics assessment in multiple sclerosis study
M1	Primary motor cortex
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite

MT	Movement time
NAWM	Normal appearing white matter
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PASAT	Paced auditory serial addition test
PIRA	Progression independent of relapse activity
PIS	Participant information sheet
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
PPMS	Primary progressive multiple sclerosis
PRO	Patient reported outcome
PROs	Patient reported outcome measures
PSAT	Postural sway assessment tool
PwMS	People with multiple sclerosis
RCT	Randomised controlled trial
REC	Research ethics committee
RPi	Raspberry Pi
RRMS	Relapsing remitting multiple sclerosis
RT	Reaction time
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SDMT	Symbol digit modalities test
SPMS	Secondary progressive multiple sclerosis
T25W	Timed 25 foot walk
TEMPA	Test d'Evaluation de la performance des Membres Supérieurs des Personnes Âgées
TMS	Transcranial magnetic stimulation

Chapter 1 Introduction

1.1 Overview of multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disorder of the central nervous system (CNS). MS is the most common cause of neurological disability in young adults and there is a female predominance of 3:1, with this disparity widening further in recent years (Koch-Henriksen and Sørensen, 2010). Currently, there are approximately 130,000 people living with MS in the UK, and 7,000 people are newly diagnosed each year (Public Health England, 2020). MS was first described in the medical literature in the 1820s, but it was not until 1868 that Jean-Marie Charcot provided a pathological insight into the disease process through a series of published lectures (Charcot, 1868; Phillips *et al.*, 2013). In the last 150 years since this description, significant advances have been made into the pathological and clinical understanding of the condition as well the development of effective treatments.

MS presents with a range of symptoms depending on which part of the brain or spinal cord is affected. Pathologically, the disease is defined by multiple demarcated regions in the white and grey matter of the brain, where myelinated neurons have had their myelin sheaths damaged, through a process known as demyelination. This is a product of immune-mediated T and B cell pathways which attack oligodendrocytes, the cells which produce the myelin sheaths surrounding neurons (Lucchinetti *et al.*, 2000; Jelcic *et al.*, 2018). These pro-inflammatory pathways lead to axonal loss in neurons and reactive changes in the surrounding glial cells which support neurons (gliosis),

resulting in the disproportionate loss of brain volume over time, a process called neurodegeneration (De Stefano *et al.*, 2016).

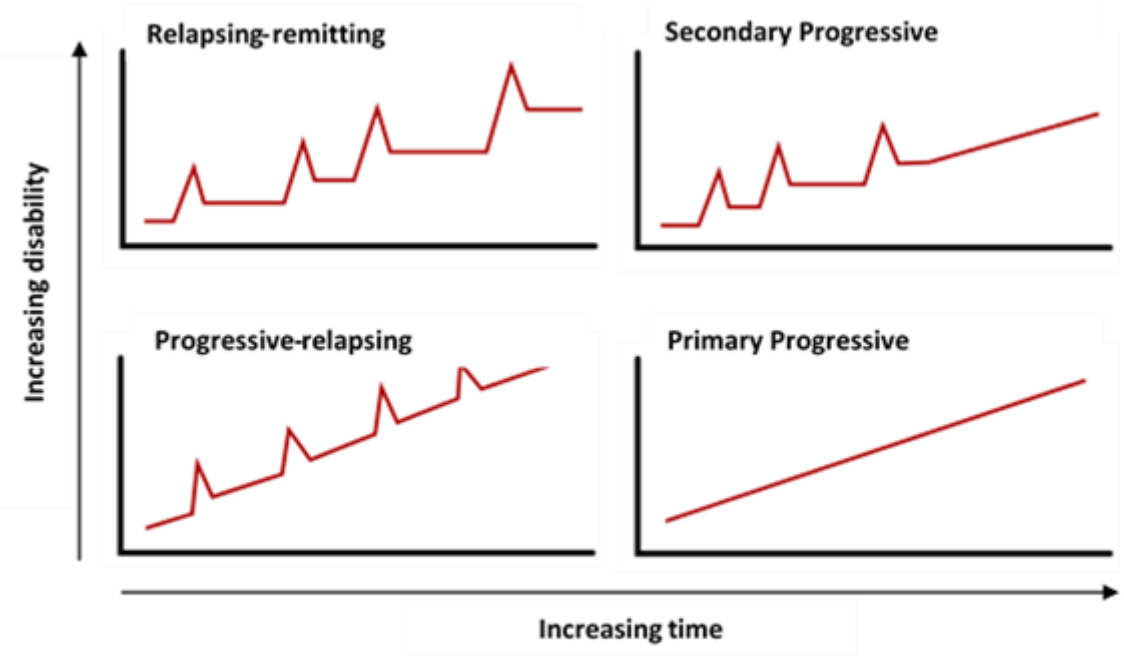
Over the last few decades, neurologists have made efforts to characterise the heterogenous clinical course of MS in more detail. There are different clinical subtypes of MS, with the most common type presenting with relapses corresponding to a symptomatic demyelinating lesion in the brain or spinal cord. These relapses, also known as clinical attacks, cause transient visual, sensory or motor disturbances that improve with time depending on the extent of the axonal injury. This form of MS is called relapsing-remitting (RRMS) and affects the majority of individuals at diagnosis. Over time, people with MS (pwMS) who continue to have relapses, accumulate disability and eventually enter a more progressive phase of the disease, termed secondary progressive MS (SPMS). A small proportion of individuals at diagnosis develop a primary progressive form of MS (PPMS), which leads to a gradual accumulation of neurological deficits without the phase of interspersed relapses seen in the other forms of the disease (Ludwin, 2006; Lublin *et al.*, 2014). The clinical course of these subtypes of MS are illustrated graphically in Figure 1. Furthermore, these MS subtypes are classified as being active or inactive, based on whether there are clinical relapses and/or MRI activity (classed as new demyelinating lesions on the MRI scan). Therefore, pwMS who have evidence of MRI activity and/or clinical relapses are termed as having active MS which has implications for treatment as described later in section 1.1.3 (Lublin *et al.*, 2014).

There is no diagnostic test for MS; instead, the diagnosis is made after consideration of clinical symptoms supported by magnetic resonance imaging

(MRI) of the CNS and cerebrospinal fluid analysis. These diagnostic criteria have been revised periodically over the last few decades resulting in the latest version of the McDonald criteria (Thompson *et al.*, 2018). The diagnosis of the different subtypes of MS is described in more details in section 1.1.2.

RRMS, the most common subtype of MS is characterised by relapses, which are transient neurological symptoms that occur over a period of days and can take weeks to resolve completely. These clinical relapses correspond to the area in the brain and/or spinal cord that has developed a demyelinating lesion, significant enough to manifest with symptoms (Scalfari *et al.*, 2010). Examples of relapses include optic neuritis, where inflammation is localised to one of the optic nerves, or transverse myelitis where inflammation in the spinal cord can cause weakness and altered sensation in one or more of the upper and lower limbs.

Figure 1.1 Traditional clinical subtypes of multiple sclerosis

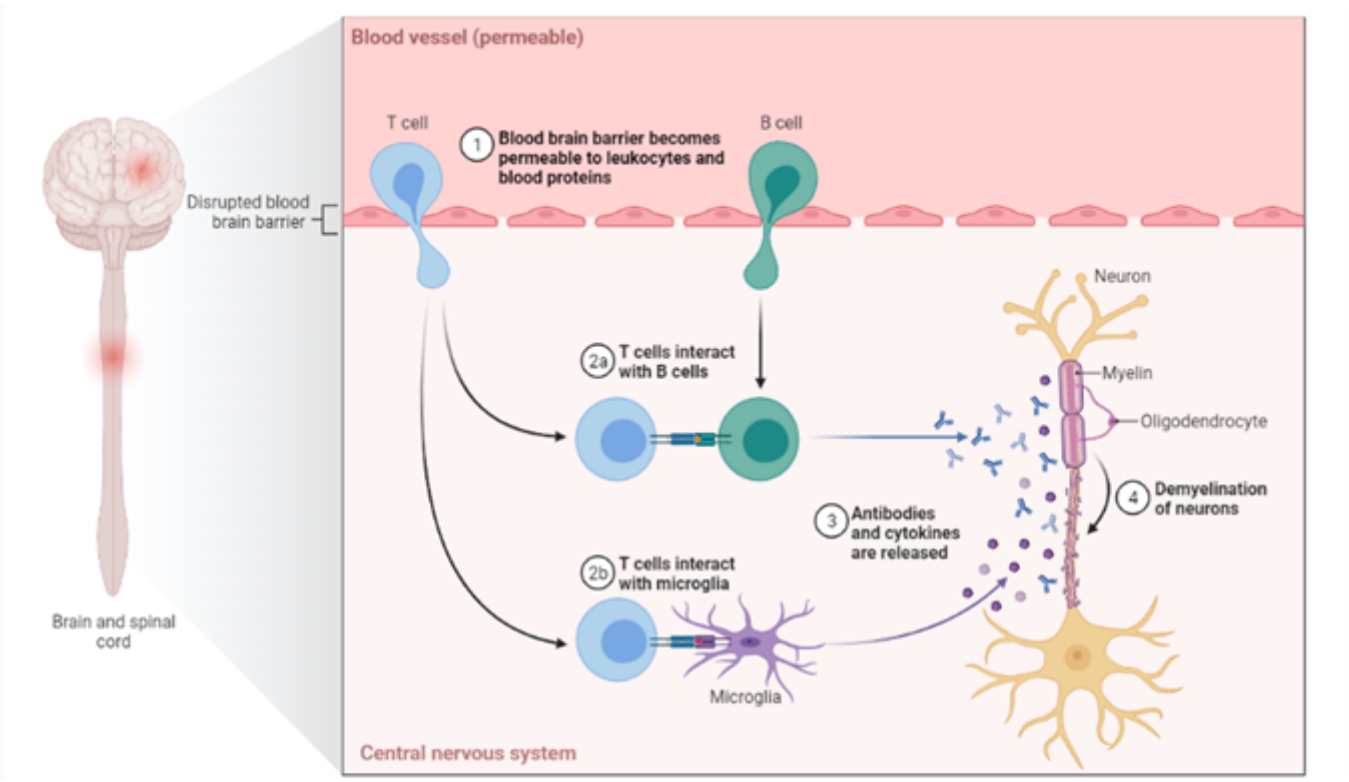


The peaks along the graphs represent relapses (clinical attacks) in which the patient has significantly worsened physical function, which then resolves to a varied extent. This recovery process can take several weeks.

1.1.1 Pathophysiology of multiple sclerosis

The characteristic pathological changes seen in MS consist of confluent demyelinating plaques in the gray and white matter of the brain and spinal cord. Peripheral immune cells gain access to the central nervous systems through the blood brain barrier which shows damage at sites of subsequent plaque development (Gay and Esiri, 1991; Vos *et al.*, 2005). These plaques are sites of active inflammation predominantly made up of macrophages and CD8+ T cells, as well as lower numbers of CD4+ T cells, B cells and plasma cells (Dendrou, Fugger and Friese, 2015). This inflammation results in areas of demyelinated axons in the grey and white matter, a reduced number of oligodendrocytes, increased macrophage deposition and myelin degradation products (Lucchinetti *et al.*, 2000). More recently, the white matter surrounding these plaques termed normal-appearing white matter (NAWM), as they appear normal on MRI, often exhibit chronic injury, characterized by the presence of axonal swelling, mild inflammation, microglial activation, and gliosis (Moll *et al.*, 2011). Overtime, chronic inflammation localised in the demyelinating plaques and as well as more diffusely in the NAWM leads to the loss of brain and spinal cord volume and development of a neurodegenerative process (Evangelou *et al.*, 2005; DeLuca *et al.*, 2006; Frischer *et al.*, 2009). An overview of the pathophysiological process is illustrated in Figure 1.2.

Figure 1.2 Pathophysiology of multiple sclerosis



Simplified overview of the pathophysiology of multiple sclerosis. Activated lymphocytes and monocyte, migrate across the blood brain barrier. Release of chemokines allow for the activation of adhesion molecules on the lymphocytes and monocytes, resulting in an interaction with the endothelial. T cells interact with B cells and microglia, which secretes a range of inflammatory mediators. This in turns recruits other inflammatory cells to the site and leads to demyelination of neurons. Created using BioRender.com

1.1.2 Diagnosis of multiple sclerosis

The diagnosis of MS has always been shaped by the lack of a singular diagnostic test. There is no serological, imaging or clinical biomarker that demonstrates an acceptable level of sensitivity and specificity for the disease. Over the decades, a number of clinical and para-clinical diagnostic criteria have been developed with periodic revisions taking into account new findings in the disease process (Schumacher *et al.*, 1965; Poser *et al.*, 1983). In 2001, an international panel of MS specialists published the Mcdonald diagnostic criteria which provided clinicians with the guidance on diagnosing the different subtypes of MS (McDonald *et al.*, 2001). Since then, these diagnostic criteria have undergone significant revisions in 2005 and 2010, with the most contemporaneous guidelines published in 2017 (Polman *et al.*, 2005, 2011; Thompson *et al.*, 2018). These diagnostic criteria are based on the principles of dissemination in space and time, as evidenced by the demyelinating lesions when seen on MRI or the presence of clinical symptoms. The 2017 McDonald diagnostic criteria have taken account of advances in MRI and detection of inflammation in the cerebrospinal fluid (CSF) to provide guidelines that allow a diagnosis of MS as early as possible whilst excluding other neuroinflammatory conditions (Gobbin *et al.*, 2019; Wattjes *et al.*, 2021). An outline of these diagnostic criteria is provided in Table 1.

The aim of the McDonald diagnostic criteria is to provide a timely diagnosis for people presenting with a clinical event suggestive of neuro-inflammation, whilst also excluding mimics of MS like neuromyelitis optica spectrum disorders and acute disseminating encephalomyelitis, to name a few. Subsequent revisions of the McDonald criteria in the last twenty years have

increased the sensitivity of the diagnosis, with the 2017 criteria demonstrating up to a 100% sensitivity, but with an impact on specificity compared to the 2010 criteria, partly due to the inclusion of CSF oligoclonal bands, in the diagnostic criteria. These oligoclonal bands are the presence of a disproportionate number of immunoglobulins in the CSF compared to blood, which when seen, indicates CNS inflammation, but can be present in a number of other neuroinflammatory diseases as well (Petzold, 2013; Gobbin *et al.*, 2019; Schwenkenbecher *et al.*, 2019).

The prompt diagnosis of MS has become more important due to the availability of a number of effective treatments primarily for RRMS, and more recently for PPMS and SPMS. However, as explained further in Section 1.1.4 later, these definitions of MS like RRMS, PPMS and SPMS are demonstrating ever similar pathophysiological characteristics, with regards to inflammation and neurodegeneration which makes consensus definitions difficult to establish.

Table 1 2017 McDonald criteria for diagnosis of multiple sclerosis in people with an attack at onset

Clinical attacks	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks*	≥2	None
≥2 clinical attacks	1	Clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI *OR* Demonstration of CSF-specific oligoclonal bands
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI *AND* Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific oligoclonal bands

*Clinical attack is defined as the development of neurological symptoms and signs that correspond to dysfunction in a region of the central nervous system. Clinical attacks can take weeks to resolve and can leave long-term impairment in function. CNS, Central nervous system; MRI, Magnetic resonance imaging. Adapted with permission from (Thompson *et al.*, 2018)

1.1.3 Treatment in multiple sclerosis

Since the approval of beta-interferon as a treatment for RRMS in 1993, there have been several different disease modifying therapies (DMTs) approved for the management of RRMS, each with their own mechanism of action and side effect profile (Finkelsztejn, 2014). Currently, thirteen different DMTs have been licensed by NICE for RRMS, including one also used for PPMS (ocrelizumab) and another two DMTs (siponimod and beta-interferon) licensed for SPMS. These immunomodulatory disease modifying treatments (DMTs) are not a cure for MS, but have been shown to reduce the number of relapses in PwMS and delay the onset of SPMS (Claflin, Broadley and Taylor, 2019). The efficacy of these DMTs is variable, based on their ability to reduce relapses and limit disease progression as measured in randomised control trials (RCTs), with some now showing evidence of being highly effective treatments compared to less efficacious platform treatments like beta-interferons that were developed earlier (Giovannoni *et al.*, 2020). Furthermore, evidence from large international patient registries, like the MSBase, have demonstrated that continued long term treatment with these DMTs significantly reduces disability accrual in RRMS over the medium to long term of up to 15 years (Kalincik *et al.*, 2021).

The availability of these treatments with different levels of efficacy and tolerability has led to significant variation in prescribing practices in the UK and in 2018 the commissioning body for DMTs, NHS England, produced a treatment algorithm that specified the appropriate treatment options based on the clinical presentation of MS and MRI findings in each case (NHS, 2018).

Concurrently, observational studies have identified that early intensive therapy with highly effective DMTs is superior to an escalation based approach where less efficacious therapies are initiated first with hopes of reducing any risk from treatment (Brown *et al.*, 2019; Harding *et al.*, 2019). This has encouraged the initiation of randomised control trials in the last couple of years in order to provide Class 1 evidence for the optimum treatment pathway for pwMS (Ontaneda *et al.*, 2020).

1.1.4 Progression in multiple sclerosis

Even with these treatments, the majority of people who have RRMS eventually enter a progressive phase of the disease, SPMS, with natural history data indicating that up to 40% of people with RRMS will develop SPMS after a decade (Weinshenker *et al.*, 1989). Whilst people PPMS are diagnosed at a later age compared to RRMS, people who develop SPMS tend to be older, having previously been through the relapsing form of the disease (Tremlett *et al.*, 2009). PPMS accounts for 10 – 15% of new diagnoses of MS, the rest being RRMS. There are a number of mechanisms underlying the accrual of disability in both PPMS and SPMS, but the acceleration of brain volume loss plays a primary role, brought about by the degeneration of chronically demyelinated axons (Sormani, Arnold and De Stefano, 2014; Mahad, Trapp and Lassmann, 2015; De Stefano *et al.*, 2016). Other factors, like smoking and vitamin D deficiency also contribute to a more rapid decline in disease associated disability (Hempel *et al.*, 2017). Pathologically, higher neurodegeneration rates are seen in people who have active inflammation, highlighting the link between inflammation driving neurodegeneration (Frischer *et al.*, 2009). Clinically, this is manifested as worsening performance both in

activities of daily living and the outcome measures used to assess physical and cognitive domains in clinic. Disability continues to accumulate throughout the course of the disease affecting mood, cognition, upper limb function and mobility with up to half of pwMS requiring the use of a wheelchair after 10 years' disease duration (Kister *et al.*, 2013; Conradsson *et al.*, 2018; Binzer *et al.*, 2019).

Despite the significant burden of progressive disease on pwMS, the treatments used in RRMS have been mostly ineffective in the progressive phase of the disease with a number of randomised controlled trials not meeting their primary endpoints (Ciotti and Cross, 2018; Faissner *et al.*, 2019). To date, Ocrelizumab, an anti-CD20 monoclonal antibody, is the only treatment licensed for PPMS. Siponimod, a sphingosine-1-phosphate receptor modulator, has been licensed for use in SPMS (Montalban *et al.*, 2017; Kappos *et al.*, 2018). Beta-interferon is also licensed for use in active SPMS, where the presence of relapses continues to affect the disease course (NHS, 2018).

There has been a significant focus on the reasons for the negative trials in progressive MS and some of the factors implicated include a different pathological mechanism driving progressive MS and the suitability of the outcome measures used in the trials (Ontaneda, Fox and Chataway, 2015). More recently, pooled data from two major clinical trials of DMTs in people with RRMS have shown that confirmed disability accumulation occurred independently of relapses in these trials (Kappos *et al.*, 2020). This has been previously alluded to in natural history studies which have demonstrated that long-term worsening is common in people with RRMS, and is largely

independent of relapse activity and is associated with accelerated brain atrophy (Cree *et al.*, 2016, 2019). This silent progression has been termed progression independent of relapse activity (PIRA) and challenges the current clinical distinction of relapsing and progressive forms of MS (Kappos *et al.*, 2020; Lublin *et al.*, 2022). In a recent population study of more than 5000 people with early MS, PIRA was an important contributor to confirmed disability accumulation. These indicate that insidious progression appears even in the earliest phases of the disease, suggesting that inflammation and neurodegeneration can represent a single disease continuum, in which age is identified as one of the main determinants of disease phenomenology (Portaccio *et al.*, 2022). In another prospective longitudinal study, long-term worsening was common in people with relapsing MS and was largely independent of relapse activity, whilst being associated with accelerated brain atrophy (Cree *et al.*, 2019). These recent studies have challenged the traditional subtypes of MS illustrated in Figure 1 and whilst these clinical subtypes are still widely used for the purposes of treatment eligibility, their pathophysiology has similar characteristics.

1.2 Function and disability in multiple sclerosis

The heterogenous clinical course of the different subtypes of MS produces a significant impact on pwMS, with regards to daily physical and psychological function. Forty percent of pwMS report some restriction in their participation with daily activities, and this increases to 80% in pwMS who have more severe disease (Cattaneo *et al.*, 2017). Around 45% of working age adults with MS have taken early retirement and/or left employment due to symptoms from their MS, and the subsequent disability during the course of their condition

(Kobelt *et al.*, 2006). The accrual of physical dysfunction in pwMS progresses in the long term, with manual dexterity, walking and cognitive ability declining over a period of 10 year in those with moderate to severe disease activity (Conradsson *et al.*, 2018). The relapse rate in the most common subtype of MS, RRMS, also impacts on the level of dysfunction and time to progression to SPMS in pwMS (Soldán *et al.*, 2015). Age and level of disability also drive cognitive impairment which can be seen in 34 – 65% of pwMS depending on disease course (Ruano *et al.*, 2017; Benedict *et al.*, 2020). Gait is also affected in up to 41% of pwMS and 74% of this cohort of people report a severe disruption to their daily lives. Up to 80% of pwMS also report significant variation in their walking ability when followed up over a period of 6 months to 2 years (LaRocca, 2011; Motl *et al.*, 2015).

1.2.1 Upper limb dysfunction in multiple sclerosis

Whilst preservation of walking ability is important for pwMS, as the disease progresses, and ambulation decreases, the preservation of upper limb function becomes an increasingly important concern (Kister *et al.*, 2013). Good upper limb function allows pwMS to use their walking aids effectively and interact with their environment allowing a level of functional independence in daily life. Even in RRMS, where ambulation is relatively preserved, impairment in upper limb function has shown a 35% reduction in home activities (Bertoni et al., 2015). Seventy nine percent of pwMS demonstrate detectable restrictions in upper limb function throughout the course of their disease, where people with PPMS and SPMS have a larger reduction in upper limb function compared to people with RRMS (Johansson et al., 2007; Holper et al., 2010). MR brain analyses of pwMS has shown that functional

abnormalities of regions involved in motor functions contribute to explain hand motor disability in pwMS (Cordani *et al.*, 2020). The incidence of sensory dysfunction in the upper limbs, along with decreased strength and dexterity is closely related to disease activity and up to 75% of pwMS demonstrate bi-manual deficits in strength and dexterity (Bertoni *et al.*, 2015). Upper limb dysfunction is also correlated with worsening cognitive impairment and perception of disability in pwMS (Yozbatiran *et al.*, 2006). Furthermore, upper limb function in pwMS is linked to the ability to complete daily tasks independently and in a recent survey of 360 pwMS, 314 (88%) of respondents reported preservation of upper limb function to be as important to them as their walking ability (Yozbatıran et al., 2006; Dubuisson et al., 2017).

1.3 Measuring function and disability in multiple sclerosis using clinical outcome measures

The heterogeneous physical, cognitive and psychological effects of MS in a given patient population make it difficult to accurately capture function and disability in pwMS and produce accurate outcome measures. However, given the lack of a biomarker with an acceptable level of sensitivity and specificity, clinicians and neuroscientists have developed several clinical outcome measures over the last few decades to assess the efficacy of interventions in MS clinical trials and practice. Clinical outcome measures are instruments used to quantity the clinical development of a disease and/or assess the impact of a treatment. Clinical outcome measures can be categorized as generic or disease-specific and are physician-based or patient-based. They

are also divided into measures of the construct of interest (e.g., walking ability) or according to the assessment aim (e.g., response to treatment) (van Munster and Uitdehaag, 2017). The three most commonly used MS-specific physician-based clinical measures in research and clinical practice are clinical relapse rate, the Expanded disability status scale (EDSS), and the Multiple Sclerosis Functional Composite (MSFC).

1.3.1 Clinical relapse rate

Clinical relapses in MS are seen in up to 85% of pwMS and as such have been used in a number of pivotal trials and in everyday clinical practice as a measure of disease activity and/or treatment efficacy (Duquette *et al.*, 1993; Polman *et al.*, 2006; Brinkmann *et al.*, 2010; Hauser *et al.*, 2017). A clinical MS relapse is defined as patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with a duration of at least 24 hours, in the absence of fever or infection (Polman *et al.*, 2011). Increased frequency of relapses in the early phase of the disease has been associated with a greater accumulation of disability and a quicker conversion to SPMS (Lublin, Baier and Cutter, 2003; Hirst *et al.*, 2008; Scalfari *et al.*, 2010). Relapse rate, therefore, continues to be used as an outcome measure in newer RCTs when testing treatments for people with RRMS (van Munster and Uitdehaag, 2017; Hauser *et al.*, 2020).

1.3.2 Expanded disability status scale

Whilst the relapse rate is a measure of clinical attacks, the level of disability in pwMS at any one point is clinically measured by the EDSS. The EDSS is a 10 point ordinal scale that has been developed to quantify impairment in seven

functional systems, namely the visual, sensory, pyramidal, brainstem, cerebellar, cerebral, and bowel and bladder systems. Ambulation ability and distance is also incorporated in the scale (Kurtzke, 1983). The scale is a neurological examination, usually carried out by a clinician trained in its administration and scoring methods. The points on the EDSS scale are illustrated in Table 2.

EDSS scores 0 to 4.5 refer to pwMS who are able to walk without any aids and the score is obtained from the combined scores of seven functional systems. EDSS scores from 5.0 to 9.5 are defined by impairment in walking and, at the higher end of this scale, by the ability of the pwMS to mobilise within their environment and carry out basic activities of daily living. An EDSS score of 10 is allocated when death has occurred due to MS. Since its development, the EDSS has been the primary outcome measure used in a number of Phase 3 trials for the approval of new DMTs (Polman *et al.*, 2006; Kappos *et al.*, 2010; Coles *et al.*, 2012). In these trials, the EDSS score has been used as a measure of disability progression, usually defined as an increase of at least 1.0 points on the EDSS scale from a baseline score of 1.0 or more, or an increase of at least 0.5 points from a baseline score of 5.0 or 6.0 that is sustained over three months. The three-month confirmation of a change in the EDSS score is required to exclude any transient changes in the EDSS measured during a clinical relapse (Sharmin *et al.*, 2022).

The complex examination and scoring system of the EDSS increases the inter- and intra-rater variability that has been shown to persist despite efforts to standardise the administration of the score (Noseworthy *et al.*, 1990; Goodkin *et al.*, 1992; Cohen *et al.*, 2021). Furthermore, early validation has established

the non-linear nature of the EDSS and demonstrated a bimodal distribution, with the majority of pwMS clustering around scores 1.0 – 2.0 and 6.0 – 6.5 (Weinshenker *et al.*, 1989). As the scores on the higher end of the scale are determined primarily by ambulation, the EDSS becomes less sensitive to change in pwMS who have higher levels of disability (Hobart, Freeman and Thompson, 2000; Meyer-Moock *et al.*, 2014). In pwMS with progressive disease, the EDSS by itself becomes less responsive to disability progression compared to pwMS with lower levels of disability. The addition of other outcome measures like the 9HPT and Timed 25 foot walk are needed to improve the responsiveness of the EDSS in this group of pwMS (Bosma *et al.*, 2009; Cadavid *et al.*, 2017)

Table 2 Expanded Disability Status Scale

Score	Description of clinical findings
0	Normal neurological exam, no disability in any FS
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m

5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting
6.5	Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally, has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms; retains some self-care functions
9.0	Confined to bed. Can still communicate and eat.
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

FS, functional system. A functional system is one of the seven major neural networks that are examined: visual, sensory, pyramidal, brainstem, cerebellar, cerebral, and bowel and bladder. Each functional system is individually scored on its own scale (not shown here) usually producing a score for each FS of between 0 (no disability) to 5/6 (severe disability). Each functional system score is termed either minimal, mild, moderate or severe disability and this is then used to identify the score on the EDSS based on the level of disability in the seven functional systems.

1.3.3 Multiple Sclerosis Functional Composite

In response to the limitations of the EDSS as an outcome measure, the MSFC was developed and recommended for use in clinical research in pwMS (Rudick *et al.*, 1997; Cutter *et al.*, 1999). The MSFC assesses three functional domains, ambulation, hand function and cognition, using three separate tests, one for each domain.

1.3.3.1 Timed 25-foot walk

The timed 25-foot walk test (T25W) was developed as part of the National Multiple Sclerosis Society's Clinical Outcomes Assessment Task Force efforts to produce a simple test of walking ability in pwMS (Rudick *et al.*, 1997). The test measures the time taken for a patient to walk, with or without walking aids, over a 25-foot distance on a flat surface, averaged over two attempts. Since its development, the T25W has been shown to correlate with the physical component of patient reported outcomes in a number of clinical trials, and a 20 – 25% change in time taken to complete the test correlates with a clinically meaningful change when compared to patient reported outcome measures (Cohen *et al.*, 2014; Motl *et al.*, 2017).

1.3.3.2 Nine-hole PEG test

The nine-hole peg test (9HPT), first introduced in 1971 has been used to measure upper limb dexterity in pwMS since the late 1990s (Rudick *et al.*, 1997). It has become the gold standard upper limb measure for pwMS both in the clinic and in trials. The 9HPT kit is shown in Figure 1.3. The psychometric properties of the 9HPT have been extensively studied with high inter-rater and retest reliability. It has also shown to be responsive to longitudinal progression

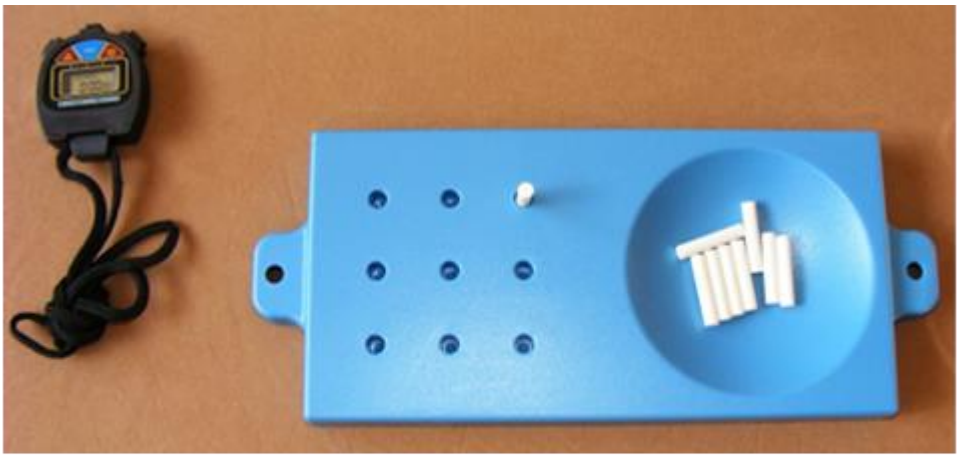
in pwMS. A greater than 20% deterioration in test performance correlates with clinically meaningful worsening (Feys *et al.*, 2017).

1.3.3.3 Paced auditory serial addition test

The Paced auditory serial addition test (PASAT) was first developed as a measure of processing speed in people with traumatic brain injuries, and has since been adapted for use in pwMS (Gronwall, 1977; Rao, 1990). The test involves an audio pre-recording of single digits presented to the participant at a speed of one digit every 3 seconds, and the patient adds each new digit to the one immediately prior to it and verbalises the answer after each digit for the duration of the test. Shorter inter-digit intervals have been used in variations of the test which has been validated in a number of other conditions with neurological dysfunction like chronic fatigue syndrome, hypoglycaemia, and depression (Tombaugh, 2006).

The MSFC score is a combination of the scores of these three tests and has shown to correlate strongly with the EDSS when measured in clinical studies and trials and provides a measure of cognition, which is lacking in the EDSS (Polman and Rudick, 2010). However, the limitations of the MSFC include practice effects related to the 9HPT and PASAT as well as the lack of consensus on the cut off for a clinically meaningful change on the total MSFC score (Schwid *et al.*, 2002; Solari *et al.*, 2005; Meyer-Moock *et al.*, 2014b).

Figure 1.3 Nine hole peg test equipment



The test measures the time taken for the participant to place nine small cylindrical pegs (7 mm diameter, 32 mm length) from a bowl into a three by three grid of nine holes and then take them out and place them back into the bowl. An average of two trials per hand is recorded

1.4 Upper limb outcome measures in multiple sclerosis

The need to comprehensively assess upper limb function in MS has always been important due to the high prevalence of upper limb dysfunction in pwMS, particularly in the progressive MS population. However specific outcomes measures for upper limb function have not been used as a primary outcome in MS trials until recently. The most commonly used outcome measure, the EDSS, used in pivotal MS clinical trials, is disproportionately focused on ambulation particularly at the higher end of the rating scale between EDSS 4.5 and 8.0, as demonstrated in Table 2 (Tur *et al.*, 2018). This may be related to the disconnect between the priorities of pwMS and clinical researchers. One recent survey in 2017, demonstrated that 93% of pwMS surveyed, thought that those who were restricted to wheelchairs shouldn't be excluded from DMT

trials, compared to only 49% of MS neurologists (Dubuisson *et al.*, 2017). This has led to a more focused approach to using the right outcome measures when quantifying upper limb dysfunction in pwMS, both for the purpose of trials and clinical practice.

1.4.1 Current clinical outcome measures of upper limb function

The most commonly used measure of upper limb function in pwMS is the 9HPT, which has been used alone and in combination with the MSFC to provide a measure of upper limb function in a number of DMT clinical trials (Meyer-Moock *et al.*, 2014a). The 9HPT shows moderate responsiveness in longitudinal studies and correlates with patient reported outcomes in pwMS, particularly those outcomes focused on unimanual activities (Feys *et al.*, 2017; Solaro *et al.*, 2019a). One study, based on 105 pwMS, defined the cut off between mild and severe upper limb dysfunction on a time score of 33.3 seconds (Lamers *et al.*, 2015). In addition to the 9HPT, other clinical outcome measures to capture upper limb function in pwMS have been developed and their properties are outlined in Table 3. These measures are used to measure upper limb dexterity and strength in pwMS and include the Action research arm test (ARAT), the Purdue pegboard test, and the box and block test (BBT), all of which have shown some reliability in clinical studies and have been validated for use in the MS population (Lamers *et al.*, 2014b). The 9HPT, Purdue pegboard test and BBT all measure repetitive unimanual movements, whilst the ARAT measures the ability to manipulate or transport large and small objects using different grasp, grip, and pinch functions. The ARAT has been studied in pwMS in one multicentre study and has been shown to have high inter-rater reliability and validity, although the participants in this study

included pwMS as well as people who had stroke and traumatic brain injury (Platz *et al.*, 2005). The BBT has been compared to the 9HPT and EDSS in a large study of 202 pwMS and has been associated with MS disease duration and EDSS, but it differed significantly from the 9HPT based on the level of disability as measured by the EDSS (Solaro *et al.*, 2020). The use of the Purdue pegboard test in measuring upper limb function of pwMS has been studied in a smaller sample of 32 pwMS and this study showed a high test-retest reliability (Gallus and Mathiowetz, 2003). The Jebsen-Taylor Hand Function Test (JTHFT) is another measure of upper limb function which has been compared to the 9HPT in a similar sized study of 43 pwMS, and showed good correlation with the 9HPT (Feys *et al.*, 2002). The exploratory studies which investigated these clinical outcome measures demonstrated the multidimensional character of upper limb function with some focused on gross motor upper limb movement and others on fine manual dexterity. Despite the prevalence of these outcome measures in studies of pwMS, their psychometric properties have not been extensively investigated, apart from the 9HPT, which has thus become the current gold standard clinical outcome measure in assessing upper limb function in pwMS (Lamers *et al.*, 2014a).

1.4.2 Patient reported outcome measures of upper limb function

There has been an increasing focus on using patient reported outcome measures (PROs) in MS as they allow people to provide a perception of their health condition, quality of life and well-being, which in turn gives clinicians and researchers an insight into the efficacy of treatment and/or intervention. A number of generic and disease-specific PROs have been developed to capture the perception of pwMS and are routinely used in current MS clinical

trials (Khurana *et al.*, 2017). More specifically, PROs designed to assess people's perception of their upper limb function have been developed and validated. Current PROs of upper limb function validated for use in pwMS are shown in Table 4.

The ABILHAND questionnaire has been the most widely studied PRO of upper limb function in pwMS. The ABILHAND was first developed as a tool to measure upper limb function in people with rheumatoid arthritis (Penta, Thonnard and Tesio, 1998). Since then, the ABILHAND has been adapted for use in a number of different conditions which affect upper limb function including stroke, systemic sclerosis, and hand surgery (Penta *et al.*, 2001). The 23-item chronic stroke version of the ABILHAND has been validated in a study of 300 pwMS demonstrating its use as a reliable measure of manual ability in MS (Barrett *et al.*, 2013). The Arm Function in Multiple Sclerosis Questionnaire (AMSQ) is a 31-item questionnaire which was developed specifically for use in pwMS and validated in a study of 301 pwMS (Mokkink *et al.*, 2015). A short form 10 item version of the AMSQ, called the AMSQ-SF has also been developed more recently and shown to correlate with the 31 item AMSQ questionnaire (Luijten *et al.*, 2018) The 36-item manual ability measure (MAM-36) scale was originally developed in a study of 44 pwMS, where it demonstrated correlation with pinch strength in the participants. (Chen *et al.*, 2007). In another study of 51 pwMS, the MAM-36 and ABILHAND questionnaires correlated significantly with each other and with the EDSS across a broad range of disability, with an EDSS range of the participants between 1.5 and 7.5. (Prada *et al.*, 2020).

The Disabilities of the Arm, Shoulder and Hand (DASH) scale is a 30-item questionnaire that has been developed as a generic PRO in people with disorders affecting their upper limb function. It uses a 5-point ordinal scale reflecting the ease or difficulty perceived while performing each of the 30 items (Hudak, Amadio and Bombardier, 1996; Beaton *et al.*, 2001). It has since been validated in a study with 300 pwMS, which showed that whilst it is a reliable measure of upper limb function in pwMS, the generic item bank meant that some items weren't relevant to pwMS (Cano *et al.*, 2011).

The ABILHAND, MAM-36 and AMSQ questionnaires have all been found to be reliable and valid in pwMS, less so for the DASH, but the responsiveness of these PROs in longitudinal studies is yet to be characterised as well as their ability to detect differences in upper limb function between the milder and more advanced progressive forms of MS (Lamers and Feys, 2018).

Table 3 Commonly administered upper limb outcome measures in multiple sclerosis

Outcome measure	Measurement	Description
Action research arm test (ARAT)	Unilateral ability to handle objects and gross motor movements	The participant uses pre-designed items to perform 19 tasks, some timed, divided into grasp, grip, pinch and gross movement tasks. The tasks are completed with each hand in turn.
Box and block test (BBT)	Unilateral gross manual dexterity	The participant moves as many cubes as possible (maximum of 150) one cube at a time, from one compartment of a box to another of equal size, within 60 seconds. The tasks are completed with each hand in turn.
Jebsen-Taylor Hand Function Test (JTHFT)	Unilateral ability to handle tests	The participant completes 7 sets of tasks, some timed, including writing, simulated page-turning, simulated feeding, lifting small objects, stacking, and lifting large, lightweight, and heavy objects. The tasks are completed with each hand in turn.
Nine-hole peg test (9HPT)	Unilateral fine manual dexterity	The test measures the time taken for the participant to place nine small cylindrical pegs from a bowl into a three-by-three grid of nine holes and then take them out and place them back into the bowl. The tasks are completed with each hand in turn.
Purdue Pegboard Test	Unilateral and bilateral fine manual dexterity	The participants place as many pins as possible from a cup into a pre-designed board with holes, using each hand and then both hands within 30 seconds. The test also includes bimanual assembly of as many pins and washers as possible by the participants within 60 seconds

Table 4 Patient reported upper limb outcome measures in multiple sclerosis

Patient reported outcome measure	Description
ABILHAND (23 item scale)	The participant rates their ability to perform 23 pre-set bimanual tasks, including with the use of aids
Arm Function in Multiple Sclerosis Questionnaire (AMSQ)	A 31-item questionnaire where the participant rates their difficulty in performing these tasks. A short form version of 10 items has also been developed (AMSQ-SF)
Manual Ability Measure (MAM-36)	The participant rates their difficulty in performing 26 unimanual and bimanual tasks
Disabilities of the Arm, Shoulder and Hand scale (DASH)	A 30-item questionnaire where the participant rates their ability to perform unimanual and bimanual activities.

1.5 Gaps in measurement of upper limb function in multiple sclerosis

The number of clinical and patient reported outcome measures in upper limb function described in the previous section, underlines the difficulty in developing outcomes that encompass the variability in disease course amongst pwMS, both individually and at a population level between different subtypes of the disease. Development of accurate outcome measures must take into account the heterogeneous clinical manifestations, unpredictable relapse rates and severity, relapse-related disability accrual as well as PIRA. Furthermore, whilst measures like the 9HPT and ARAT provide robust quantitative measures, they measure activity levels as a whole and do not provide detailed quantitative measures on the components of simple tasks

performed during the test. For example, the 9HPT assesses only the ability to perform fine dextrous manual movements and does not evaluate other important aspects of upper limb function, such as in-hand manipulation of objects, movements in the proximal part of the upper limb, gross manual dexterity, or complex coordinated bimanual tasks (Feys *et al.*, 2017). In addition, aspects of patient dysfunction that cause them to perform poorly on these tasks are not captured. For example, a patient with upper limb tremor and another patient with grip weakness will both perform poorly on the 9HPT, but the reasons for their poor performance on the test are not captured as part of the final outcome (the timed score). A large cross-sectional study of 9HPT in a random group of pwMS showed there were signs of floor and ceiling effects in the 9HPT scores in pwMS with low or high levels of disability (indexed by an EDSS score <3.0 or >6.0). Furthermore, hand asymmetry increased with accumulated disability, highlighting the difficulty in identifying whether pwMS have unimanual or bimanual dysfunction based on the overall 9HPT (Solaro *et al.*, 2019b) These findings raise concerns about the use of 9HPT in pwMS who have advanced disease.

In order to differentiate between pwMS with high levels of disability, more robust and detailed tests are needed, that are capable of measuring individual aspects of upper limb function like strength and dexterity. In order to develop these assessment tools, further understanding of the basic movements involved in upper limb function are required.

1.6 Overview of Prehension

The fundamental actions involved in all measures of upper limb performance including the 9-HPT and ARAT, is the ability of the subject to reach and grasp an object and manipulate it, given a predefined set of instructions. Split into its separate components, reaching involves moving the hand to an object and grasping involves fine manipulation of the thumb and fingers to create a suitable grip around the object. This basic ability to reach and grasp, known as prehension, allows individuals to perform the activities of daily living, by providing the capability to reach, grasp and manipulate a myriad of objects in any given task.

The act of prehension involves three primary components; the spatial positioning of the arm (the reaching or transport component), anticipatory posturing of the hand (the grip formation component), and object manipulation with the hand. The opposable thumb and high degree of independence of the fingers of the hand allow for several manipulative and prehensile activities (Jakobson and Goodale, 1991). A functional description of these hand movements, known as grip, when manipulating objects was given by Napier in 1956. He described two main types of grip with the human hand, the power grip and precision grip. In precision grip the object is pinched between the flexor aspects of the fingers and that of the opposing thumb. In a power grip, the object is held between the flexed fingers and the palm, with counter pressure being applied by the thumb (Napier, 1956).

Despite prehension describing the fundamental activity of object reaching and manipulation, the large number of degrees of freedom granted by the human hand and arm prevented a more accurate measurement of prehensile

activities until the 1980s when Jeannerod and others laid out a systematic approach to the measurement of prehension using kinematic techniques (Jeannerod, 1984, 1986). Through a series of experiments in which participants were recorded reaching for and grasping objects at a table, Jeannerod's team was able to describe the fundamental aspects of prehensile activities. This included concepts like hand velocity when reaching for objects, as well as grip aperture (GA) which is the distance between the fingertips (usually the index fingertip) and the tip of the thumb when reaching for objects (Jeannerod, 1984). This method of kinematic analysis of prehension activities became more common with a standardized reach and grasp movement adopted for experiments where the subject moved their hand from a starting position near the body axis and reached for an object placed at different distances in front of them, usually at the same horizontal level as the starting position. Recordings from markers placed on three anatomical landmarks also became more common during these experiments; one on the wrist, another one at the tip of the index finger and the third one at the tip of the thumb (Marteniuk *et al.*, 1990). As a result, a number of components of the reach to grasp motion in addition to hand velocity and grip aperture have been defined and characterised in healthy populations and in a number of neurological conditions. For example, reaction time (RT) defines the time taken for the initiation of the reaching movement after a stimulus. Movement time (MT), usually indicates the time from onset of the reaching motion to the completion of the grasping motion (Küper *et al.*, 2011).

Further experiments in 1986 showed that the cortex acts on somatosensory and visual feedback during prehensile activities to manipulate the hand shape

when grasping an object, and object parameters like width are directly proportional to the size of the maximum grip aperture of the hand when reaching for the object (Jeannerod, 1986; Marteniuk *et al.*, 1990). In addition, the parameters of any additional activity once the object has been grasped have also been shown to influence the hand shape and velocity when reaching for the object (Ansuini *et al.*, 2006, 2008). This anticipatory pre-shaping of the hand is also reflected in the more proximal muscles of the arm, which demonstrate changes based on the shape of the object and it's position (Martelloni, Carpaneto and Micera, 2009). The parameters of the object, type of grip and end goal also affect the amount of grip force applied on the object by the hand when grasping, known as grip force scaling. Less grip force is used when manipulating objects with a higher surface friction and the distribution of the grip forces changes based on the parameters of the object being handled (Kinoshita, Kawai and Ikuta, 1995; Pylatiuk *et al.*, 2006). These standard kinematic assessment techniques have been used in the last twenty years in various study populations of children and adults, in health and in disease, to map out a detailed physiological profile of prehension and how it can be affected in pathological states (Grafton, 2010).

1.6.1 The neural control of prehension

The kinematic measurement of prehension has developed alongside the understanding of the cortical control of reach and grasp. The primary studies that identified the neural networks involved in reach and grasp were carried out in macaque monkeys and other monkey species (Castiello, 2005; Castiello and Dadda, 2019). More recently, the development and widespread use of neuroimaging like MRI, has enabled the mapping of the prehension neural

networks in humans by studying disease states like stroke (Turella and Lingnau, 2014). Furthermore, other techniques like transcranial magnetic stimulation (TMS) have also provided non-invasive methods of induction of a focal current in the brain and transient modulation of the function of the targeted cortex, resulting in a transient “virtual lesion” (Pascual-Leone, Bartres-Faz and Keenan, 1999). This has allowed a number of studies to identify the role of cortical networks in the reach and grasp pathways using these “virtual lesions”. In monkeys, the reach and grasp pathways have been mapped to the frontoparietal cortex, and termed the dorsomedial and dorsolateral pathways, respectively. The dorsomedial pathway projects through the parietal reach region, from the visual area in the occipital cortex, to the dorsal premotor cortex (PMd) and then to the primary motor cortex (M1) (Vesia and Crawford, 2012). The dorsolateral pathway projects through the anterior intraparietal sulcus (aIPS) to the ventral premotor cortex (PMv) and from there to M1 (Turella and Lingnau, 2014). These cortical reach and grasp pathways in monkeys and their homologues in humans are illustrated in Figure 1.4.

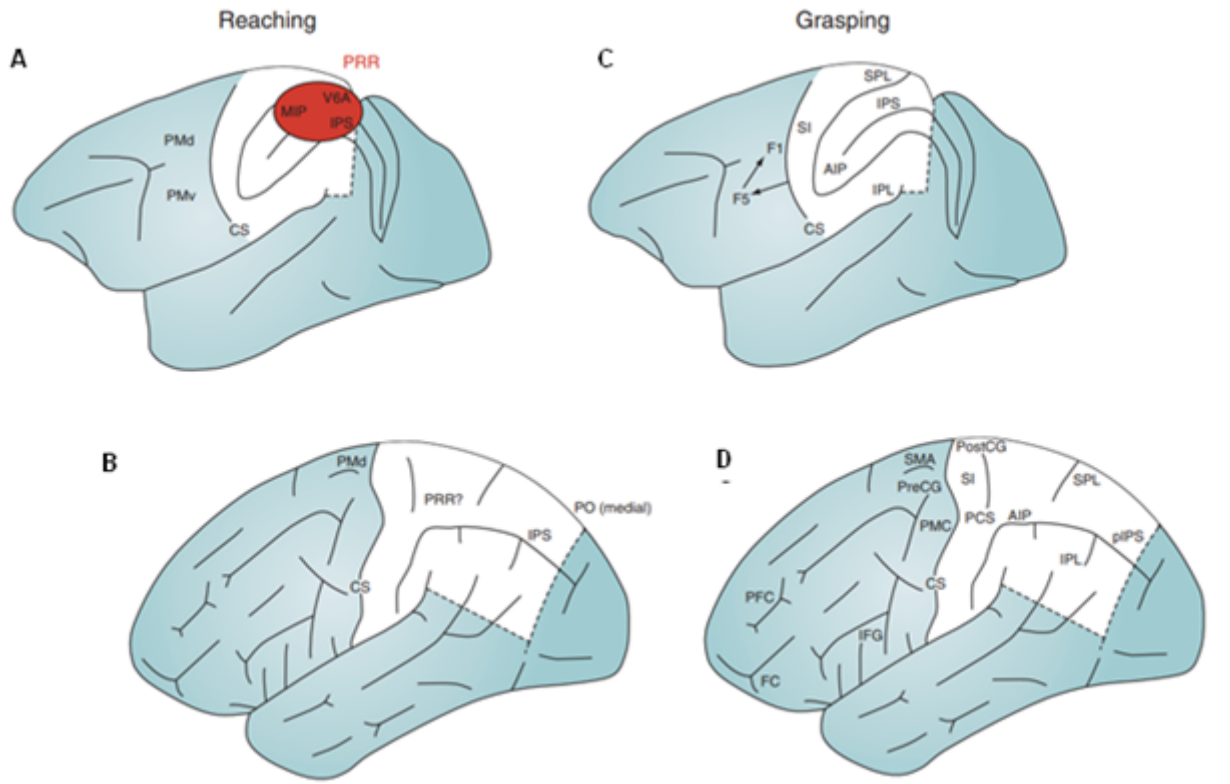
In humans, the posterior parietal complex is implicated during reaching for objects under visual guidance, specifically the aIPS, which is also activated during tactile manipulation of objects under visual guidance (Kertzman *et al.*, 1997). This is shown in a study of a patient with optical ataxia due to hypoxic brain injury, who demonstrated grip timing errors in tasks requiring reaching in the peripheral visual field, but no grip error when there was minimal reaching needed in the task in the central field of vision (Cavina-Pratesi *et al.*, 2010). This is supported by functional MRI analysis of cortical activity during reaching

tasks in healthy participants where central vision is involved, where a restricted network including the medial intraparietal sulcus (mIPS) and the caudal part of the dorsal premotor cortex (PMd) is activated. Reaching in peripheral vision also activated the parieto-occipital junction (POJ) and a more rostral part of PMd. These results show that reaching to the peripheral visual field engages a more extensive cortical network than reaching tasks in the central visual field (Prado *et al.*, 2005). fMRI analysis of the posterior parietal cortex during reach and grasp tasks has also shown that despite variability in cortical topography, visually guided grasping selectively and consistently activates an area located at the junction of the aIPS and postcentral sulcus contralateral to the involved hand (Frey *et al.*, 2005). This has been also shown in a TMS study, where the production of a virtual lesion in the aIPS, led to impairment in grasping with the contralateral hand (Rice *et al.*, 2007). The critical nature of the aIPS in humans is also highlighted in another fMRI study which shows that the aIPS is involved in the type of grip used, i.e., precision or power grip. Increased activation of the aIPS was seen when subjects in this study naturally adopted a precision grip to grasp the object but showed a much weaker response when a power grip was used (Begliomini *et al.*, 2007).

In summary, fMRI and TMS studies have revealed similarities between human and macaque cortical organization for hand movements, but the areas involved in different hand movements in humans are not functionally isolated cortical regions. Rather, there are highly distributed, overlapping parieto-frontal networks with gradients in preference for one movement compared to another. The knowledge of these cortical networks allows a more detailed

understanding of how impairments in these networks might lead to altered prehension in pwMS.

Figure 1.4 Cortical control of the reach and grasp networks in monkeys and humans



Comparison between neural circuits for reaching and grasping in the macaque monkey and humans. Lateral view of the monkey and human cerebral cortex for both reaching (A and B, respectively) and grasping (C and D, respectively) circuits. (A) Parietal reach region for reaching as identified in monkeys. (B) Reaching areas in humans as identified by neuroimaging studies. (C) Visuomotor stream for grasping as identified in monkeys. (D) Grasping areas as identified in humans by neuroimaging studies. Cortical areas that control grasping are also connected with basal ganglia and cerebellar circuits (these circuits, although involved in grasping, are not depicted here). AIP, anterior intraparietal area; CS, central sulcus; FC, frontal cortex; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; IPS, intraparietal sulcus; MIP, medial intraparietal area; PCS, postcentral sulcus; PFC, prefrontal cortex; PreCG, precentral gyrus; PostCG, postcentral gyrus; pIPS, posterior intraparietal sulcus; PMC, premotor cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PO, parietooccipital; PRR, parietal reach region; SI, primary somatosensory cortex; SMA, supplementary motor area; SPL, superior parietal lobule. Adapted with permission from U. Castiello, A.C. Pierno, Reaching and Grasping, Encyclopedia of Neuroscience, 2009.

1.7 Reach and grasp in multiple sclerosis

Studies investigating the reach and grasp function in pwMS are few compared to other neurological conditions like stroke, brain injury and Parkinson's disease, which have been more extensively studied, both via fMRI studies and kinematic assessment of patients (De Baets *et al.*, 2013; Parma *et al.*, 2014; Schwarz *et al.*, 2019; Latchoumane *et al.*, 2020). In the last couple of decades, the development of accelerometers and portable motion capture technology has allowed more studies to be carried out in these patient groups, and recently these techniques have been employed to delineate upper limb dysfunction in pwMS.

Electromyography (EMG) has shown that the activation and organisation of muscle synergies in upper limbs of pwMS is systematically different compared to healthy controls, with the progressive MS group being the most adversely affected. Reach movements requiring co-activation of multiple upper limb muscle groups are slower, less smooth and less accurate in pwMS compared to healthy controls in one study using surface EMG (Pellegrino *et al.*, 2018). Another study in pwMS who had upper limb dysfunction, used EMG to demonstrate that muscle activation in reaching tasks which needed synergistic muscle movements was inco-ordinated (Valè *et al.*, 2020). During the grasping stage, excessive grip force application in static and dynamic manipulation tasks were seen in pwMS who reported a mild dysfunction in their hand function (Krishnan and Jaric, 2008; Krishnan, De Freitas and Jaric, 2008). In another study, this variability in grip force when grasping objects was shown to be increased in pwMS and correlated with MRI changes in the white matter in the vicinity of the somatosensory and visual cortex. The variability in grip

force also correlated with the EDSS in this patient group (Reilmann *et al.*, 2013). These differences in grip forces are also significantly different between pwMS and healthy controls when grip needs to be reactive to an unpredictable grasping activity like catching an object (Allgöwer, Kern and Hermsdörfer, 2017). Furthermore, impairments in finger velocity and thumb-finger oppositional forces are even detected in pwMS with mild upper limb dysfunction (Bonzano *et al.*, 2013). More recently, Corona et al. measured the kinematics of hand to mouth movements in pwMS and healthy controls, demonstrating significant differences between the upper limb movements of the two groups. These kinematic data also correlated with the EDSS and 9HPT score in the patient group, although the authors transformed the kinematic parameters into a synthetic index for purposes of analysis that was not previously validated in pwMS (Corona *et al.*, 2018). These results were supported by another study which measured the kinematic profile of hand movements (to the mouth) and gait in pwMS. This study showed that although there was a significant correlation between EDSS scores with gait measurement, the correlation was modest with the upper limb kinematic outcomes, suggesting variations in upper limb function are not well-captured by the EDSS (Coghe *et al.*, 2019).

Carpinella et al. used an instrumented version of the ARAT alongside accelerometers and gyroscopes to show significant differences between pwMS and healthy controls with regards to smoothness and velocity of hand movement. The authors were also able to discriminate between the control and MS group to reveal subtle arm alterations that were not detectable on the standard ARAT score (Carpinella, Cattaneo and Ferrarin, 2014).

Other studies have also used kinematic assessment of reach and grasp activities as a motor marker after rehabilitation in pwMS who demonstrate upper limb dysfunction. In a single-blinded randomized controlled trial, investigators tested the efficacy of a 10-week virtual upper limb rehabilitation programme in pwMS. They showed significant improvements in the post-treatment assessment for coordination, speed of movements, and fine and gross upper limb dexterity for the group that underwent the virtual rehabilitation programme (Cuesta-Gómez *et al.*, 2020).

The differences in upper limb function between the relapsing and progressive subtypes of MS were more recently demonstrated using a two-sensor engineered glove which measured the kinematics of hand movements when pwMS performed the 9HPT. Glove-derived kinematic variables significantly differed between people with relapsing-remitting and those with progressive MS, with similar or slightly higher correlations of the 9HPT with clinical variables. The authors also showed greater correlations of the quality of life physical component scores with glove-derived variables than with the 9HPT, and a significant correlation of its mental component with the glove-derived variables but not with the 9HPT (Carmisciano *et al.*, 2020).

In a similar study, a virtual version of the 9HPT was administered to pwMS who reported upper limb impairment, with the authors able to identify and quantify tremor in the range of 3-5Hz in some participants using a frequency analysis, demonstrating the sensitivity of the instrumented version to quantify impairments not captured by the standard 9HPT (Lambercy *et al.*, 2013).

These kinematics studies have begun to provide a more detailed characterisation of upper limb function in pwMS via measurement of

prehensile activities, and in some studies have been shown to be more sensitive at detecting variation in upper limb function compared to the standard clinical outcome measures used. However, a limitation in most of these studies is the lack of proper clinical characterisation of the participants. For example, the subtype of MS, the presence or absence of concurrent relapses and the use of DMTs can all impact on the findings. Furthermore, the instruments used in these studies are not easily portable, limiting their potential expansion into the clinical space for use in routine practice. Studies like the one using the instrumented glove, have also adjusted pre-existing tests like the 9HPT but the movements assessed are the same. In order to understand the detailed aspects of upper limb dysfunction, the movements assessed need to be simple and based on the fundamental aspects of prehension. Also, the ability of these kinematic assessment techniques to detect longitudinal changes in upper limb function in pwMS needs to be explored as well as their correlation with perceived upper limb function as reported by pwMS.

The focus of this thesis is the first study to attempt to develop a kinematic assessment protocol with reasonable portability in order to explore and understand the fundamental aspects of prehension specifically in people with progressive MS. Furthermore, the use of PROs and established clinical measures enables a comprehensive assessment of any aspects of upper limb dysfunction detected by the kinematic protocol.

1.8 Summary

MS is the most common cause of neurological disability in young adults, and impacts on the cognitive, psychological and physical aspects of daily function. MS is a neuro-inflammatory condition, which has different clinical courses which has been described as active or inactive RRMS, PPMS and SPMS. In the last three decades several effective DMTs have been developed primarily for RRMS, with clinical trials and real world evidence demonstrating delayed disease progression over long term treatment.

RCTs in people with progressive MS (PPMS and SPMS) have not reached their primary endpoint for most DMTs that have been successful in the RRMS population. A different disease mechanism underlying progressive MS has been explored as well the suitability of outcome measures used in the trials in progressive MS.

People with progressive MS tend to have more advanced disease, which limits their ambulation and thus good upper limb function is of primary import in maintaining independence in activity and participation. Established clinical measures like the EDSS and 9HPT have been used in clinical trials and studies of upper limb function, but there is evidence of gaps in the measurement of upper limb function. More recently, kinematic assessment techniques provide a novel and more granular approach to the assessment of upper limb function.

There is a need to explore upper limb function, specifically in people with progressive MS, who have historically been excluded from trials. The development of a kinematic assessment protocol in order to assess and follow-

up people with progressive MS can explore specific aspects of upper limb function in this population.

1.9 Aims and Objectives

1.9.1 Aims

The aim of this thesis was to develop and use kinematic assessment techniques to characterise the extent and progression of upper limb dysfunction in people with progressive MS and to compare these techniques to existing clinical outcome measures.

1.9.2 Objectives

The objectives of this thesis to achieve the aim were as follows:

1. Develop a kinematic assessment protocol and kit to assess upper limb function
2. Identify appropriate people from the local multiple sclerosis population with SPMS and PPMS and recruit to the study
3. Recruit a healthy control population to the study with no upper limb dysfunction
4. Collect demographic and clinical information on the stage and progression of each participant's MS through neurological history and examination
5. Administer baseline clinical measures including the EDSS and 9HPT
6. Collect patient reported outcome measures of upper limb function
7. Evaluate differences in upper limb function as measured by the kinematic assessment protocol between pwMS and healthy controls
8. Follow-up participants recruited to the study and re-administer the clinical and kinematic assessment, as well as patient reported outcome measures at 6 months to identify any changes in upper limb function

Chapter 2 Materials and Methods

2.1 Ethical approval

This thesis is based on the clinical study *"Kinematic Assessment in Multiple Sclerosis (KAIMS)"* which received ethical approval from the National Research Ethics Committee (REC) and from the Health Research Authority (REC reference code: 19/SC/0542) in November 2019. This is an observational, prospective cohort study. The study also received approval from the local research and innovation department of Leeds Teaching Hospitals NHS Trust (R&I No: NE19/126048) in November 2019. This study was conducted on the clinical premises of the Leeds Teaching Hospitals Trust which was the sponsoring organisation of the study. The study has been registered on clinicaltrials.gov (NCT04283071). This study also received approval from the trial management committee of the contemporaneously active MS-STAT2 trial (NCT03387670), to be registered as a local sub-study for the trial. MS-STAT2 is a national phase 3 randomised, double blind, clinical trial investigating the effectiveness of repurposed simvastatin compared to placebo, in SPMS. Patients in the MS-STAT2 trial in Leeds who met the inclusion criteria for KAIMS were offered the opportunity to take part in both studies.

2.2 Patient involvement

The draft protocol of the study, patient information sheet (PIS) and consent forms which had been developed by the researcher were disseminated to the Leeds MS Society steering committee. The committee subsequently identified two patient representatives who agreed to individually review and provide

feedback on the draft protocol, PIS and consent forms. The pwMS communicated with the researcher via email and a face to face meeting was held separately with each of the two patient representatives in September 2019 once they had reviewed the study documents. During this meeting the patient representatives provided feedback on the protocol design and content of the PIS and consent forms to the investigator. Following the feedback from these meetings, there was no change to the study protocol, but the content of the PIS and consent forms were adjusted to be made clearer to potential participants. These corrected study documents were then submitted for ethical approval as detailed in section 2.1

2.3 Recruitment

Recruitment for the study began in November 2019 after ethical approval was granted. Participants in the patient group were recruited from the MS outpatient clinics at Leeds Teaching Hospitals NHS Trust. The MS neurologists and nurse specialists who deliver the clinics were provided with information on the study inclusion and exclusion criteria to identify prospective interested participants. Only patients with a clinical diagnosis of PPMS or SPMS were approached about taking part in the study. If interested, prospective participants were given a paper copy of the PIS (patient version) and contact details of the researcher. Participants in the control group, were recruited from a pool of healthy volunteers who had previously given consent to have their names and contact details listed on the “Successful Ageing research volunteer panel”, which is managed by senior researchers in the School of Psychology, University of Leeds. The volunteers on this database had consented to be approached about participation in psychology research

studies. The researcher contacted volunteers in the database via email and interested potential participants were provided with copies of the PIS (control version). Once prospective participants in the patient and control group had reviewed the PIS, a screening call took place with the researcher during which the eligibility criteria were applied, prior to arranging a study appointment.

2.4 Eligibility criteria

The eligibility criteria for the patient and healthy control volunteers were confirmed during the screening phone call, with confirmation from healthcare records in the case of the patient group and also during the initial study appointment.

2.4.1 Patient inclusion criteria

- Age above 18 years at the time of enrolment into the study
- Diagnosis of MS that has entered the primary or secondary progressive stage for at least 12 months, confirmed from healthcare records
- Self-reported difficulty with hand function
- Able to complete the 9-HPT, with at least the preferred hand.

2.4.2 Patient exclusion criteria

- Age below 18 years at the time of enrolment into the study
- Relapsing remitting MS (RRMS)
- Unable to complete the 9-HPT, with at least the preferred hand
- Any self-reported or clinically documented cognitive impairment
- Presence of co-morbidities that affect upper limb function e.g., stroke, arthritis etc.

2.4.3 Healthy control inclusion criteria

- Age above 18 years at the time of enrolment into the study
- Able to complete the 9-HPT in both hands

2.4.4 Healthy control exclusion criteria

- Unable to complete the 9-HPT with either hand
- Any self-reported or diagnosed cognitive impairment
- Presence of co-morbidities that affect upper limb function e.g., stroke, arthritis etc.

2.5 Study sample size

The Leeds MS register includes approximately 400 PPMS and SPMS patients living in Leeds although only a proportion of these patients attend clinics regularly.

Other studies exploring the use of instrumented tests to measure upper limb function in pwMS have included anywhere between 16 and 41 participants to obtain statistically significant differences when comparing between and within groups of pwMS. (Carpinella et al., 2014, 2012; Coghe et al., 2019; Krishnan et al., 2008; Valè et al., 2020). These kinematic studies have been shown to be more sensitive when compared to clinical outcomes and therefore a smaller study sample size has generally been used. As this was a pilot study, there was no effect size that had previously been elucidated using this kinematic protocol. Based on previous kinematic studies, a target sample of 40 was set anticipating a low recruitment rate from the study population. This is primarily because this patient population has moderate to severe disability with regards to their daily activities that makes it difficult to attend hospital sites. 84 patients

with progressive MS from the local MS register were screened; of these 42 patients were recruited to the study. Twenty healthy volunteers from the research volunteers panel expressed interest and of these 15 volunteers were recruited to the study, as five volunteers were unable to attend the study site within the testing period or had co-morbid conditions that affected upper limb function.

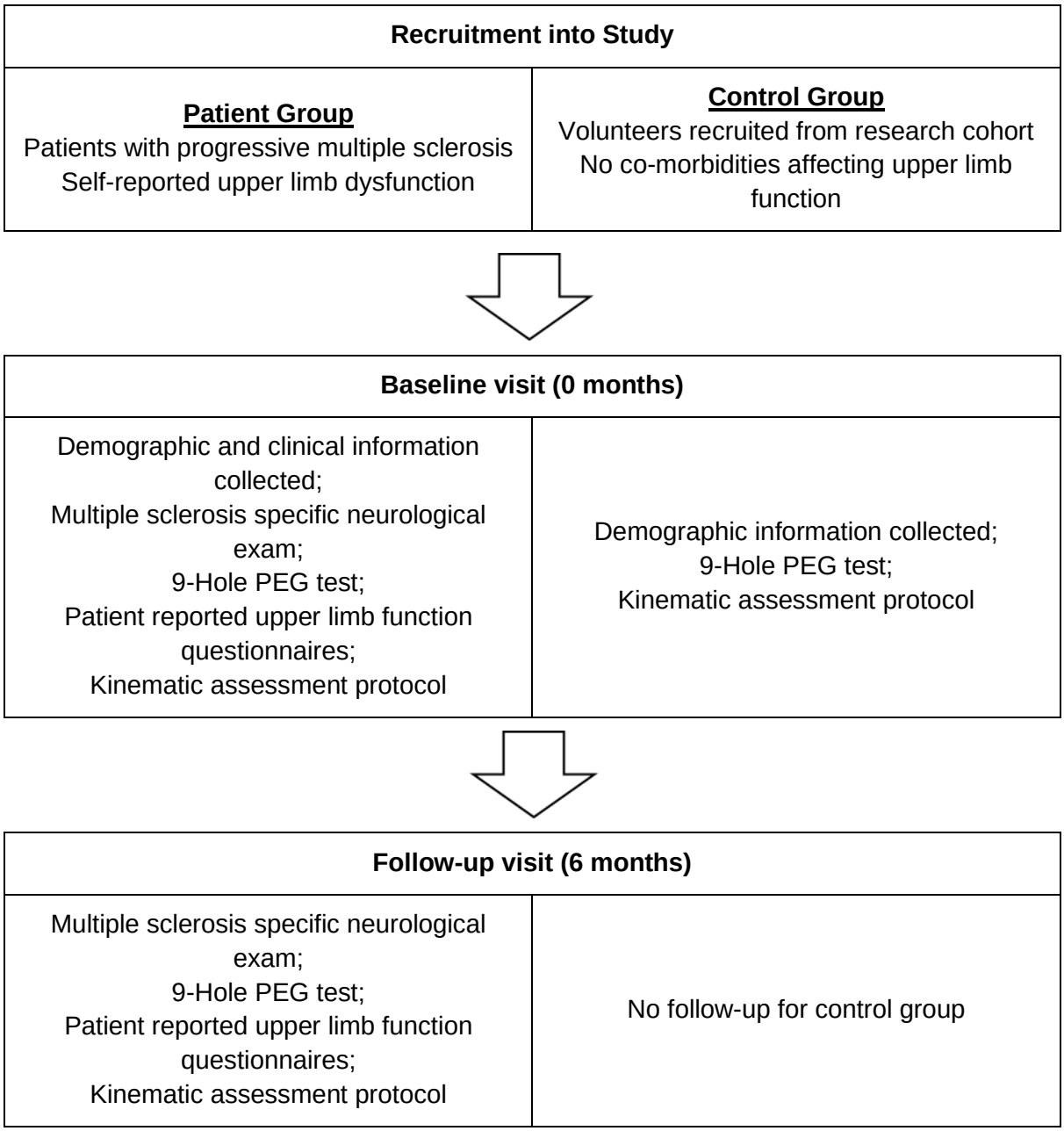
2.6 Consent

Written informed consent was obtained when the participant attended the hospital for the first study visit. The researcher confirmed that the participant had read and understood the previously distributed relevant PIS. They then completed the written consent form and progressed to the baseline assessment during the same visit. It was made clear to study participants that they were able to withdraw from the study, despite having signed the consent form, at any point without needing to provide an explanation for their withdrawal to the researcher.

2.7 Study design

This was a prospective, cohort study, with baseline measurements for the control and patient group and repeated measurements at follow-up for the patient group. The study design is illustrated in the flowchart in Figure 2.1.

Figure 2.1 Study flow diagram



2.8 Clinical assessment

2.8.1 Demographic and clinical information

Participants completed the consent process and then proceeded to the baseline visit. At the beginning of the baseline visit, demographic details including date of birth, age, and gender were collected from all participants.

Participants in the patient group were also asked the following questions:

- When did you first develop neurological symptoms, later attributed to MS?
- When were you diagnosed with MS and what type of MS?
- If initially diagnosed as RRMS, when were you diagnosed with SPMS?
- Have you had any relapse due to your MS in the last 3 months?
- Are you currently on any disease modifying treatment? If so, which one?

Patients and their partners, if they attended, were asked if they had noticed any cognitive impairment or concerns in the patient. One of the exclusion criteria was the report of any cognitive concerns. This was primarily because cognitive dysfunction has been shown to have an impact on motor movements of the upper limb in other neurological disorders and more weakly in MS (Cattaneo *et al.*, 2017; Bank *et al.*, 2018). The clinical records of all prospective participants in the patient group were also screened for any mention or discussion on cognitive impairment. However, a cognitive assessment test was not administered on entry to the study.

2.8.2 Hand preference

Each participant's handedness was determined by administering the four-item Edinburgh handedness inventory (short form) in order to determine the preferred and non-preferred hands (Oldfield, 1971; Veale, 2014). This inventory was used instead of hand dominance as pwMS might have had their dominant hand affected by the disease asymmetrically leading to a change in their hand preference. When the handedness inventory returned a result of ambidexterity, the dominant hand was taken as the preferred hand.

2.8.3 EDSS examination

After the demographic and clinical information was collected, the participants in the patient group were then administered the EDSS neurological examination which is used in the majority of clinical trials in pwMS (Kurtzke, 1983). The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent increasing levels of disability. EDSS steps 1.0 to 3.5 refer to people with MS who are able to walk without any aid and are based on measures of impairment in seven functional systems; pyramidal, cerebellar, brainstem, sensory, bowel and bladder function, visual function, and cerebral functions. A functional system represents a network of neurons in the brain associated with particular tasks. EDSS steps 4.0 to 9.5 are defined primarily by the participant's ambulation. The participants in the patient group were examined by the researcher and assigned an EDSS score between 0 and 9.5 based on the criteria as outlined in the table in Chapter 1.

2.8.4 Patient reported questionnaires

Participants in the patient group then completed two questionnaires designed to measure their self-reported hand function.

The ABILHAND questionnaire has been developed to measure manual ability for adults with upper limb impairments (Penta et al., 1998). A 23-item version of the questionnaire has been developed for use in people after stroke, but has been validated in the MS population and has been used in a number of MS studies of upper limb function as a patient reported outcome measure (Barrett et al., 2013; Marrie et al., 2017; Penta et al., 2001). The questionnaire consists of 23 daily activities and the participant is asked to estimate the ease or difficulty of performing each activity when the activities are done without help, irrespective of the strategies used to perform the activity. The participant scores their perception of their ability to do each activity on a scale of “Impossible", "Difficult" or "Easy", scored as 0, 1 or 2 respectively. Activities not attempted in the three months prior to the questionnaire date are recorded as unknown. The final score is based on the sum of the all individual activity scores providing a range of scores from 0 to 56, with a higher score indicating better performance. The raw score can then be inserted into a Rasch model of online analysis, which converts the raw scores into a linear measure. (“ABILHAND - Rasch analysis specific to chronic stroke patients - Rehab-Scales.org,” n.d.) For the purpose of this study, participants scoring between 39 and 56 inclusive, were classed as having “mild dysfunction”, those scoring between 20 and 38 inclusive, were classed as having “moderate dysfunction” and those scoring between 0 and 19 inclusive were classed as having “severe dysfunction”. Use of the ABILHAND questionnaire is covered by a creative

commons attribution, non-commercial, no-derivation 3.0 license and the test packages and instructions for administration were obtained from the rehab scales website (“ABILHAND - Downloads,” n.d.).

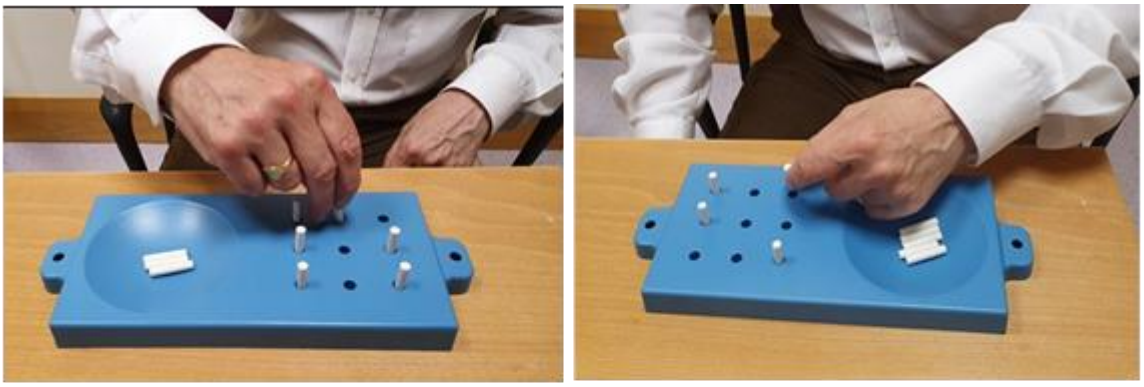
The AMSQ-SF is a 10-item questionnaire which has recently been adapted from the 31-item Arm Function in Multiple Sclerosis Questionnaire (Luijten et al., 2018; Mokkink et al., 2015). This uni-dimensional questionnaire, unlike the ABILHAND and other upper limb patient questionnaires has been developed specifically for use in the multiple sclerosis population and has been validated in MS populations in multiple countries (Ertekin et al., 2021; Tacchino et al., 2020). However, its recent development has meant that it has not been used in clinical trials. In the AMSQ-SF the participant is asked to score each of 10 bimanual activities, on a scale of six, based on how limited they have been in these activities in the last two weeks. If they have not done the activity in the previous two weeks, they are asked to imagine how they would perform on the activity if they completed it in the two weeks prior to the test. A score of one is given for the activity if the participant finds no limitation in doing the activity at all and a score of six is given if the participants is no longer able to do the activity due to limitations from their MS. Each point of the scale in between increases based on the level of difficulty the participant has with the activity. Thus, a lower score indicates a better performance in the AMSQ-SF in contrast to the ABILHAND questionnaire. The maximum possible score for each activity is 6 and the final score is the sum of all 10 activities, giving a range between 0 and 60. For the purpose of this study, participants scoring between 0 and 20 inclusive, were classed as having “mild dysfunction”, those scoring between 21 and 40 inclusive were classed as having “moderate dysfunction” and those

scoring between 41 and 60 inclusive were classed as having “severe dysfunction”. Permission to use the AMSQ-SF questionnaire in the study was personally obtained by the researcher from the research team who developed the questionnaire (Luijten et al., 2018).

2.8.5 9-HPT administration

Participants in the control and patient group were administered the 9-HPT as described in Chapter 1. After explaining the instructions for the test, the time taken to move the nine pegs from the bowl to the peg holes and then back to the bowl was measured using a stop clock. Two trials were completed for each hand, to obtain a total of four scores. Figure 2.2 outlines an example trial in progress with each hand.

Figure 2.2 Participant completing the 9HPT with each hand



A) Trial with right hand. **B)** Trial with left hand. For each trial, the participant can only move the pegs with one hand in any order they wish, and if a peg is dropped off the board they will continue with the trial whilst the researcher will place the displaced peg back in the bowl for them to move again. The bowl with the pegs is placed toward the hand that is being tested. The researcher will also keep the board in position, by holding one of the protruding plastic tabs on either side of the board to prevent it from moving during the trial.

2.9 Kinematic assessment set-up

After completing the clinical assessments, the participants in the control and patient groups proceeded to the kinematic assessment.

2.9.1 Boxed Infrared Gross Kinematic Assessment Tool

The Boxed Infrared Gross Kinematic Assessment Tool (BIGKAT) is an optical motion capture system, which records the movements of infrared light emitting diodes (IREDs) in three-dimensional (3D) space by triangulating images from a pair of infrared cameras. These cameras are controlled by separate controllers which work in synchrony with each other as a single stereo pair for the stereo triangulation of the point source, in this case the IREDs, in 3D space. 3D data points can then be further analysed to extract useful output measures to quantify movements. For example, in a prehension movement, one can extract the speed of, and distance travelled by, each IRED. The BIGKAT camera system is illustrated in Figure 2.3.

BIGKAT uses two Raspberry Pi 3 Model B (RPis) single board computers, each connected to an infrared camera module (PiNoIR) camera. The RPis communicate with each other over an ethernet cable. The master RPi is connected to a computer displaying a graphical user interface (GUI) which will allow the researcher to operate the BIGKAT software (installed on the master RPi) to collect demographic information and record movement videos, directly saving to a specified folder in external storage, with on-board data processing facility. Post-processing of the movement videos will also be performed using BIGKAT software on computers.

Prior to its use in the kinematic assessment, once BIGKAT had been placed in the study site, the cameras were calibrated by the researcher using

techniques previously developed in the lab (Zhang, 1999). The focal length and distortion parameters of each of the two cameras (intrinsic parameters), as well as the position and orientation of the two cameras relative to each other (extrinsic parameters) were calibrated using a chequerboard with pre-specified dimensions. This calibration process was an iterative process, with the calibration script from the first static frame analysis then being tested and refined on subsequent static and then movement videos. The BIGKAT cameras recorded at 60 frames per second, providing a timed error rate of $1/60^{th}$ second (60Hz) and the accuracy of the IRED measurement was within the width of each IRED itself which was 5mm. Through the use of a calibration script in Python (software programme) individual static frames of the chequerboard were analysed and the intrinsic and extrinsic parameters of the cameras were then set and thereafter applied to the videos recorded by BIGKAT during the kinematic assessment trials.

Figure 2.3 BIGKAT camera system as seen from the participant's view

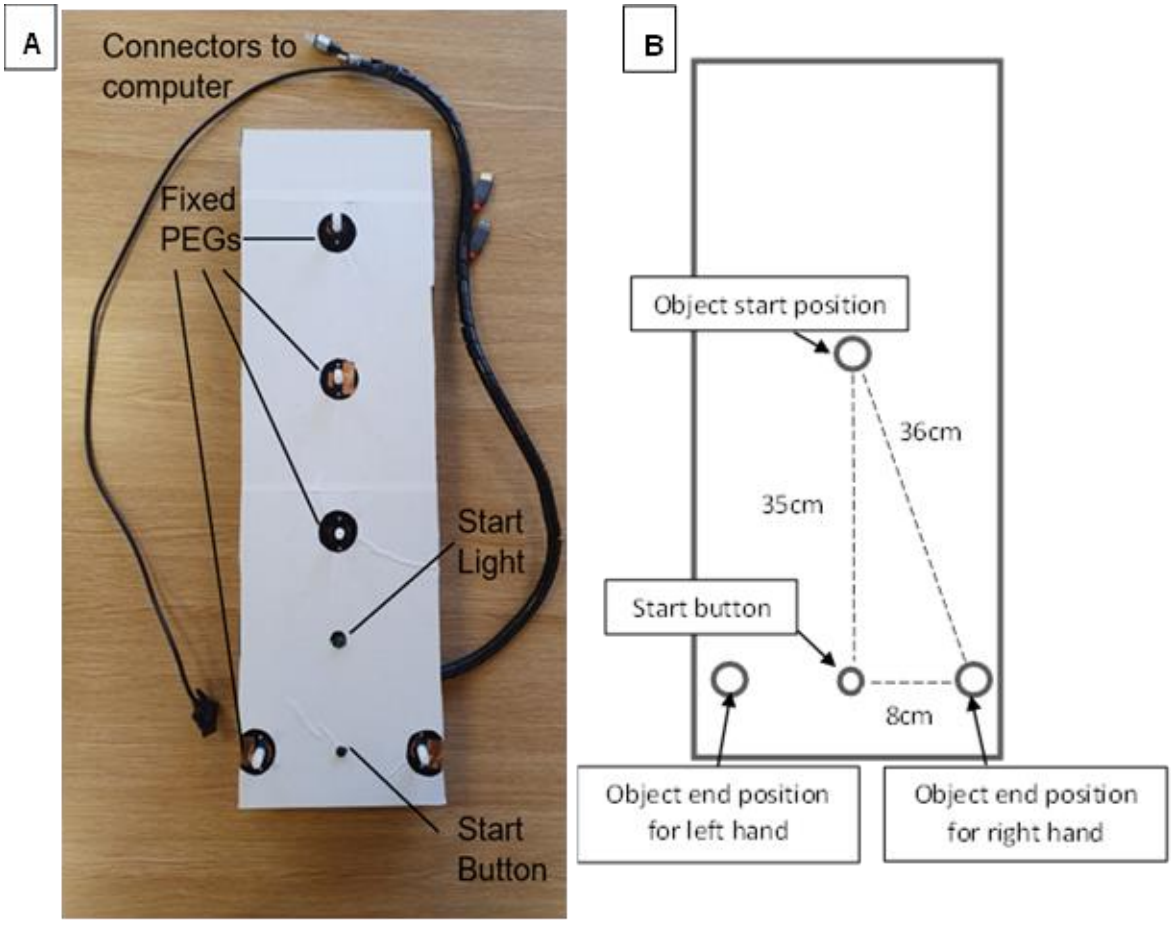
Both cameras are covered by an infrared filter and connected to a pair of Raspberry Pi boards. The system is connected to an external monitor and computer system to manipulate the trials and observe the data collection. The system is placed on a tripod and positioned at a height of 6 feet, with the cameras angled down toward the participant

2.9.2 Event detection kit

An event detection kit (EDK) was also developed with input of engineering colleagues in the lab. The EDK and its dimensions is shown in Figure 2.4. The EDK has been designed with a number of pegs standing at a height of 2 cm at predefined positions on the board. The pegs are connected to a start button and each other via a breadboard circuit and in turn linked to a Raspberry Pi 3 Model B (RPi) single board computer. Each peg has a copper contact around its base, which is activated when one of the cylindrical objects used in the study is placed over the peg and down over the contact. The EDK generates timed data from the pegs situated on the board, depending on which contacts

at each peg are activated. The EDK is symmetrical allowing mirrored movements across the board with either hand. The board is connected to an external monitor and computer system to manipulate the trials and observe the data collection. Whilst BIGKAT can record the position of IREDs (and therefore the hand if the IREDSs are places on it) throughout the movement, the EDK only records time points at which objects contact or leave the base.

Figure 2.4 Overview and dimensions of the event detection kit



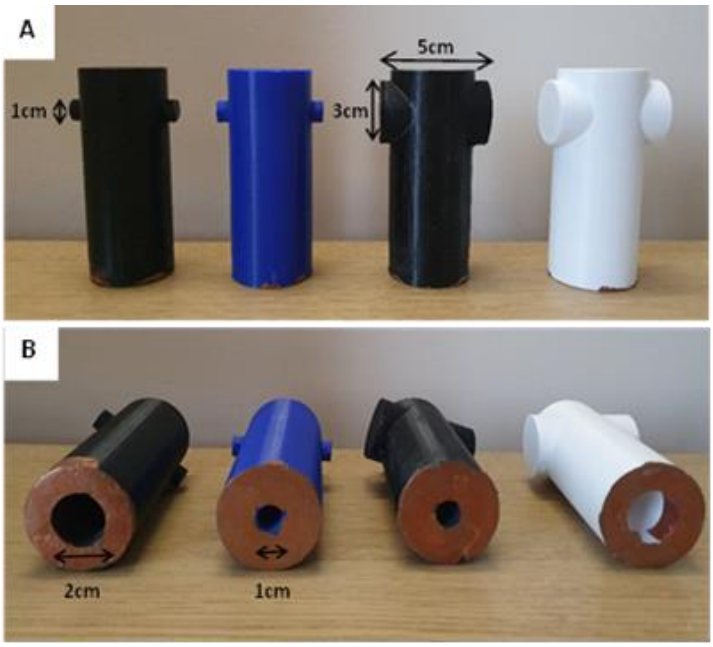
A) Aerial overview of the event detection kit **B)** Salient dimensions of the event detection kit, illustrating the distances between the starting button, object start and end positions, which is the distance the participant moves their hand across during the trial. The object end position on the left of the start button is the where the patient moves the object when using their left hand, and the object end position of the right of the start button is used for the trials with the right hands

2.9.3 Objects used in the reach and grasp trials

The objects used in the study were designed using Solidworks software and were 3D-printed. Four objects were used in the trials and their specifications are shown in Figure 2.5. Apart from the grasp surface size and base hole diameter, the objects were identical in their dimensions. Each object weighed 50 grams. The objects were designed to mimic the size of everyday objects that might be picked up with one hand, e.g., a small cup. Previous studies have shown that the available surface for grasping an object determines the pre-shaping of the hand and grip aperture (Verheij, Brenner and Smeets, 2014). The size of the base hole diameter at the bottom of the object was designed as a means of replicating the alignment of the object with the peg at the end of the movement, similar to the alignment of the pegs with their holes in the 9HPT. Furthermore, as the holes were at the base of the object, it would limit the visual feedback when placing these objects on the peg on the EDK. The lack of visual feedback has been shown to increase the time taken for object manipulation and movement and it we hypothesized that objects with the smaller base hole diameter would take longer to place than objects with the larger base hole diameter (Timmis and Pardhan, 2012). It was also theorised that all participants would take longer to reach for objects with the smaller grasp surface size compared to the larger grasp surface size based on previous work done in the lab (Mon-Williams and Bingham, 2011). These objects properties would allow any effect of grasping and base hole parameters on the reach and grasp of pwMS to be elicited and we hypothesized that these differences at a group level would be significantly greater than the differences seen in the control group. The manipulation of

these object factors would also allow us to identify if the kinematic assessment protocol would be sensitive enough to detect these changes in reaching and grasping behaviour in our cohort, as we know these alterations exist in the healthy populations. This would ultimately allow an understanding of the important of object characteristics and visual feedback on the upper limb function of pwMS.

Figure 2.5 Objects used in the kinematic assessment trials



(A) The 3D printed cylindrical objects used for the kinematic assessments include four objects, each with a width of 5 cm between the two grasp surfaces. Two of the objects have a 1 cm grasp surface size. Two objects have a 3 cm grasp diameter. **(B)** The bottom of two of the objects have a 1 cm diameter hole, to allow the object to be placed on the corresponding peg on the event detection kit, which are just less than 1 cm in diameter. The other two objects have a 2 cm diameter base hole diameter. The copper tape on the bottom of the objects allows the event detection kit to pick up the contact of the object once it is placed on a peg.

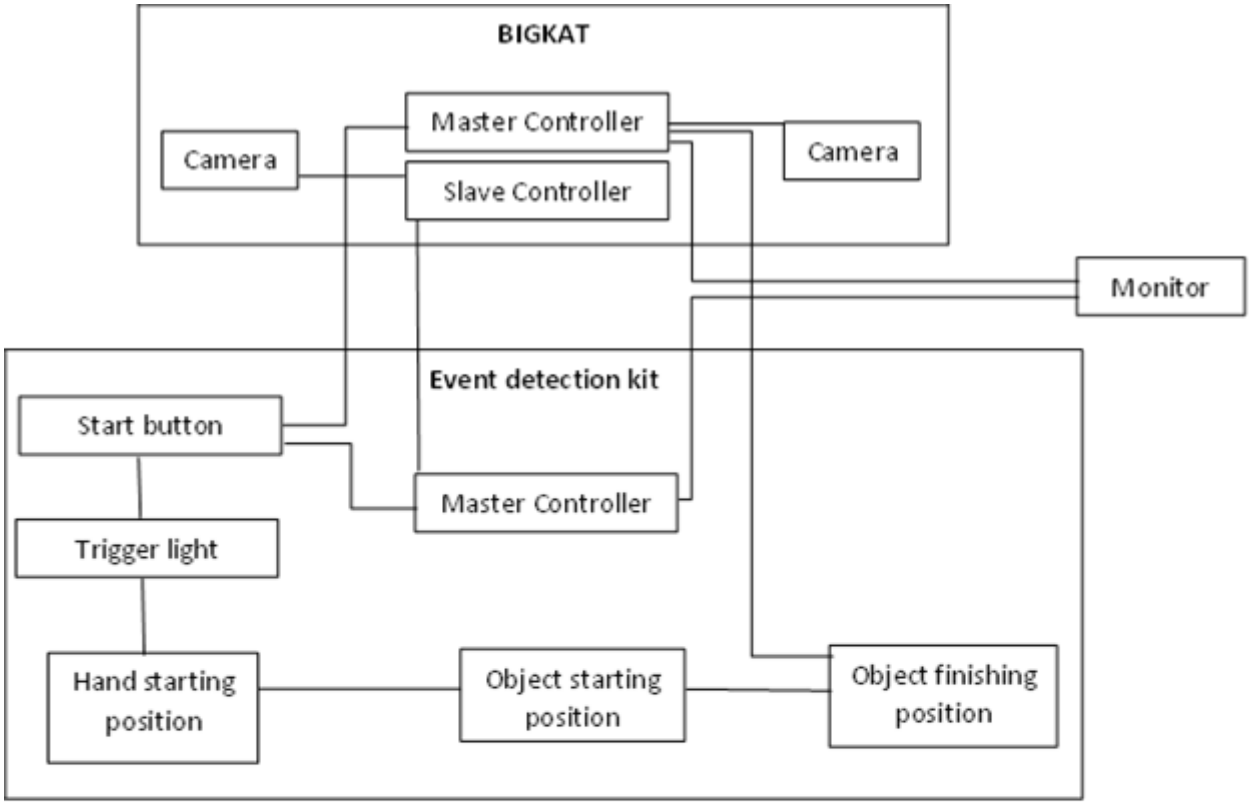
2.9.4 Integration of BIGKAT and the EDK

In order to allow BIGKAT and the EDK to record movements across the EDK simultaneously, the two systems were linked so that trial initiation would trigger recording in both systems simultaneously. A schematic overview of BIGKAT and the EDK is shown in Figure 2.6.

BIGKAT cameras were calibrated to the three IREDs that would be used on the hand during the study and required parallel connection to the EDK. Once BIGKAT and the EDK had been connected, the Python programming script running the EDK was modified to synchronise with the cameras on BIGKAT. The researcher performed a number of sample trials to identify the optimum lighting environment and position of BIGKAT in relation to the EDK, so that the kinematic parameters extracted were consistent across trials between hands and across all four objects.

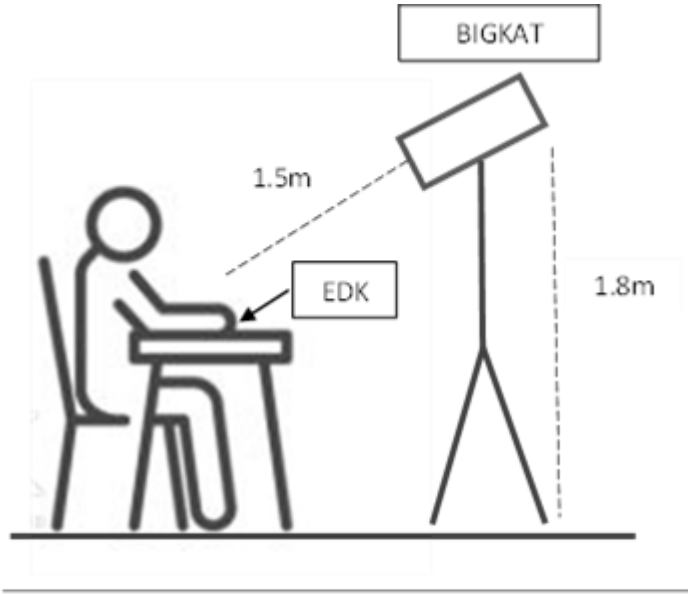
The position of BIGKAT in relation to the participant is shown in Figure 2.7. The position of the table, EDK and BIGKAT were unchanged throughout the trials with all participants, in order to limit variation in the distance between the cameras and the EDK. The same testing room was used for all the participants in the study for the baseline and follow-up study visits.

Figure 2.6 Schematic of BIGKAT and the event detection kit



The two master controllers and one slave controller in BIGKAT and the event detection kit represent raspberry pi processors which are connected to the cameras and the contacts on the event detection kit, respectively. BIGKAT and the event detection kit are both connected to monitors to allow the researcher to monitor the data collection contemporaneously. The connectivity between BIGKAT and the event detection kit also means that the cameras only record for the duration of the trial and stop recording thereafter, allowing the researcher to move on to the next trial immediately. This reduces the time required to perform all the trials.

Figure 2.7 Kinematic assessment set up

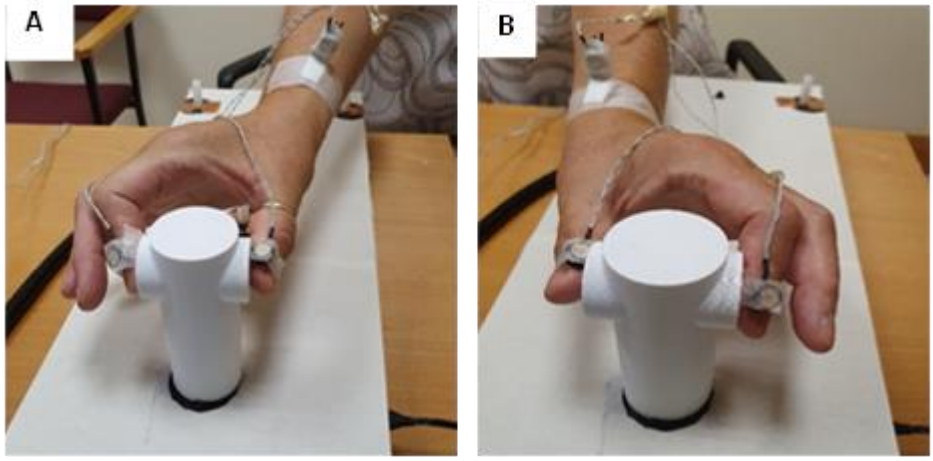


Distance between BIGKAT on its stand and the participant when they are sat at the table with the event detection kit. BIGKAT is placed across from the participant in front of the table.

2.9.5 IRED placement during the trials

Three IREDs were used for the trials, in order for the BIGKAT cameras to capture the movement of the participants' hands. The IREDs were fixed to the tip of the thumb, index finger and radial aspect of the wrist, just proximal to the anatomical snuff box. Figure 2.8 shows the placement of the IREDs on a participant's hands as they reach for one of the objects during a sample trial. The participants were asked to always reach for, grasp and move the objects using the pincer grip only, which involves just the thumb and forefinger in opposition as demonstrated in Figure 2.8.

Figure 2.8 Placement of the IREDs during the reach and move trials



Placements of the three IREDs on the participant's right **(A)** and left **(B)** hands. The IREDs were affixed with small strips of tape to the participant's forefinger, thumb and radial aspect of the wrist as shown. The pictures show the pincer grip the participant uses to grasp the object, as instructed. The wires from the IREDs were affixed to the forearm with a small strip of tape to minimise any impedance on the reaching movement of the participant.

2.9.6 Kinematic assessment protocol

The participant was asked to sit at the table with the EDK placed on it, across from BIGKAT as shown in Figure 2.7. The participant was seated close enough to the table so that they could reach across the EDK without leaning forward. The IREDs were affixed to one hand at a time, so all the trials were completed on one hand before affixing the IREDs to the other hand and completing the trials in that hand. The kinematic trials were carried out in a moderately lit environment, to prevent the cameras from detecting reflective surfaces as this would interfere with the recording of the three IREDs.

The sequence of events for each trial is illustrated in Figure 2.9 and outlined below:

1. For each trial the participant would move one of the cylindrical objects illustrated in Figure 2.5 from its position on the object start position as shown in figure 2.8A, to the object end position on the EDK. The object was placed on the object start position by the researcher at the start of each trial
2. The trial started with the participant's thumb and forefinger opposed in a pincer position and they were asked to hold down the start button on the EDK whilst focusing on the start light on the EDK, shown in Figure 2.4. Figure 2.9 illustrates the starting position for each hand.
3. The investigator triggered the start of the trial recording remotely on the computer, at which point the start light lit up green after a random delay of between 0.5 and 1.5 seconds.
4. Once they saw the start light flash green, the participant reached for the cylindrical object using a precision (pincer) grip as shown in Figure 2.8, picked it up, moved it to and placed the object on the object end position. This completed one trial. Figure 2.10 demonstrates key instances in a trial as recorded by BIGKAT.
5. The trial was then repeated five times with the same object. The researcher repositioned the object on its starting position on the EDK after each trial.
6. After five recorded trials the object was then switched to one of the other three objects and five further trials were recorded with each of the objects. The order in which the objects were used was determined by a random number generator in Microsoft Excel with a block size of 10.
7. The IRED markers were then affixed to the other hand and the participant performed steps 1 - 6 again.

8. At the end of the kinematic assessment the participant had performed 5 trials with each of the four objects in both hands, recording 20 trials per hand, and 40 trials in total.

In total, the kinematic assessment lasted between 15 – 20 minutes depending on the level of the participants' hand dysfunction. The participant was offered the opportunity of a few minutes rest between testing each hand, but none of the participants during the study requested a break.

Figure 2.9 Participant starting position for each trial

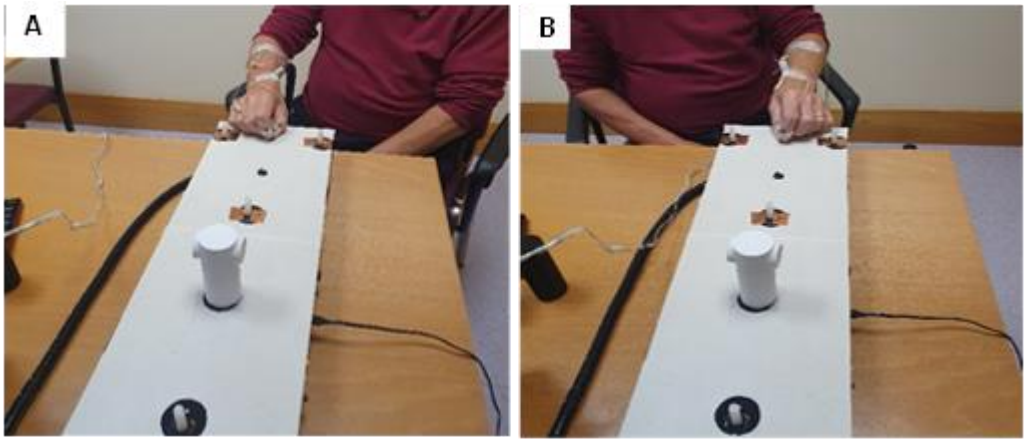
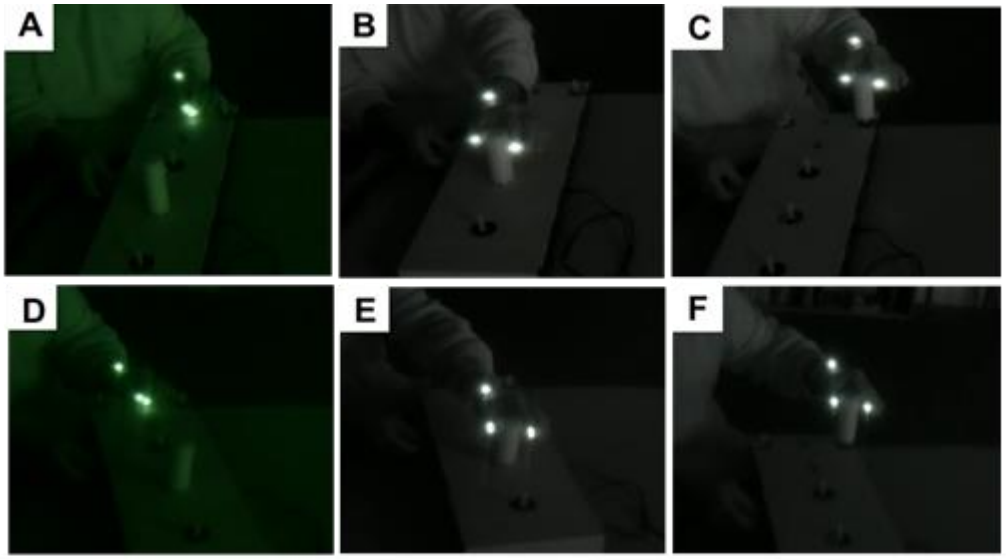


Illustration of the starting position of the hand before each trial for the right **(A)** and left **(B)** hand. The thumb and forefinger are opposed in a pincer grip and the participant is shown pressing down the start button and awaiting the green light on the event detection kit. One of the objects used in the trials is placed on the event detection kit in the object starting position as shown.

Figure 2.10 BIGKAT recording of a sample reach and move trial



Still images taken from the BIGKAT recording of a single trial completed with the left hand **A**,**B** and **C** are taken from the right facing camera showing the starting position, instance when the participant is picking up the object and the instance when the participant is placing the object on its end position, respectively. **D**,**E** and **F** are simultaneous screenshots taken from the left facing camera, showing the same instances of the trial as viewed from the second camera's angle.

2.10 Kinematic data processing

Previous work in the lab measuring postural sway in children to identify developmental disorders has led to the development of a postural sway assessment tool (PSAT) (Flatters et al., 2014). PSAT was then developed into BIGKAT with included the protocol to analyse the movement of the IREDs during the kinematic trials as recorded by BIGKAT cameras. This protocol allows for the stereo triangulation of a point source (IRED) in 3D space and the extrapolation of specified kinematic parameters. The BIGKAT software in Python, uses Open source computer vision library (OpenCV) to find the IRED position from frame-to-frame from each camera recording and then perform

triangulation, using the previously determined calibration parameters, to determine the depth of each marker in each frame. The cartesian (x, y and z) coordinates from each of the IREDs were used to calculate the positional separation between the three IREDs relative to each other at any given point during the recording. Further offline analysis allowed the derivation of distance and velocity parameters for each of the IREDs. Once the 3D data of the IREDs had been obtained from each trial, R scripts were used to visualize and extract the kinematic parameters of interest.

2.10.1 Kinematic parameters

Offline analysis in R studio of the IREDs was used to derive the two main kinematic profiles of interest during the trials; grip aperture and wrist velocity. The IREDs affixed to the tip of the forefinger and thumb were used to derive the grip aperture profile and the IRED affixed to the wrist was used to extract the wrist velocity profile. Grip aperture and wrist velocity profiles from a sample trial are shown in Figure 2.11. A velocity threshold of 5 cm/s was used in all trials to determine the start and end of a movement. So, whenever a wrist velocity of greater than 5cm/s was recorded, the hand was designated as moving when the wrist velocity was less than 5cm/s the hand was designated as stationary. This velocity threshold of 5cm/s has previously been used in the lab in other experimental studies looking at kinematic assessment (Coats *et al.*, 2016). The other accepted method for velocity thresholds is a pre-set percentage of the peak velocity during the movement phase usually set at 10% (Coats and Wann, 2012). If the velocity threshold is set as a percentage of the peak velocity, a wide range of peaks velocities will affect the movement time during which the hand is classed as moving. In this study, we expected a wide

range of movement velocities based on the range of upper limb dysfunction in the MS group and therefore, the absolute velocity threshold of 5cm/s was selected. In addition, the movement at the end of the move phase, called the hover phase, described below enabled the detection of time spent below a velocity threshold of 5cm/s which was extracted as a separate kinematic parameter. The kinematic parameters of interest were extracted from the grip aperture and wrist velocity profiles using R studio and are defined as follows:

1. Reach phase – the time taken for the participant to reach the object from the starting position, measured as the time period between which the wrist velocity becomes greater than 5cm/s at the start position and then reduces below 5cm/s for the first time at the object position. This principle of calculating the time period based on the wrist velocity was used to extrapolate other time periods during the trial as well, as described in the following points. (time parameter)

2. Move phase – the time period from when the wrist velocity goes above 5cm/s once the object has been picked up from table to the next time when the wrist velocity decreases below 5cm/s. In the move phase, unlike the reach phase, described in the previous step, the participant has the object in their hand and is transporting it to the object placement position on the EDK. (time parameter)

3. Maximum grip aperture – the maximum distance between the tip of the thumb and forefinger during the trial which occurs sometime during the reach phase when the participant is reaching for the object. (distance parameter)

4. Time to maximum grip aperture – the time from the start of the movement to the time of maximum grip aperture (time parameter)

5. Maximum wrist velocity (reach phase) – the maximum wrist velocity when the participant is reaching for the object during the reach phase (velocity parameter)

6. Time to maximum wrist velocity (reach phase) – the time from the start of the movement to the time at which the wrist reached maximum velocity when the participant is reaching for the object (time parameter)

7. Maximum wrist velocity (move phase) – the maximum wrist velocity when the participant is moving the object from its start position to the end position during the move phase. (velocity parameter)

8. Time to maximum wrist velocity (move phase) – the time from the start of the move phase to the time when the wrist reaches maximum velocity. (time parameter)

9. Object pick-up – the time taken for the participant to pick up the object. This phase comes immediately after the reach phase and is just before the move phase. The wrist velocity in this phase is below the 5cm/s threshold, indicating the participant is attempting to pick up the object (time parameter)

10. Hover phase – the time taken for the participant to place the object on the peg on its end position on the kit. This phase is at the end of the trial and this time period was determined as the period of time from when the wrist velocity reduced below 5cm/s at the end of the move phase to the time at

which the object made contact with the contact-point on the EDK, which also stopped the BIGKAT recording as it was connected to the EDK, (time parameter)

11. Wrist deceleration time (reach phase) – the time when the wrist is slowing down from its maximum velocity in the reach phase to when it reduces to the threshold of 5cm/s.

12. Wrist deceleration time (move phase) – the time when the wrist is slowing down from its maximum velocity in the move phase to when it reduces to the threshold of 5cm/s.

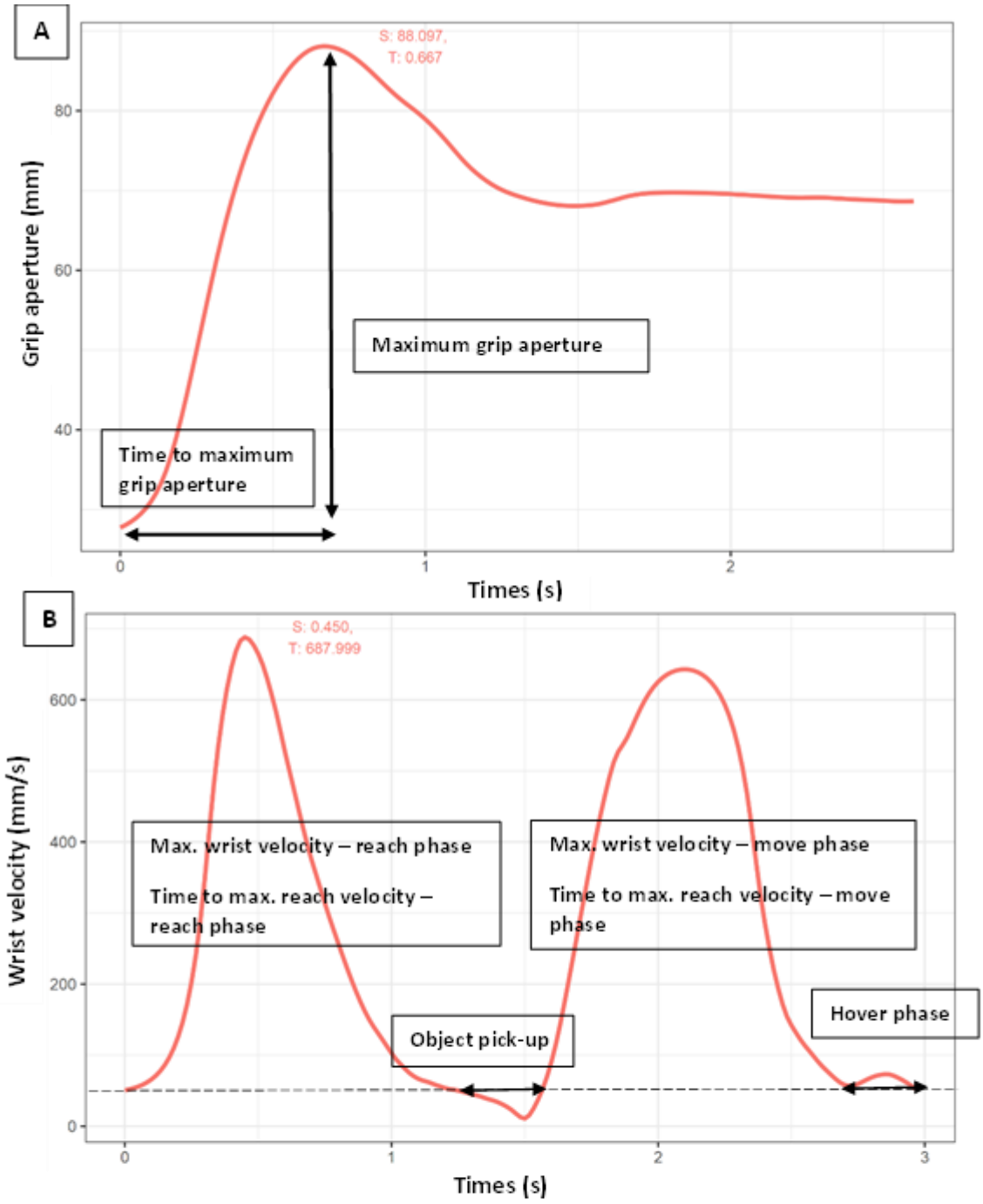
The EDK also recorded three timepoints during the trials, concurrently but independently of the kinematic parameters described above. The timepoints recorded by the EDK are based on the instances when the objects make contact with the copper connectors on the object start and end positions. Thus, these timepoints are not influenced by the motion of the IREDs as recorded by BIGKAT and measure the reach and move times based on when the object is moved between the copper connection points rather than any wrist velocity threshold. Therefore, the EDK recorded time parameters during each trial in parallel, but separate to BIGKAT. These time parameters are as follows:

1. EDK reaction time – the time from when the green light appears on, signalling that the participant can move, to when the start button was released (as described in step 4 of section 2.10.6). (time parameter)
2. EDK reach time – the time from when the start button was released to when the contact of the object with the surface of the EDK was broken, indicating it was picked up. (time parameter)

3. EDK move time – the time taken between the participant lifting the object from its starting position on the EDK to placing it on its end position, when the object makes contact with the contact surface of the EDK again, indicating it was placed. (time parameter)

The kinematic parameters extracted from BIGKAT had previously been studied in the lab when comparing reach and grasp in young and older adults (Coats *et al.*, 2016), Furthermore, kinematics parameters like wrist velocity, grip aperture and movement time are fundamental aspects of the reach and grasp movement that have been extensively studied in other neurological conditions like stroke (Schwarz, Christoph M. Kanzler, *et al.*, 2019; Villepinte *et al.*, 2021). Therefore, the kinematic parameters described in the previous section were derived, as these parameters have been shown to describe the reach and grasp movement in a standardised way.

Figure 2.11 Grip aperture and wrist velocity kinematic profiles extracted from a sample BIGKAT recorded trial



A) Grip aperture profile demonstrates the distance between the tip of the thumb and forefinger throughout the trial. **B)** Wrist velocity profile demonstrates the velocity of the wrist throughout the trial; the first peak in the graph is when the participant is reaching for the object and the second peak in the graph is when the participant is moving the object from the object starting position to the object end position. The labels illustrate the parts of the kinematic profiles from which they have been obtained. The dotted horizontal line reflects the velocity threshold set at 5cm/s.

2.11 Data management

The clinical datapoints from the study including the participant demographics, questionnaire scores, 9HPT results, EDSS scores, and disease-specific details were captured using case reports forms (CRFs) that had been approved during the ethical application process (Appendices 1 – 3). The CRFs and other study specific documentation like recruitment and screening details, were stored in a study site file which was kept on the hospital site in a secure location. The data points from the CRFs were anonymised and transcribed to electronic data collection sheets on Microsoft Excel throughout the study. These electronic data collection sheets were then matched and combined with the kinematic data obtained from BIGKAT and the EDK. All electronic data was stored securely and anonymised by the researcher before further statistical analysis was performed.

2.12 Statistical analysis

Once the clinical and kinematic data were combined, all statistical analysis was carried out in R studio (version 1.4.1106). Mean values for each of the kinematic dependent parameters described in 2.10.1 were derived from the five trials performed for each unique condition. For the baseline timepoint of the study, the independent variables of interest are participant group (patient, control), hand (preferred, non-preferred), object grasp surface size (1 cm, 3 cm) and object base hole diameter (1 cm, 2 cm). This produces a 2 x 2 x 2 x 2 design. A series of mixed analyses of variance (ANOVAs) were used to test for statistical significance which was set at an alpha of 0.05, after applying Levene’s test for equality of variances. During the baseline analysis for the

ANOVAs, participant group was the between-subject factor and hand, grasp surface size, and base hole diameter were the within-subject factors. Only interactions involving participants groups was investigated further with pairwise testing, as this was the main research question.

For the patient group only, the six month follow-up delivered one additional independent variable of interest, namely timepoint (baseline, follow-up). In addition, for the follow-up analysis the data from the control group was excluded thereby removing the participant group as the variable of interest. For the follow-up analysis, a series of repeated measures ANOVAs were used to test for statistical significance which was set at an alpha of 0.05, after applying Levene's test for equality of variances. The timepoint (baseline and follow-up) was the between-subject factor and hand, grasp surface size, and base hole diameter were the within-subject factors. Interactions are reported initially, followed by main effects. When significant interactions were found, these were explored using paired samples t-tests to examine the differences at each level, using Bonferroni correction for multiple analyses when testing for significance. For all dependent variables, when the sphericity assumption was violated F and p values generated using the Greenhouse-Geisser correction are reported. Categorical demographic and clinical data between participant groups were compared using Chi-squared test or Fisher's exact test. Continuous variables were correlated using Spearman's rank correlation coefficient to explore the relationship between the kinematic and clinical parameters. Data was inspected for distribution and residuals to ensure assumptions of normality were not violated.

Chapter 3 Baseline Results and Discussion

3.1 Demographic and clinical details of participants

3.1.1 Demographic details of all participants

Forty-two pwMS were recruited to the patient group and 15 healthy volunteers were recruited to the control group for the study and performed the baseline assessments. The demographic details at the time of the baseline assessments are summarised in Table 5. The control group were significantly older than the patient group ($p<0.05$), but the patient and control groups were matched for gender ($p=0.734$) and handedness ($p=0.253$). The recruitment for this study and the study visits took place during the peaks of the SARS-CoV 2 pandemic between 2020 and 2012. Therefore, recruitment was difficult after an initial period of study suspension between March to June 2020. When recruitment did resume, many of the prospective multiple sclerosis patients who were eligible to take part in the study were apprehensive about visiting hospital during the peak of the pandemic and many of them were classified as being in the clinically vulnerable group, which meant the ethics of recruiting these patients for an observational study had to considered carefully. The pandemic also affected recruitment of healthy volunteers for the control group. It was difficult to reach out more generally to healthy volunteers and most avenues of advertising for healthy volunteers prioritised SARS-CoV 2 research. The control group was recruited from research database of volunteers at the School of Psychology as the main source of participants. The members of this group usually volunteered for ageing research which meant

that most of the members were older adults above 60 years, which affected the mean age of the control group in this study.

3.1.2 Clinical details of the patient group

Of the 42 participants in the patient group, nine had PPMS and 33 had SPMS. The mean duration since first neurological symptoms (disease duration) was 20.6 years (SD 8.92), whilst the mean time since diagnosis at the time of the baseline testing was 14.6 years (SD 8.04). There was an average 6 years lag time from symptom onset to a confirmed diagnosis for this sample of patients. In the PPMS subgroup, progression was evident from diagnosis as per the definition of the disease course. In the SPMS subgroup, there was a mean of 12.1 years (SD 6.87) from a diagnosis of RRMS to progression to SPMS. Seven patients were on DMTs during the course of the study; five on Ocrelizumab (NICE approved for PPMS treatment), two on Siponimod (NICE approved for SPMS treatment). The rest of the 35 patients were not on any DMTs. Median EDSS was 6.5 with scores ranging from 5.0 to 7.5. With regard to hand function, 24 patients were found to have sensory disturbance in their upper limbs on the EDSS examination. Ten patients reported a change in their handedness due to the asymmetrical effect of MS on their preferred hand.

Twenty-six patients in the study were also concurrently enrolled in the MS-STAT2 clinical trial (ClinicalTrials.gov Identifier: NCT 00647348), and two patients were concurrently enrolled in the EXPAND clinical trial (ClinicalTrials.gov Identifier: NCT01665144). The KAIMS study received formal approval to be included as a sub-study of MS-STAT2 by the MS-STAT2 Trial Quality Management Group in October 2020. The patients in the MS-

STAT2 trial were receiving either simvastatin 80mg once a day or a placebo medication. The 26 patients from this trial included in our study continued to take their trial medication during their participation in the kinematic assessments and the researcher was blinded to their trial medication.

3.2 Baseline clinical measures

3.2.1 Patient reported outcome measure scores (PROs)

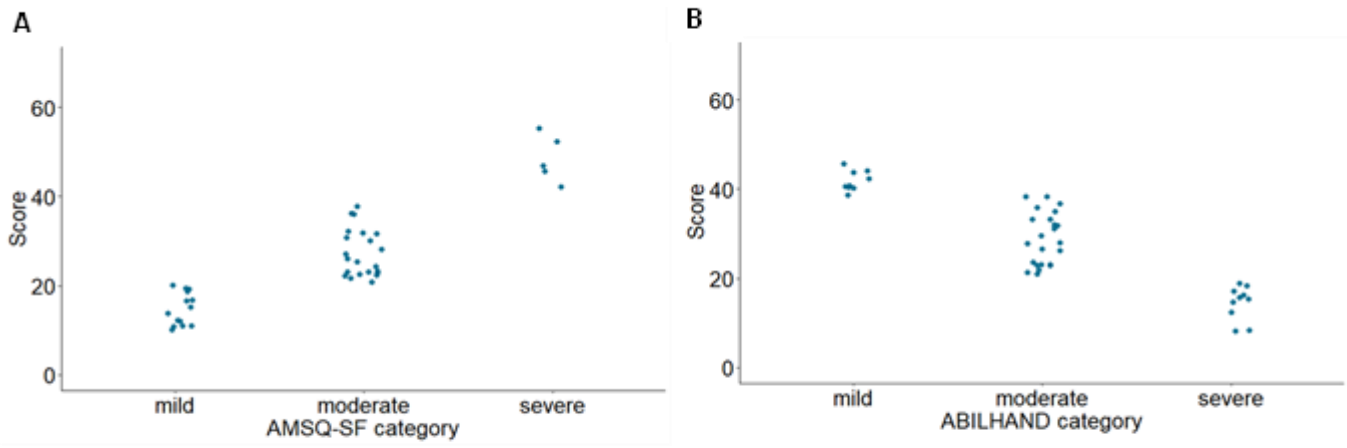
Participants with MS completed the ABILHAND and AMSQ-SF questionnaires which both measure the patients' perception of their upper limb function. As detailed in the Methods chapter, the scores on the ABILHAND and AMSQ-SF questionnaires were divided into mild, moderate and severe categories, with a higher score on the ABILHAND and a lower score on the AMSQ-SF reflecting better upper limb function. On the ABILHAND questionnaire, 9 patients scored as mild upper limb dysfunction, 23 patients scored as moderate dysfunction and 10 patients scored as severe dysfunction. On the AMSQ-SF questionnaire, 14 patients scored as mild dysfunction, 23 patients scored as moderate dysfunction and 5 patients scored as severe dysfunction. The individual scores are illustrated graphically in Figure 3.1.

Table 5 Demographics of the patient and control group at baseline

		Patient (n = 42)	Control (n = 15)	Mean Difference (95% CI), p-value
Age, years (SD, range)		55.2 (6.5, 39 - 67)	71.5 (3.0, 66 - 77)	16.2 (12.9, 19.9), p<0.05
Gender (M : F)		12 : 30	3 : 12	X = 0.42 (p = 0.734)
Handedness (L : R)		10 : 32	1 : 14	X = 2.08 (p = 0.253)
	Disease specific characteristics of the patient group			
MS subtype	PPMS (number of participants)			9
	SPMS (number of participants)			33
	Disease duration*, years (SD)			20.6 (8.92)
	Time since SPMS diagnosis, years (SD) (for SPMS cohort of 33)			5.1 (3.97)
	Age at SPMS diagnosis, years (SD)			50.3 (7.97)
	Time since PPMS diagnosis, years (SD) (for PPMS cohort of 9)			14.4 (8.13)
	Age at PPMS diagnosis, years (SD)			49.9 (7.72)
	Median EDSS for full cohort of 42 (range)			6.5 (5.0 – 7.5)

*Denotes the time period since the patient first experienced neurological symptoms, that were subsequently attributed to their MS, rather than the time period since clinical diagnosis, for both the PPMS and SPMS cohort combined

Figure 3.1 Patient reported outcomes of upper limb function



Individual patients' scores on the AMSQ-SF questionnaire **(A)** and the ABILHAND questionnaire **(B)**. A higher score on the AMSQ-SF questionnaire implies poor upper limb function, whilst a higher score on the ABILHAND relates to better function.

3.2.2 Performance on the 9HPT between the patient and control group

The participants in the patient and control group completed the 9HPT, with two attempts in each hand, providing a total of four trials for each participant. Five of the participants in the patient group were not able to complete the 9HPT with their non-preferred hand, within the 180 seconds time limit set for the test in this study, and so their 9HPT scores are solely from the preferred hand. The rest of the participants in the patient and control group completed four trials each. Therefore, in the participants who completed four trials, their score with each hand is a mean of the two attempts with that hand.

The patient group completed the 9HPT with the preferred hand within a mean time of 33.6 (SD 13.5) seconds, compared to the control group who completed it within a mean time of 21.3 (SD 2.1) seconds. There was a significant mean difference between the two groups of 12.3 seconds ($p<0.05$). When testing the non-preferred hand, the patient group completed the 9HPT within a mean of

40.4 (SD 16.8) seconds, compared to the control group time of 22.5 (SD 4.4) seconds. There was a significant mean difference between the two groups of 17.9 seconds ($p<0.05$). All participants in the control group performed within the accepted normative timeframes for age matched controls, when compared to a large population study of the 9HPT, with the mean right and left 9HPT scores from the study being 22.49 and 22.11 seconds respectively. In this study by Grice et al., 703 healthy volunteers ranging in age from 21 to 71 years performed the 9HPT to provide a normative dataset. In the patient group, 38 out of 42 participants performed significantly worse than age matched controls from the same population study, where the significance was measured as being more than 2 standard deviations from the mean (Grice et al., 2003).

In the patient group, 22 participants took longer than 33.3 seconds to perform the 9HPT based on their mean scores, indicating severe upper limb function based on a previous study that quantified the variability in the 9HPT in a sample of 105 pwMS with upper limb impairment. (Lamers et al., 2015)

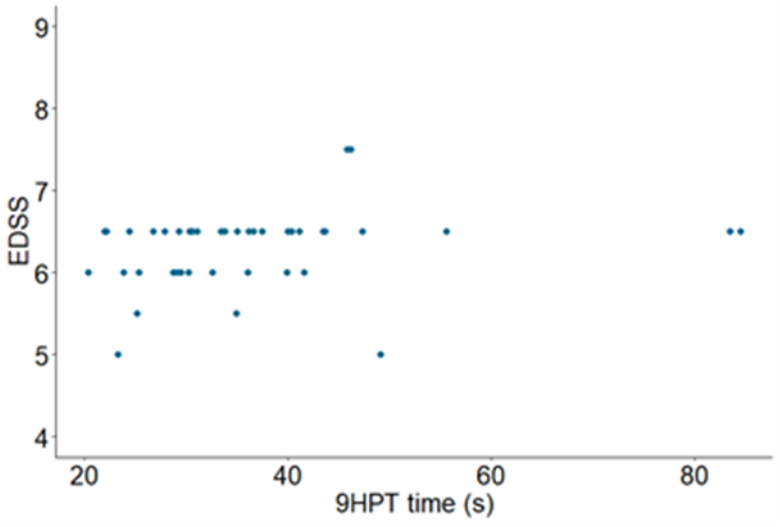
3.2.3 9HPT times do not correlate with EDSS scores in patients

In the patient group, there was no significant correlation between the EDSS score and the average 9HPT time ($p = 0.12$), with wide variation in the 9HPT times across an EDSS range between 5.0 and 7.5. This is illustrated in Figure 3.2. There was also no significant difference in the mean 9HPT times between patients who had sensory impairment in their upper limbs during the EDSS examination, and those without any sensory deficit ($p=0.09$).

3.2.4 9HPT times based on patient reported outcome measures

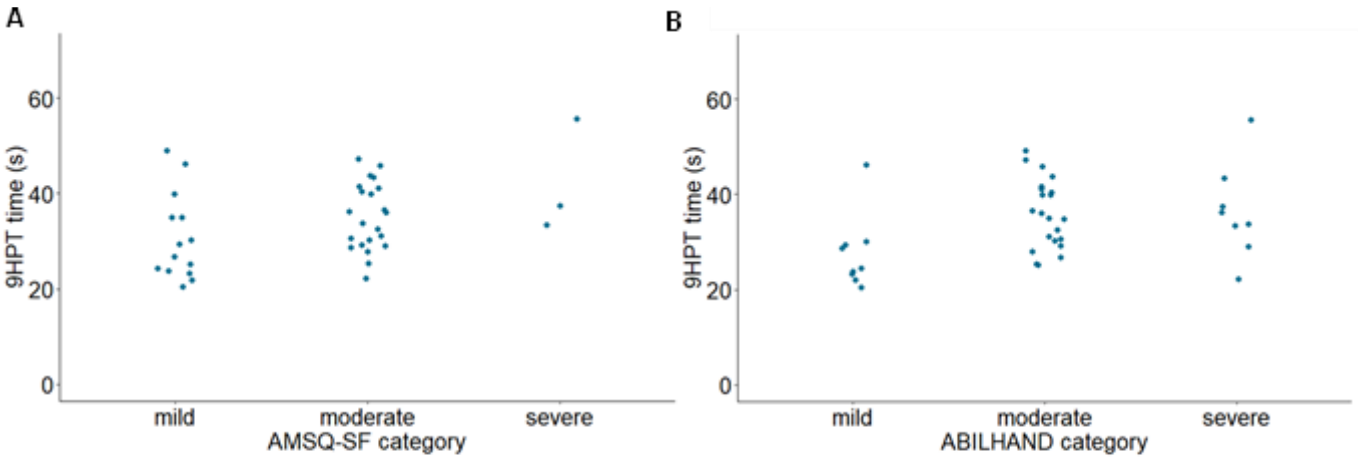
There was no significant difference between patients on the average 9HPT times based on their perceived level of upper limb dysfunction as scored on the ABILHAND questionnaire, $F(2,38) = 2.94$, $p = 0.065$. However, there was a significant difference between average 9HPT times based on the level of dysfunction as scored on the AMSQ-SF questionnaire, $F(2,28) = 4.75$, $p < 0.05$. Post hoc testing between the mild, moderate and severe groups on the AMSQ-SF questionnaire showed that there was a significant difference between the 9HPT times of the mild and severe groups ($p<0.05$), but no significant difference between the mild – moderate or moderate – severe groups. The 9HPT times based on the mild, moderate and severe categories of the two questionnaires are illustrated in figure 3.3.

Figure 3.2 EDSS and 9HPT scores in the patient group



The mean 9HPT scores, averaged across both hands are shown, illustrating one data point per patient

Figure 3.3 9HPT scores based on patient reported outcome measures



Scatter plots of the mean 9HPT times for individual patients categorised by their response on the AMSQ-SF questionnaire **(A)** and the ABILHAND questionnaire **(B)**, demonstrating the distribution of 9HPT times amongst perceived mild, moderate and severe upper limb dysfunction.

3.3 Baseline kinematic assessment measures

3.3.1 Kinematic data validation

The kinematic data from the study visit were collected and analysed as described in the Methods chapter. The timepoint data from the event detection kit (EDK) were collected separately but contemporaneously with the kinematic data recorded by the BIGKAT infra-red 3D motion capture system. Given each participant performed five reach and grasp trials for each condition and each participant had to complete eight unique conditions (4 objects x 2 hands), the total possible trials for each participant at the baseline visit was 40 trials. For the 57 participants tested at baseline, this gave a possible total of 2280 trials, with each trial producing a dataset on the kinematic parameters as recorded by BIGKAT and the EDK. Once the data were extracted from BIGKAT and the EDK, they were analysed in R studio to ensure all the pertinent data points

required for analysis were recorded. For the EDK, these data points were timepoints for each trial as described in the Methods chapter.

While all the participants in the control group were able to complete five trials for each of the eight conditions, 12 of the participants in the patient group had difficulty completing some of the trials based on the object characteristics, due to the severity of their upper limb dysfunction. These 12 patients completed fewer than 40 different trials. In total, 2102 out of a possible maximum of 2280 reach and grasp trials were recorded by BIGKAT and the EDK during the baseline assessment for the study. The corresponding data files for each trial recorded by BIGKAT and the EDK were coded by unique identifiers so that the data files recorded by these two methods could be matched prior to analysis. All the EDK data passed the validation testing in R studio and were therefore included in the analysis. The validation testing is described in the Methods chapter. Figure 3.4 shows the breakdown of the number of trials included in the analysis.

The wrist velocity and grip aperture graphs produced by BIGKAT were further validated in R studio to ensure these graphs were in keeping with expected patterns of movement. The wrist velocity graphs, for example, were supposed to have captured two peaks in the wrist velocity, one for the reach phase and one for the move phase. This was done because it was noticed during initial testing with BIGKAT that the IREDs on the wrist, forefinger and thumb needed to be picked up in most frames by both infra-red cameras to produce accurate kinematic graphs of the movement. In some trials one of the IREDs wouldn’t be captured by one of the cameras in some of the video frames and therefore the kinematic graphs produced didn’t accurately capture the movements

predicted during the reach and grasp trials. These would then lead to illogical grip aperture and velocity graphs that didn't describe the movement during the trials. Figure 3.5 illustrates examples of valid and invalid grip aperture and wrist velocity graphs. Trials like those in Figure 3.5B, and 3.5D, which didn't pass the validation process were excluded from further analysis, which included the extraction of the kinematic parameters of interest. During the baseline assessments, 1696 out of 2102 (80.7%) trials recorded by BIGKAT passed validation and were used for further analysis. The number of trials that passed validation varied per participant, with participants in the patient group who reported more severe upper limb impairment posting a larger number of invalid trials. This was primarily because the participants who have move severe upper limb impairment reshaped their hands when grasping in order to maximise their grip such that the IREDs on the thumb and forefinger would usually be obscured for at least a few frames as recorded by BIGKAT. Therefore, although the trial was completed adequately, the recording of the IREDs was incomplete and couldn't be included in the analysis. Techniques to improve the pick-up of the hand movements without the need for the IREDs are described later in the Conclusions chapter section 5.3.3.

The main effects of the kinematic parameters captured are shown in Table 6 and the interactions and individual factor comparisons are expanded upon in the following sections in this chapter.

Figure 3.4 Flowchart illustrating the number of baseline trials recorded and used for analysis

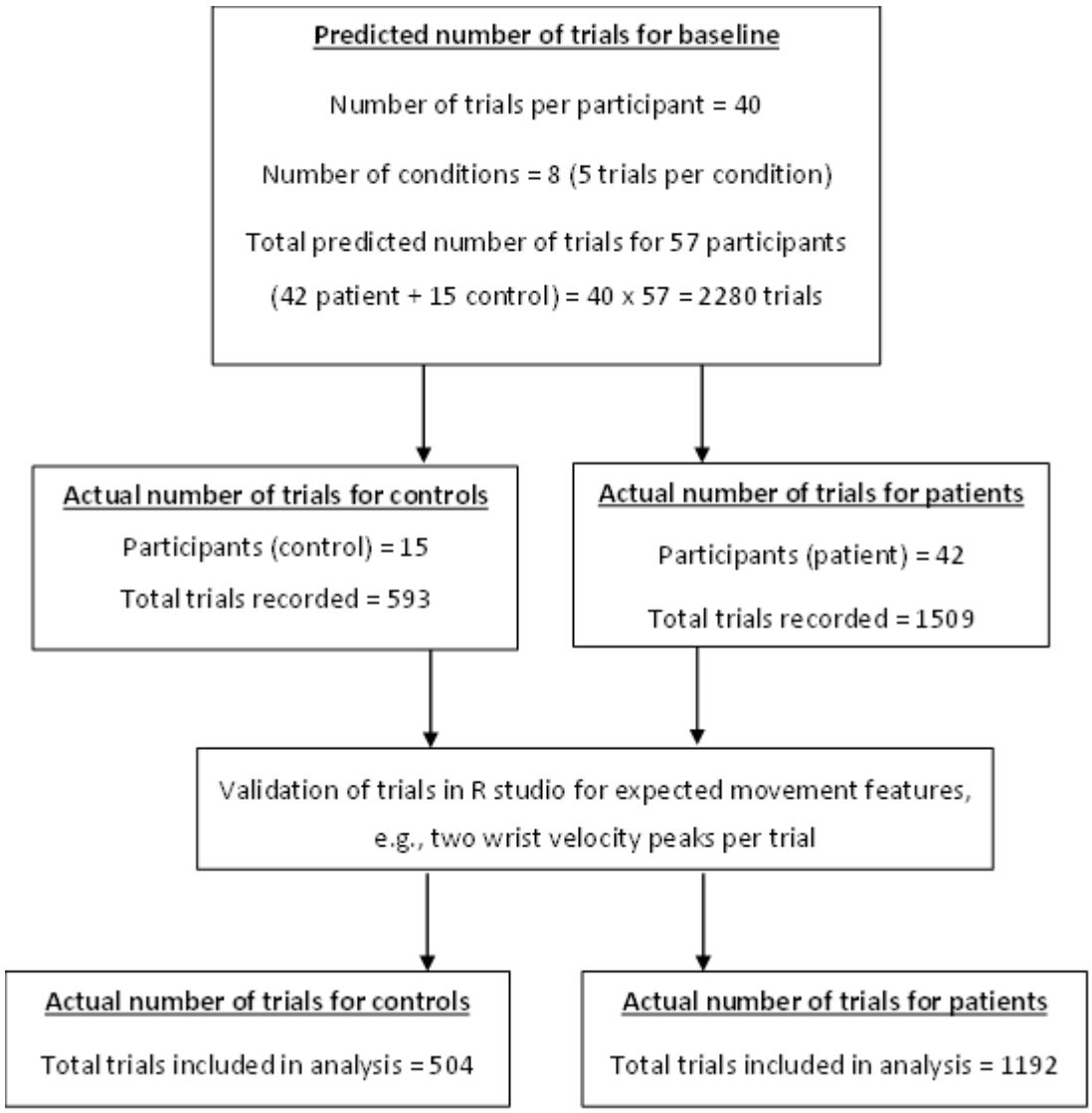
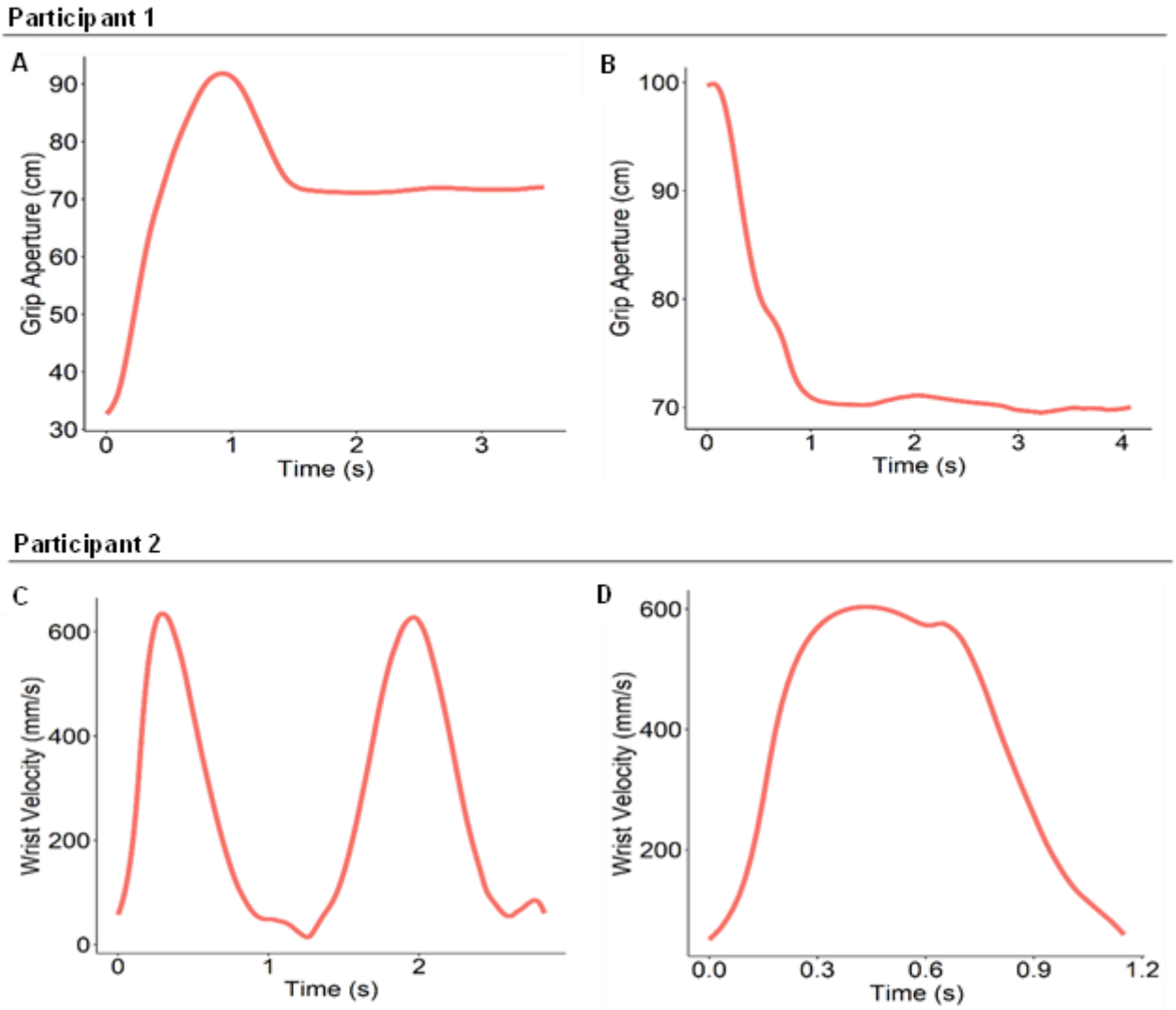


Figure 3.5 Sample grip aperture and wrist velocity graphs of individual trials



Sample grip aperture graphs (**A** and **B**) from **Participant 1**, and sample wrist velocity graphs (**C** and **D**) from **Participant 2. A**) Sample grip aperture graph demonstrating the expected increase in the participant's grip aperture as they reach for the object achieving a peak grip aperture (maximum grip aperture) and then a steady grip aperture is maintained as the object is moved. **B**) This grip aperture graph doesn't have the initial increase in grip aperture expected during the reach phase suggesting one or more of the IREDs were not captured by the cameras during the initial phase of the recording. **C**) Sample wrist velocity graph showing the peak in wrist velocity for the reaching phase and then another peak in wrist velocity during the movement phase. **D**) This wrist velocity graph only shows one peak in wrist velocity indicating that either the wrist velocity for the reach of movement phase wasn't captured in order to produce the expected double peak

Table 6 Main effects of the kinematic parameters between the control and MS group

Dependant kinematic variable	F-value	d.f.	ηp2	p-value
Reaction time	9.42	1,53	0.15	0.003
Reach time	7.80	1,54	0.13	0.007
Move times	14.5	1,52	0.22	<0.001
Time spent in reach phase	6.37	1,53	0.11	0.015
Time spent in move phase	4.11	1,53	0.07	0.048
Object pickup time	9.18	1,51	0.15	0.004
Object placement time	15.2	1,47	0.25	<0.001
Maximum wrist velocity (reach phase)	9.06	1,50	0.15	0.004
Proportion of time in wrist deceleration (reach phase)	6.94	1,42	0.14	0.012
Maximum wrist velocity (move phase)	4.99	1,51	0.09	0.030
Proportion of time in wrist deceleration (move phase)	0.00	1,54	0.00	0.948
Maximum grip aperture	0.161	1,49	0.00	0.690
Proportion of time to reach maximum grip aperture	0.08	1,50	0.00	0.772

ηp2 effect size reported as partial Eta squared

3.3.2 Event detection kit kinematic parameters

3.3.2.1 Reaction time, reach time and move time

Reaction time

There was a significant main effect of group ($F(1,53) = 9.42$; $p<0.05$, $\eta p^2 =0.15$) with patients taking longer than controls to react to the green light indicating the start of the trial. There was no significant main effect of grasp surface size, base hole diameter or hand. There were no significant interactions.

Reach time

When reaching for the objects there was a significant interaction between group and grasp surface size ($F(1,249) = 4.09$; $p<0.05$, $\eta p^2 =0.02$). Pairwise t-tests showed that both controls and patients took significantly longer to reach for the objects with the smaller grasp surface size ($p<0.05$) than the larger grasp surface size. Pairwise t-tests at the group level demonstrated that the patient group took significantly longer to reach the objects than the controls ($p<0.05$) with both the smaller and larger grasp surface size. A significant interaction between group and hand also emerged ($F(1,251) = 8.59$; $p<0.05$, $\eta p^2 =0.03$). The patient group took significantly longer to reach for the object with their non-preferred hand, compared to their preferred hand ($p<0.05$). This was not seen in the control group where there was no significant difference between hands. At the group level, the patient group took significantly longer than the control group to reach for the object with both their preferred and non-preferred hands ($p<0.05$). There was also a significant main effect of group ($F(1,54) = 7.80$; $p<0.05$, $\eta p^2 =0.13$), with the patient group taking significantly

longer to reach the object. There was a significant main effect of grasp surface size ($F(1,249) = 45.6$; $p<0.05$, $\eta p^2 = 0.15$) and hand ($F(1,251) = 4.20$; $p<0.05$, $\eta p^2 = 0.01$) on the reach times. Participants took significantly longer to reach objects with a smaller grasp surface size and when using their non-preferred hand. There was no significant main effect of base hole diameter.

Move time

When moving the objects, there was a significant interaction between group and grasp surface size ($F(1,253) = 11.1$; $p<0.05$, $\eta p^2 = 0.04$). Paired testing at the group level, showed that the patient group took significantly longer to transport the objects with the smaller grasp surface size compared to the control group, with no significant difference between groups noted with objects with the larger grasp surface size. At the grasp surface size level, paired testing showed that the patient group took significantly longer to transport objects with the smaller grasp surface size compared to the larger grasp surface size. This difference between grasp surface sizes was not seen in the control group.

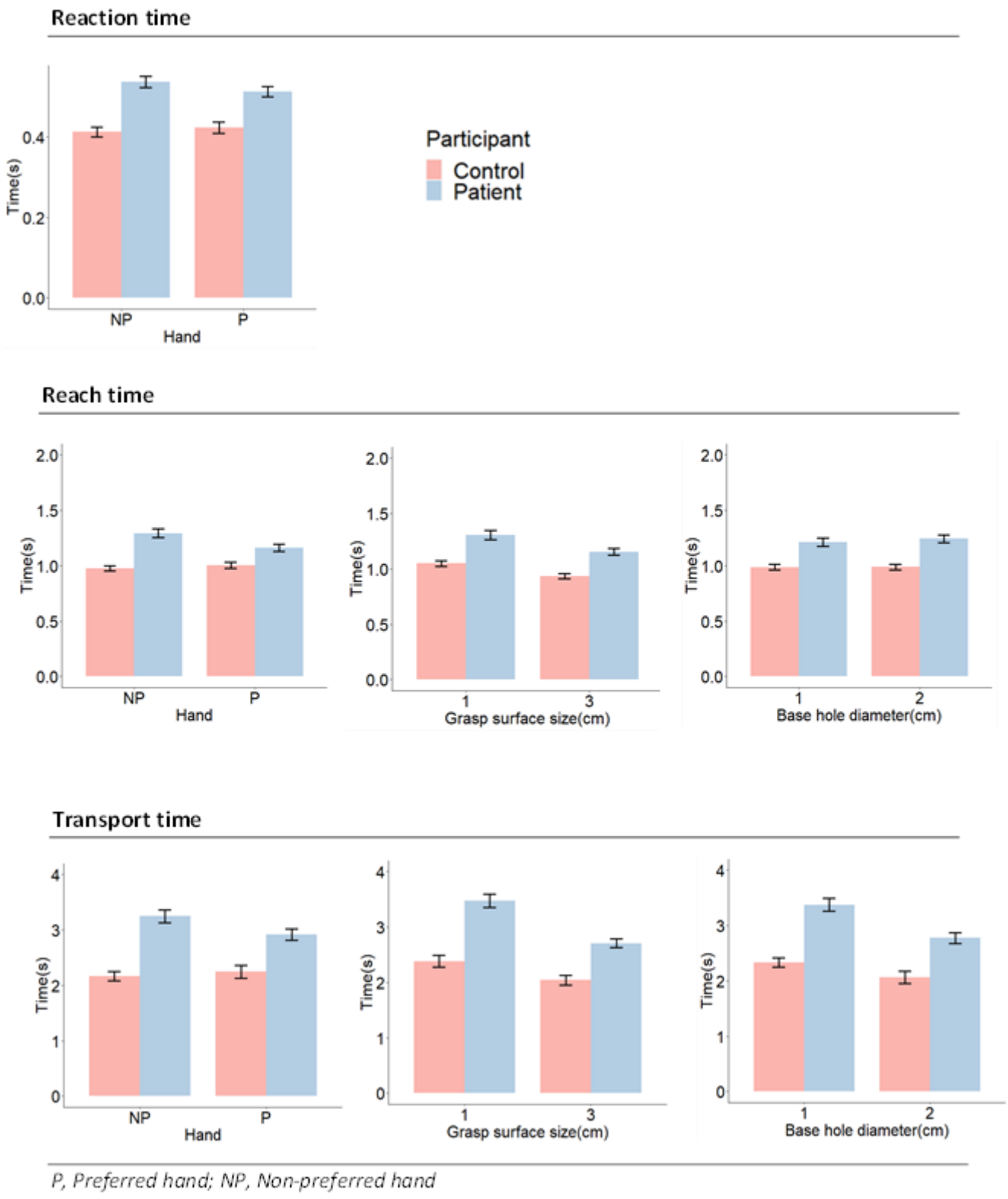
There was a significant interaction between group and base hole diameter ($F(1,248) = 5.05$; $p<0.05$, $\eta p^2 = 0.02$). This was driven by the patient group taking significantly longer to move the objects with a smaller base hole diameter ($p<0.05$); this was not seen in the control group where there was no effect of hole diameter. The patient group took significantly longer than the control group to move the objects with the smaller and larger base hole diameters. There was also a significant interaction between group and hand ($F(1,256) = 6.63$; $p<0.05$, $\eta p^2 = 0.03$). Pairwise comparisons showed that the patient group took significantly longer to move the objects with their non-

preferred hand compared to their preferred hand, whilst for the controls there was no effect of hand. At the group level, the patient group took significantly longer than the control group to move the objects with both their preferred and non-preferred hands.

There was a significant main effect of group ($F(1,52) = 14.5$; $p<0.05$, $\eta p^2 =0.22$), with the patient group taking longer to move the object than the control group. There was also a significant main effect of grasp surface size ($F(1,243) = 43.4$; $p<0.05$, $\eta p^2 =0.15$), with the patient group taking significantly longer to move objects with the smaller grasp surface size compared to the larger grasp surface size. A significant main effect of base hole diameter ($F(1,248) = 21.9$; $p<0.05$, $\eta p^2 =0.08$) was driven by the patient group taking significantly longer to move the objects with the smaller base hole diameter compared to the larger base hole diameter. There was no significant main effect of hand.

These results show that the patient group took significantly longer to react to the trigger (green light) indicating the start of the trial. The patient group also took significantly longer to reach for and move the objects with both their preferred and non-preferred hands, compared to the control group. Objects with a smaller grasp surface size took longer to reach for and pick-up, and objects with a smaller base hole diameter took longer to place, but these significant differences were only seen in the patient group and not in the control group. The results from the EDK recorded parameters are illustrated in Figure 3.6.

Figure 3.6 Reaction, reach and move times measured by the event detection kit



P, Preferred hand; NP, Non-preferred hand

3.3.3 BIGKAT kinematic measures

The BIGKAT kinematic parameters extracted from these trials are analysed in detail in the following sections demonstrating the granular differences between and within the patient and control groups.

3.3.3.1 Peak wrist velocity when reaching and moving objects

Reach phase

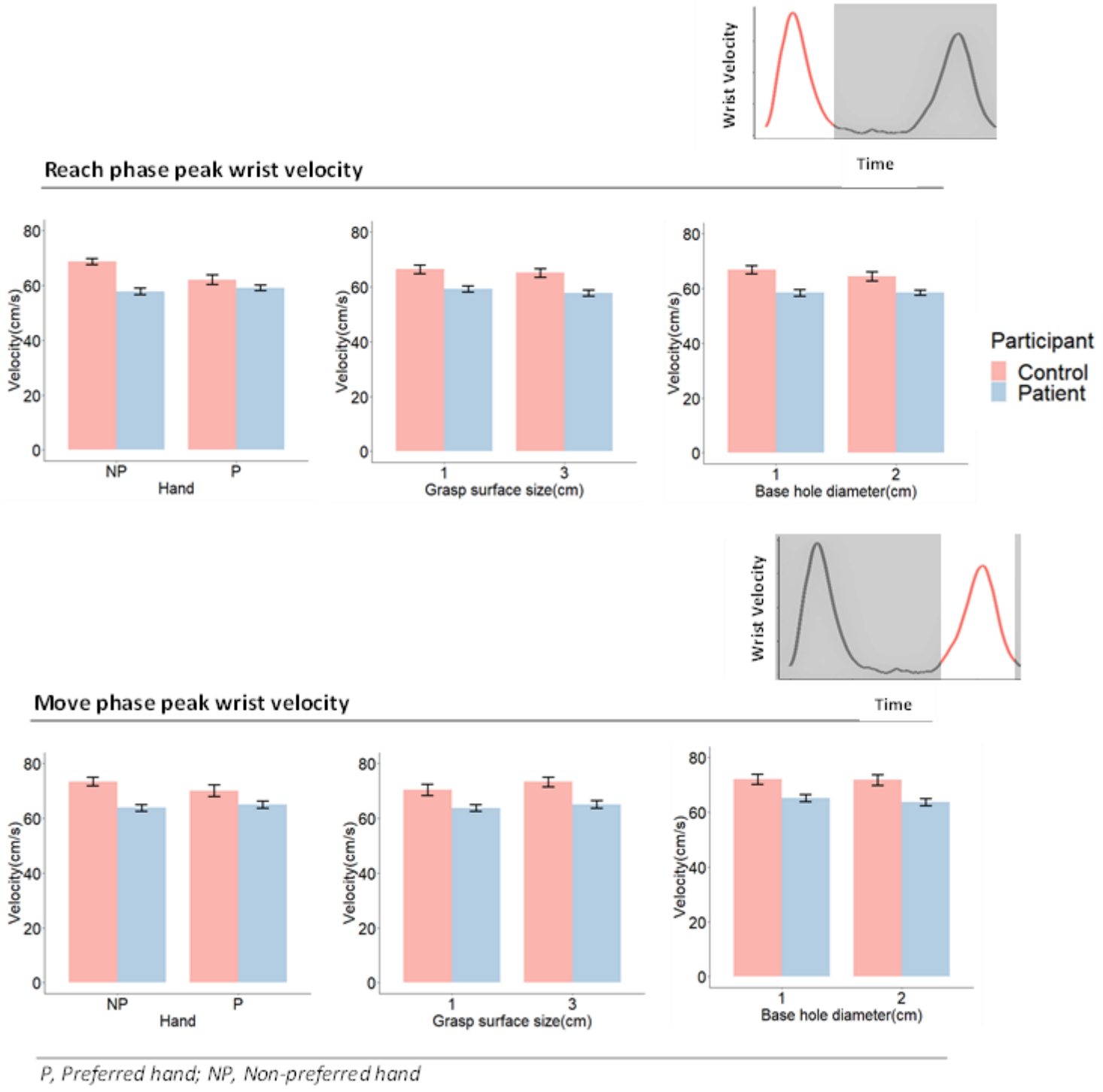
When the participant was reaching for the object the peak wrist velocities showed a significant interaction between group and hand ($F(1,261) = 9.55$; $p<0.05$, $\eta p^2 = 0.04$). Pairwise testing showed that the control group had significantly higher peak wrist velocities with their preferred hand compared to their non-preferred hand ($p<0.05$). This difference between hands was not seen in the patient group. At the group level, the patient group demonstrated significantly lower peak wrist velocities compared to the control group, but only when using the non-preferred hand ($p<0.05$). The peak wrist velocities demonstrated a significant main effect of group ($F(1,50) = 9.06$; $p<0.05$, $\eta p^2 = 0.15$) which was driven by the patient group demonstrating significantly lower peak wrist velocities compared to the control group. There was also a significant main effect of hand ($F(1,260) = 6.03$; $p<0.05$, $\eta p^2 = 0.02$) which was driven by the control group only, demonstrating significantly lower peak wrist velocities when using their non-preferred hand compared to their preferred hand. There was no significant main effect of grasp surface size or base hole diameter.

Move phase

During the move phase of the trial, there were no significant interaction but the interaction between participant group and hand approached significance ($p=0.054$). There was a significant main effect of group again, with the patient group demonstrating lower peak wrist velocities compared to the control group ($F(1,51) = 4.99$; $p<0.05$, $\eta p^2 =0.09$). There was no significant main effect of hand, grasp surface size or base hole diameter. The peak wrist velocities during the reach and move phases as recorded by BIGKAT are illustrated in Figure 3.7.

These wrist velocity analyses show that the speed with which the patient group reached for and moved all the objects were slower than the control group and this was particularly evident with their non-preferred hand.

Figure 3.7 Peak wrist velocities when reaching for and moving objects



P, Preferred hand; NP, Non-preferred hand

3.3.3.2 Wrist deceleration during the reach and move phases of the trials

Reach phase

The proportion of reach time during which the wrist was decelerating as the hand approached the object was measured. This showed a significant three-way interaction identified between group, grasp surface size and hand ($F(1,245) = 4.27$; $p<0.05$, $\eta p^2 = 0.02$) . Pairwise t-tests at the level of the grasp surface size showed that this interaction was driven by a significantly longer wrist deceleration time when reaching for the objects with the smaller grasp surface size, with the non-preferred hand only compared to the larger grasp surface size in both groups. At the group level there wasn't a significant difference in wrist deceleration proportion between the patient and control group.

There was a significant main effect of group, with the patient group spending a significantly longer proportion of the reach phase slowing down their hand when approaching the object compared to the control group ($F(1,43) = 6.94$; $p<0.05$, $\eta p^2 = 0.14$). There was also a significant main effect of hand on the proportion of time spent in deceleration ($F(1,264) = 11.9$; $p<0.05$, $\eta p^2 = 0.04$), which was driven by a significantly longer wrist deceleration proportion with the non-preferred hand compared to the preferred hand. There were no other significant interactions or main effects.

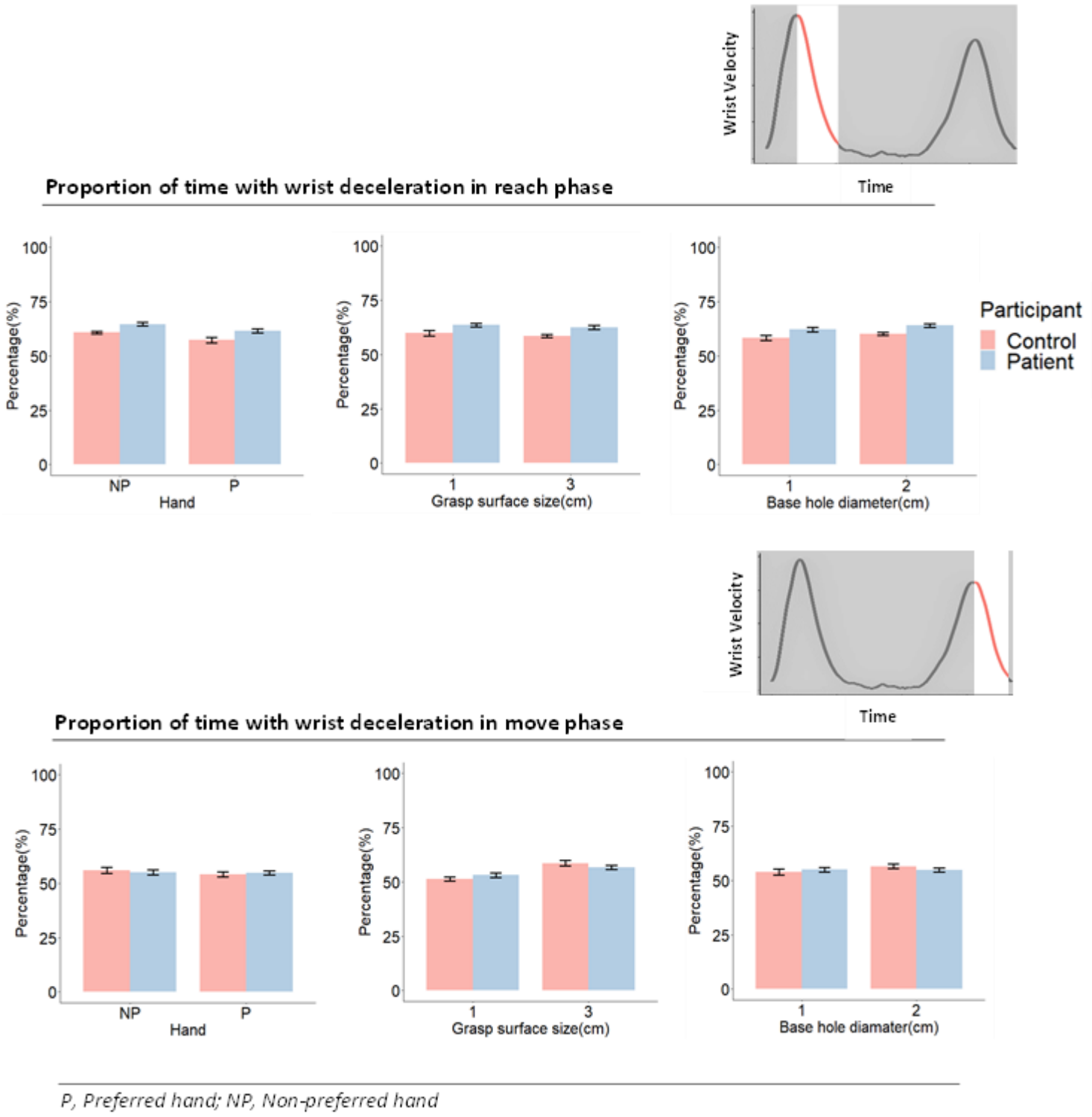
Move phase

In the move phase of the trial, when the participant was moving the object to its final position, no significant interactions emerged. There was a significant main effect of grasp surface size with the participants demonstrating a

significantly longer wrist deceleration proportion when transporting the objects with a larger grasp surface size ($F(1,272) = 20.1$; $p<0.05$, $\eta p^2 = 0.07$). There was no significant main effect of group, hand or base-hole diameter on the proportion of time the wrist spent in deceleration.

These results are illustrated in Figure 3.8. These results show that the patient group on average spent a longer proportion of the reaching time slowing down their hand when reaching for the objects, compared to the control group. This pattern was not seen in the move phase when transporting the objects.

Figure 3.8 Proportion of the reach and move phase during which the wrist is decelerating



P, Preferred hand; NP, Non-preferred hand

3.3.3.3 Time spent in the reach and move phase of the trials

The time taken in the reach and move phase of the trials as recorded by BIGKAT is different to the time in these phases of the trials when recorded by the EDK. Although the EDK produces time parameters that can be split into reach and move times, EDK times include the time to pick-up and place the objects based on the object contact with the kit. The time parameters as recorded by BIGKAT for the reach and move phase are only for the time when the wrist velocity is more than 5cm/s in each phase. Therefore, the reach and move phase of the trial only extracts the times periods when the wrist is actually moving by more than 5cm/s. The object pick-up and placement time is excluded as the wrist velocity is below 5cm/s during these specific parts of the trial. As such, BIGKAT provides a more accurate measure of the movement of the hand during the trials. These definitions are provided in the Methods section 2.11.1

Reach phase

There was a significant main effect of group, with the patient group taking significantly longer in the reach phase than the control group ($F(1,53) = 6.37$; $p<0.05$, $\eta p^2 = 0.11$). There were no other significant main effects or interactions between grasp surface size, base hole diameter or hand.

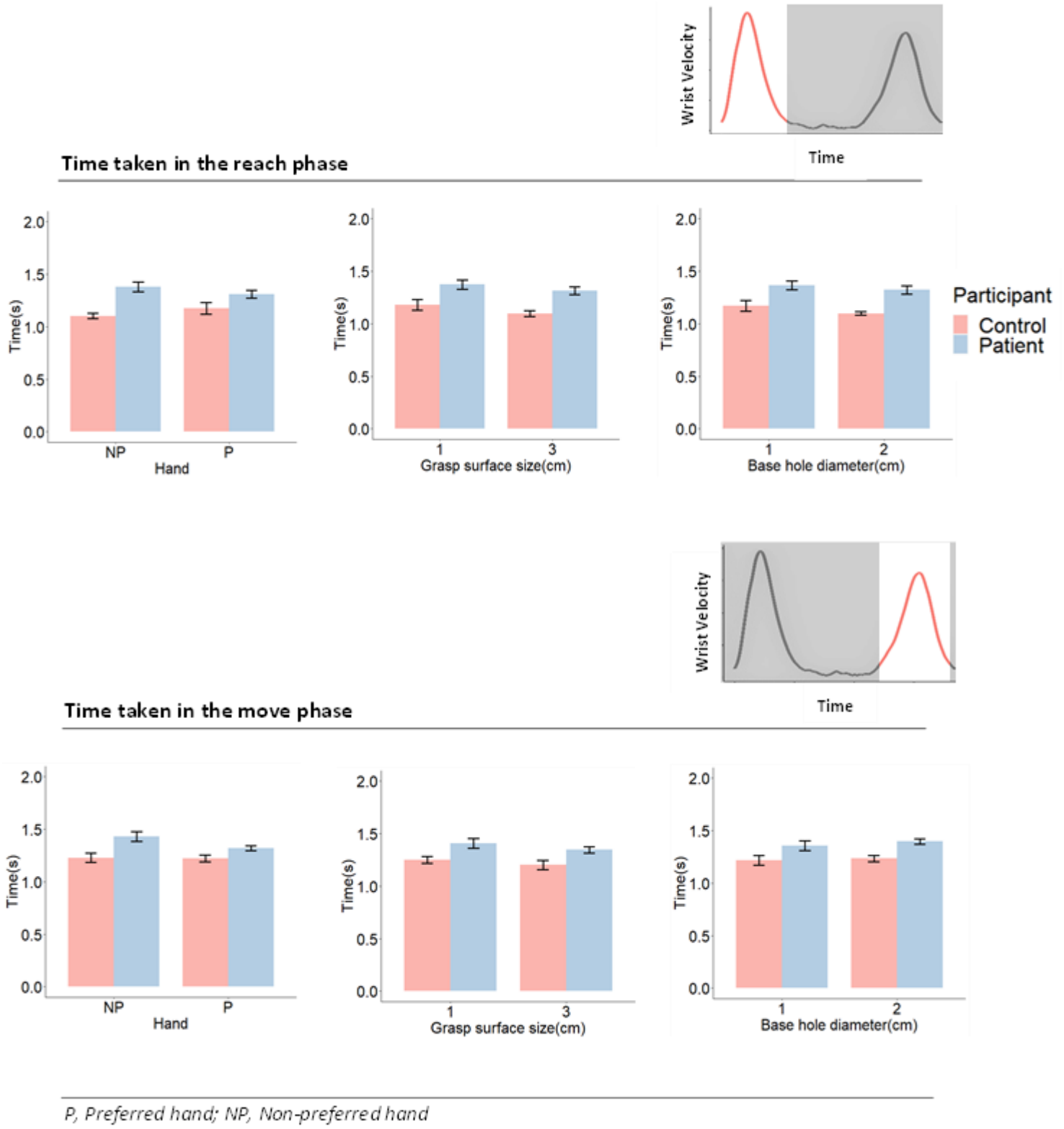
Move phase

In the move phase of the trial, there was a significant main effect of group with the patient group taking longer ($F(1,53) = 4.11$; $p<0.05$, $\eta p^2 = 0.07$). There were no other significant main effects or interactions between grasp surface size,

base hole diameter or hand. These results are illustrated graphically in Figure 3.9.

These results show that even when object manipulation is excluded from the time taken in the reach and move phase, the time spent moving the hand is still slower in the patient group both with and without the object in hand.

Figure 3.9 Time taken in the reach and move phases as recorded by BIGKAT



P, Preferred hand; NP, Non-preferred hand

3.3.3.4 Time taken to pick-up and place objects

Object pick-up time

When analysing the time taken to pick-up the objects, there was a significant two-way interaction between group and grasp surface size ($F(1,260) = 3.91$; $p<0.05$, $\eta p^2 = 0.01$). Pairwise testing showed that both the control and patient group took significantly longer to pick-up the objects with the smaller grasp surface size compared to the larger grasp surface size. At the group level, the patient group took significantly longer than the control group to pick up objects with both large and small grasp surface sizes.

Furthermore, there was a significant interaction between group and hand ($F(1,267) = 5.28$; $p<0.05$, $\eta p^2 = 0.02$). Pairwise testing showed that this interaction was driven at the level of the group with the patient group taking significantly longer than the control group to pick-up objects with both their preferred and non-preferred hands ($p<0.05$). There was no significant difference between pick-up time when comparing the preferred to the non-preferred hand in each group. There were no other significant interactions.

There was a significant main effect of group ($F(1,51) = 9.18$; $p<0.05$, $\eta p^2 = 0.15$) with the patient group taking significantly longer than the control group. There was also a significant main effect of grasp surface size identified ($F(1,260) = 60.2$; $p<0.05$, $\eta p^2 = 0.19$) with participants taking longer to pick-up objects with the smaller grasp surface size.

Time to place objects

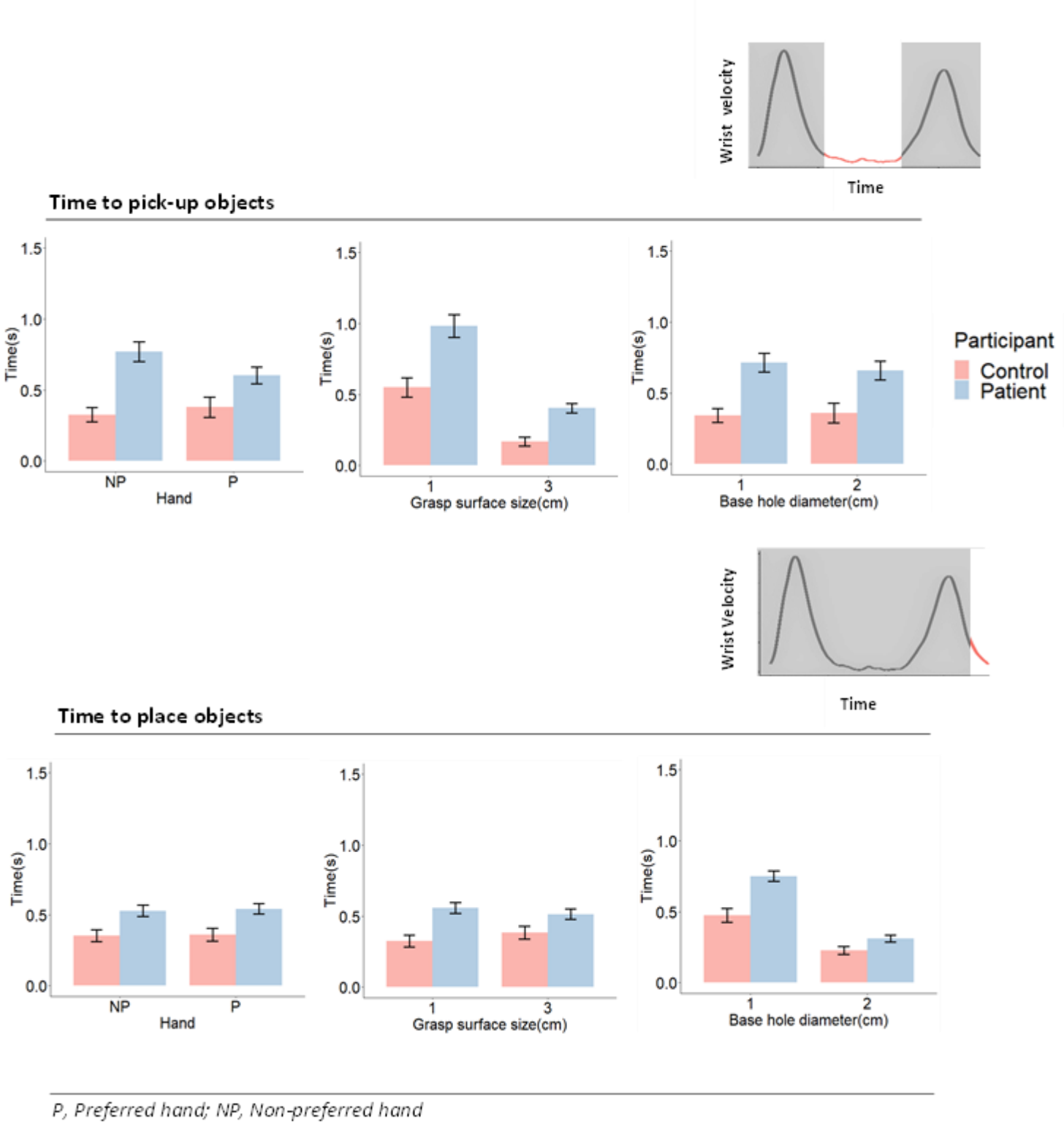
The time taken to place the objects, also known as the hover phase, showed a significant two-way interaction between the group and base hole diameter

($F(1,258) = 5.16$; $p<0.05$, $\eta p^2 = 0.02$). Pairwise testing at the level of the base hole diameter showed that both the patient and the control groups took significantly longer to place the objects with the smaller base hole diameter compared to those with the larger base hole diameter ($p<0.05$). At the group level, the patient group took significantly longer than the control group when placing the objects with both small and large base hole diameters ($p<0.05$). There were no other significant interactions.

There was a significant main effect of group with the patient group taking significantly longer than the control group ($F(1,47) = 15.2$; $p<0.05$, $\eta p^2 = 0.25$). There was also a significant main effect of base hole diameter on the time taken to place the object ($F(1,258) = 76.5$; $p<0.05$, $\eta p^2 = 0.25$), with the participants taking longer to place the objects with the smaller base hole diameter. There were no other significant interactions.

These results are illustrated in Figure 3.10. These results importantly show that the patient group took longer with the actual manipulation of the objects, that is, to pick-up all objects and place them compared to the control group. These differences were more pronounced with the non-preferred hand and with objects that were difficult to grasp due to their smaller grasp surface size. Furthermore, the object placement took significantly longer for both groups with the objects with the small base hole diameter compared to the large base hole diameter.

Figure 3.10 Time taken to pick-up and place objects



P, Preferred hand; NP, Non-preferred hand

3.3.3.5 Maximum grip aperture and time to reach maximum grip aperture

Maximum grip aperture

When measuring the grip aperture, the maximum grip aperture during each trial was extracted. There were no significant interactions evident. There was no significant main effect of group. However, there was a significant main effect of grasp surface size on the maximum grip aperture recorded ($F(1,254) = 5.27$; $p<0.05$, $\eta p^2 = 0.02$) with participants demonstrating a significantly larger maximum grip aperture when reaching for the object with the larger grasp surface size compared to the smaller grasp surface size. There was also a significant main effect of hand on the maximum grip aperture ($F(1,259) = 6.39$; $p<0.05$, $\eta p^2 = 0.02$) with participants demonstrating a significantly larger maximum grip aperture when reaching for objects with their preferred hand compared to their non-preferred hand. This suggests that opening the hands is affected differently in the preferred and non-preferred hand in both controls and patient groups. This may be due to the faster movement time in the reach phase and higher wrist velocity with the preferred hand, which might lead to a larger maximum grip aperture when reaching to allow for more error that comes with higher speeds.

Time to reach maximum grip aperture

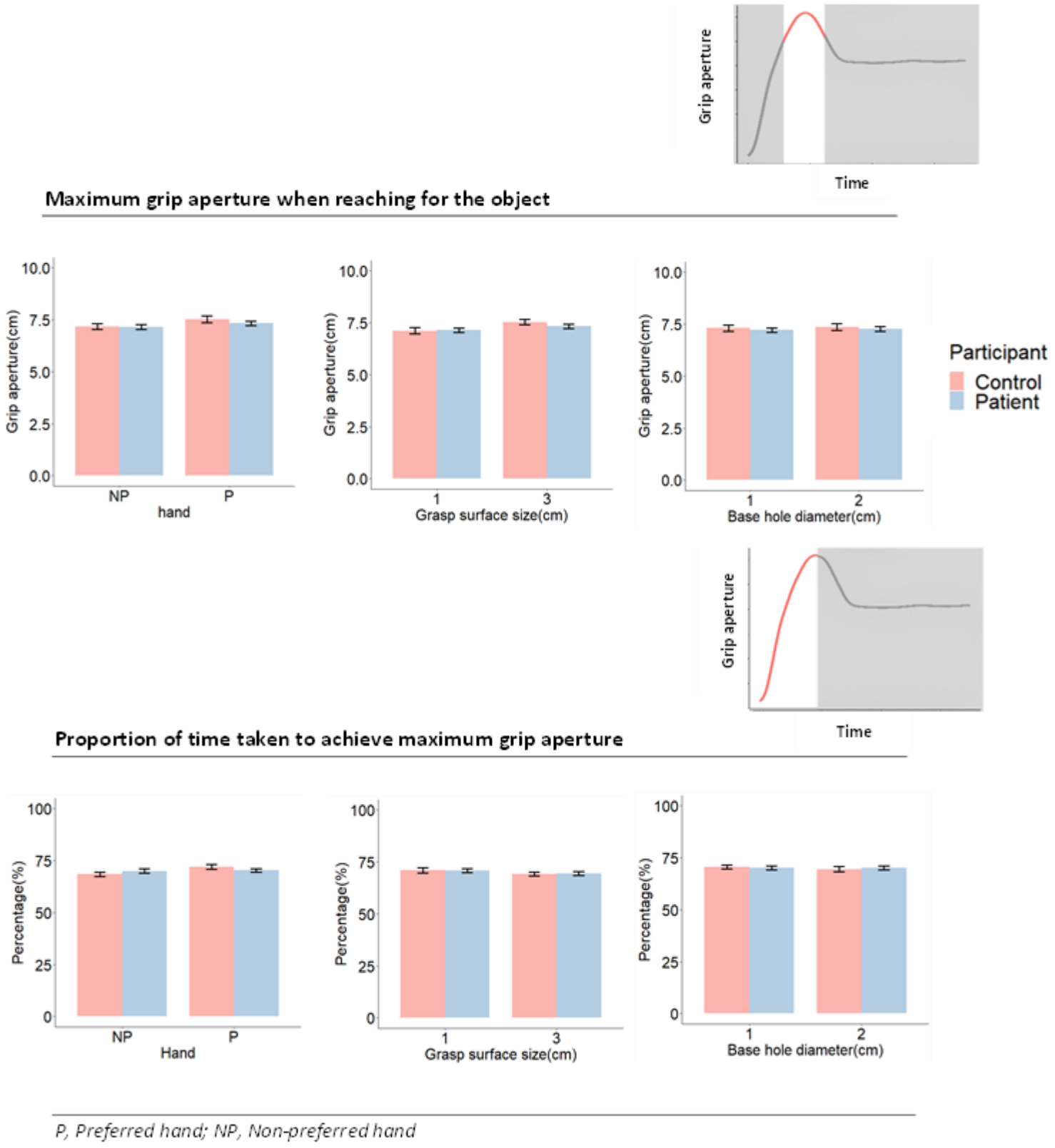
The time taken for the participants to open their hand to achieve the maximum grip aperture when reaching for the object was recorded as a proportion of the time taken in the reaching phase in total. There was a significant two-way interaction between group and hand ($F(1,268) = 5.32$; $p<0.05$, $\eta p^2 = 0.02$). Two-way testing at the level of the hand revealed that this was driven by the control group taking a significantly longer proportion of the reach phase to

achieve maximum grip aperture with their preferred hand compared to their non-preferred hand ($p<0.05$). This difference was not seen in the patient group. At the group level, there was no difference in proportion of time to reach maximum grip aperture between the patient and control groups for either hand. There were no other significant interactions.

There was no significant main effect of group, grasp surface size or base hole diameter. There was a significant main effect of hand ($F(1,268) = 4.15$; $p<0.05$, $\eta p^2 = 0.02$) with participants taking a significantly longer proportion of time during the reach phase to reach the maximum grip aperture with their preferred hand compared to their non-preferred hand.

These results are illustrated in Figure 3.11. These results show that the actual shape of the hand, measured as the grip aperture shows similar profiles for the patient and control group unlike other kinematic parameters in previous sections. Furthermore, hand preference has a significant impact on how quickly the hands open when reaching for an object and the shape of the hand posture.

Figure 3.11 Maximum grip aperture and time taken to reach maximum grip aperture



P, Preferred hand; NP, Non-preferred hand

3.3.4 BIGKAT measures show significant correlation with event detection kit parameters

BIGKAT measures showed significant correlation with the kinematic measures recorded by the EDK in the patient and control groups. These correlation variances as well their significance levels are shown in Table 7. Whilst some correlations might be statistically significant, they are not clinically meaningful and therefore the pertinent correlations from the table are described here.

The reach and move times recorded by the EDK correlated significantly with the reach and move times recorded by BIGKAT. The time to place and pick-up objects also showed significantly positive correlation with the reach and move times as recorded by the EDK, suggesting that participants who took longer in the movement parts of the trials also took longer to manipulate the objects, that is, picking-up and then placing them. The reaction time recorded by the EDK, showed a significantly negative correlation with the peak wrist velocity when reaching. This demonstrated that participants who took longer to react to the green light at the start of the trial, also demonstrated lower peak wrist velocities when reaching for the object. The reaction time was also significantly positively correlated with the time taken in the reach phase as recorded by BIGKAT, showing that participants who took longer to react to the green light, also took longer in the reach phase itself.

The time spent in the reach time as recorded by the EDK, was significantly positively correlated with the proportion of the reach time spent in deceleration. This demonstrates that participants who spent a longer time in the reach phase also spent a longer proportion of this time slowing down their wrist. The opposite was seen in the move time recorded by the EDK, as it correlated

significantly negatively with the time spent decelerating. This suggests that participants who spent longer in the move phase, spent a smaller proportion of this time slowing down their wrist. However, a confounder that is not accounted for in these correlations of wrist deceleration with time are the object pick-up and placement times.

The significant correlations between many of the BIGKAT and EDK parameters suggest that the EDK itself can be used to measure the time parameters during these trials in a clinical setting. However, as this was the first time such a kinematic protocol was administered in pwMS, we wanted to use both BIGKAT and EDK to identify whether the longer movement times reflected on the EDK were due to solely to factors like delayed reaction time and object manipulation or whether wrist velocities during movement were also affected. The significant correlation between the two systems shows that pwMS are affected on multiple facets of the reach to grasp movement. BIGKAT will be useful in the identification of other movement-based factors like jerk or deceleration, which the EDK will be unable to pick-up. However, these correlations have shown that the patterns seen in the EDK will translate to the kinematic patterns elucidated via BIGKAT, without the need for the measurement of the wrist velocity profiles during these assessments in everyday clinical practice. This allows for a more portable but robust system of measuring the upper limb performance of patients using a more simplified equipment set-up. The EDK itself is lightweight and transported easily between clinical locations, whilst it easy set-up on a table-top makes it an ideal candidate for use in the clinical space as we have demonstrated during the course of this study.

Table 7 Correlation matrix between BIGKAT and event detection kit measures

BIGKAT parameters	Event detection kit parameters		
	Reaction time	**Reach time**	**Move time**
Peak wrist velocity (reach phase)	-0.36**	-0.77****	-0.74****
Peak wrist velocity (move phase)	-0.26	-0.73****	-0.85****
Reach phase time	0.49****	0.68****	0.61****
Move phase time	0.33*	0.8****	0.78****
Time to pick-up object	0.30*	0.70****	0.85****
Time to place object	0.23	0.33*	0.46****
Maximum grip aperture when reaching	0.17	-0.04	-0.02
Proportion of time to reach maximum grip aperture	0.01	0.23	0.33*
Proportion of reach phase decelerating	0.19	0.61****	0.56****
Proportion of move phase decelerating	-0.27*	-0.43**	-0.39**

Significance values - $p < .0001$ '****'; $p < .001$ '***', $p < .01$ '**', $p < .05$ '*'

3.3.5 Kinematic parameters correlate with 9HPT scores

The participants' scores on the 9HPT demonstrated significant correlation with a number of the kinematics measures recorded by the EDK and BIGKAT as demonstrated in Table 8. There was a significant positive correlation demonstrated between performance on the 9HPT and the reaction, reach and move times on the EDK, suggesting that participants who took longer to complete the 9HPT, also took longer on all aspects of the reach and move trials as recorded by the EDK.

There was a significant negative correlation between time taken to complete the 9HPT and the peak wrist velocities during the reach and move phases of the trials as recorded by BIGKAT. This demonstrates that participants who took longer to complete the 9HPT had significantly slower peak velocities when completing the reach and move trials. This is an important demonstration, as it confirms the face validity of the kinematic measures and indicates they are quantifying behaviours that are known to be clinically useful.

There was also a significant positive correlation between the time taken to complete the 9HPT and the time spent in each phase of the reach and move trials, with participants who took longer on the 9HPT demonstrating longer times to pick-up and place the objects during the reach and move trials. There was no correlation between performance on the 9HPT and the maximum grip aperture or time to reach maximum grip aperture. There was a significant positive correlation between the 9HPT time and the time spent decelerating during the kinematic trials when reaching for the object, but there was no significant correlation during declaration when moving the object.

These significant correlations between the 9HPT and the kinematic parameters show that participants who perform worse on the 9HPT demonstrate a different kinematic profile than those who perform better. Wrist velocities, time taken to pick-up and place objects as well as time taken moving the hand itself are all affected separately although they correlate strongly with each other. Together, they contribute to explaining the variation in performance seen during these reach and grasp trials.

Table 8 Correlation matrix demonstrating correlation between 9HPT scores and kinematic measures

	Kinematic parameter	9HPT score
Event detection kit measure	**Reaction time**	0.30*
	Reach time	0.63****
	Move time	0.78****
BIGKAT measure	**Peak wrist velocity (reach phase)**	-0.69****
	Peak wrist velocity (move phase)	-0.59****
	Reach phase time	0.51****
	Move phase time	0.72****
	Time to pick-up object	0.60****
	Time to place object	0.35**
	Maximum grip aperture when reaching	0.24
	Proportion of time to reach maximum grip aperture	0.13
	Proportion of reach phase decelerating	0.40**
	Proportion of move phase decelerating	-0.19

Significance values - $p < .0001$ '****'; $p < .001$ '***', $p < .01$ '**', $p < .05$ '*'

3.3.6 Performance differences measured by kinematic parameters also show differences in patient reported outcome measures (PROs)

The kinematic outcome measures as recorded by the EDK and BIGKAT were compared using one-way ANOVAs to the PROs as recorded on the ABILHAND and AMSQ-SF questionnaires on upper limb function by the patient group. One-way ANOVA demonstrated that there was a statistically significant difference in the time taken to place objects as measured by BIGKAT, between the severity categories of the AMSQ-SF (one-way ANOVA $F(2,38) = 4.25$, $p<0.05$). Two-way testing showed that this significance was driven by a significant difference between the mild – moderate and mild – severe disease categories. One-way ANOVA also demonstrated a significant main effect of AMSQ-SF severity category on the time taken for the participant to move the object as measured by the EDK (one-way ANOVA $F(2,38) = 3.53$, $p<0.05$). Two-way testing shows that this significance was again driven by a significant difference between the mild – moderate and mild – severe disease categories.

Furthermore, one-way ANOVA showed a significant main effect of the AMSQ-SF severity category on the time taken for the patient to slow down their hand when reaching for the objects during the kinematic trials (one-way ANOVA $F(2,38) = 4.72$, $p<0.05$). Two-way testing demonstrated that this was driven by a significant difference between the mild – moderate disease categories.

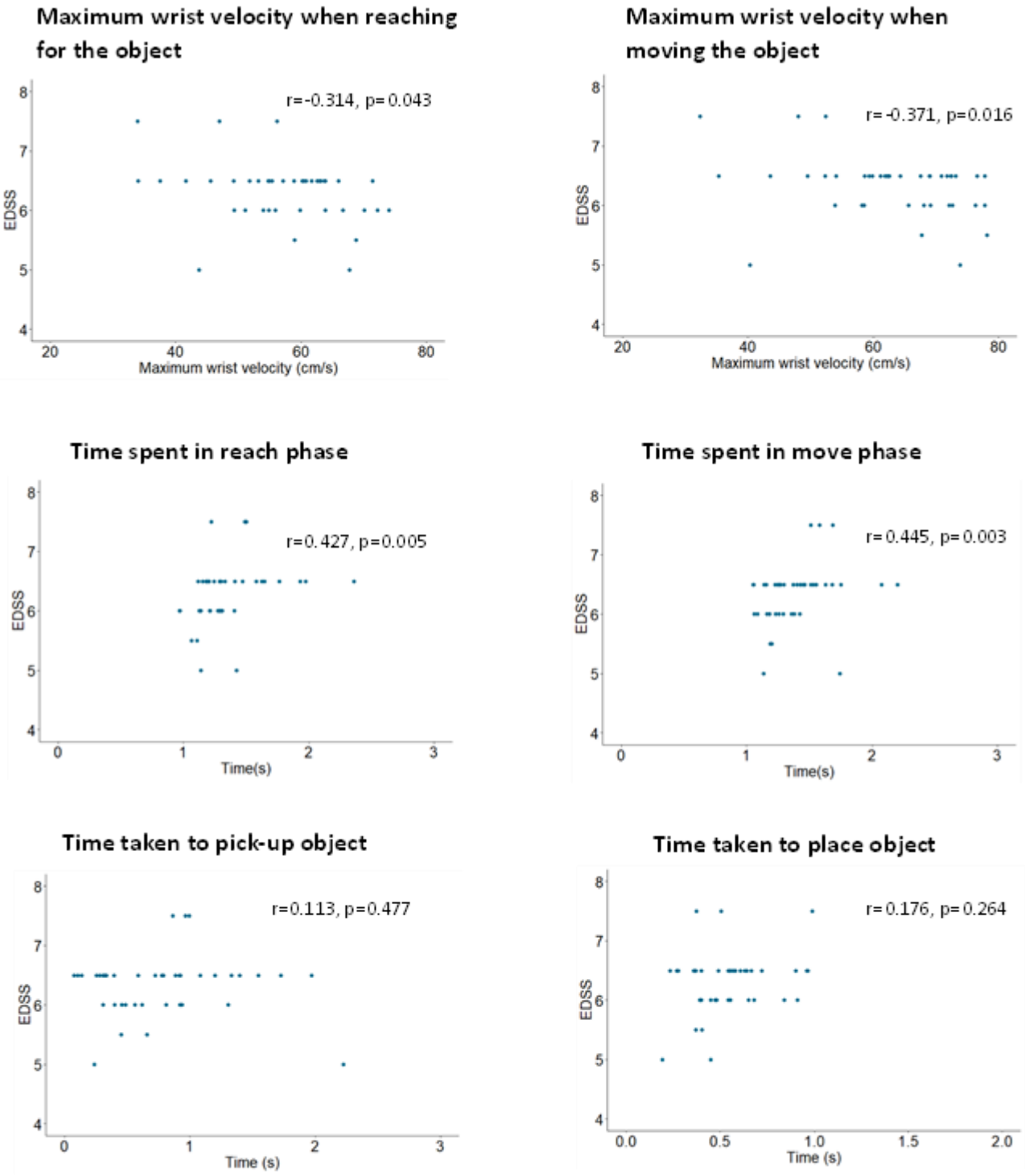
One-way ANOVA also demonstrated a significant main effect of the AMSQ-SF severity category on the time taken to complete the 9HPT (one-way ANOVA $F(2,38) = 4.75$, $p<0.05$). However, two-way testing didn’t demonstrate

any significant differences between the severity category scores on the AMSQ-SF questionnaire. One-way ANOVA didn't show any significant main effect of the ABILHAND questionnaire scores on any of the kinematic parameters measured during the kinematic trials or the patients' performance on the 9HPT.

3.3.7 Kinematic parameters showed some correlation with EDSS score

The kinematic parameters were compared to the EDSS score recorded during the baseline assessments in the patient group. The EDSS score showed a significant negative correlation with the maximal wrist velocities measured during the reach ($R^2(40) = -0.32$, $p<0.05$) and move ($R^2(40) = -0.35$, $p<0.05$) phases as recorded by BIGKAT. This suggests that patients who scored higher on the EDSS and therefore demonstrated increased disease severity, had lower peak wrist velocities during the reach and move trials. The EDSS score also demonstrated a significant positive correlation with the time taken to move the objects as measured by BIGKAT ($R^2(40) = 0.31$, $p<0.05$). The EDSS didn't show a significant correlation with any of the other kinematic parameters or the 9HPT score. The correlations of EDSS scores with BIGKAT parameters are shown in Figure 3.12.

Figure 3.12 Scatterplots demonstrating EDSS correlation with BIGKAT kinematic parameters in patients



Scatterplots demonstrating the correlation between the EDSS scores in the patient group and their performance as measured by the kinematic parameters.

3.4 Baseline results summary

Forty two participants with progressive MS (pwMS) and 15 healthy participants performed reach and grasp tasks with different sized objects, while hand movement trajectories were captured by the kinematic assessment system for the baseline assessments. PwMS demonstrated significantly longer reaction times, reach times and took longer to move objects between pre-defined positions, compared to controls. There was no difference between the maximum grip aperture when reaching between pwMS and controls, but the time to reach maximum grip aperture was longer for pwMS. PwMS took longer to pick up objects after arriving at them, and spent more time on the placement of objects. PwMS had lower peak wrist velocities when reaching and moving objects. In pwMS, object reach and movement times correlated with their performance on the 9HPT, which was significantly longer than the control group. There was no correlation between upper limb performance on the kinematic assessment kit and EDSS score in pwMS apart from a negative correlation seen with peak wrist velocities. PwMS who reported severe upper limb dysfunction in the PROs demonstrated longer reach and grasp times and smaller peak velocities.

3.5 Discussion of baseline results

3.5.1 Patient and control group demographics

The results outlined in this chapter demonstrate the usefulness of kinematics to analyse upper limb function in a group of people with progressive MS and healthy controls. There is no other study that has analysed the reach and grasp of people with progressive MS specifically, and so these results represent novel work. The participants in the patient group were screened for any clinical evidence of relapses in the three months prior to the baseline assessment and none of the participants reported any such relapses, which allows the assumption that their performance in the reach and grasp trials was an accurate reflection of their baseline level of dysfunction.

The average age at the onset of progression of the SPMS subgroup of 33 participants was 50.3 years which is similar to the age of progression in the MS population as evidenced by a large population cohort study which found the median age at diagnosis of SPMS to be 49.0 years (Tremlett, Zhao and Devonshire, 2008). The median period of time from a diagnosis of RRMS to SPMS in this population study by Tremlett et al. was 18.9 years which is longer than in our study cohort of SPMS which was 9.5 years. This might be explained by a possible delay in making the diagnosis of MS in some patients, which means their transition from RRMS to SPMS might seem quicker. When looking at the time from symptom onset to diagnosis of SPMS in our study cohort, the mean duration was 18.3 years (SD 7.05), which is more in keeping with the results seen in the population study. When looking at the PPMS subgroups of 9 participants, the mean age of diagnosis of the participants was 48 years

which is older than the median age at diagnosis of 41.0 years seen in the population study of Tremlett et al. These figures show that our patient cohort was fairly representative of the SPMS population, whilst our PPMS cohort was diagnosed at a later stage when compared to population studies. Importantly when looking at the level of disability as measured by the EDSS in our patient cohort as a whole, they had a median EDSS of 6.5 with an average age of 55 years. This is very similar to the level of disability seen in a large natural history study of pwMS by Confavreux et al., who found that pwMS reached an EDSS of 6.0 by the time they were on average 55 years of age. (Confavreux and Vukusic, 2006).

With regards to the control group, they were significantly older than our patient group, but had all reported to be in good health and had no co-morbidities that affected their hand function which made them ideal controls to our patient group. However, there was no difference in the proportion of male and female participants in our control and patient groups. In addition, the fact that these assessments took place during the SARS-CoV 2 pandemic and lockdown meant that it was difficulty to recruit healthy volunteers to attend hospital premises for a face to face assessment.

PROs, namely the AMSQ-SF and ABILHAND were administered to the patient group in order to understand their perception of their upper limb function. The AMSQ-SF has been developed specifically for pwMS and the ABILHAND has been validated in pwMS, so we expected that the scores we received would be valid for the study patient cohort (Barrett *et al.*, 2013; Luijten *et al.*, 2018; Tacchino *et al.*, 2020). The scores on both outcome measures varied from mild to severe dysfunction with all patients reporting some form of upper limb

dysfunction. This was to be expected, as one of the eligibility criteria for participation in the study in the patient group was self-reported upper limb dysfunction.

3.5.2 Performance on the 9HPT and comparison to the EDSS in the patient group

The patient group took significantly longer than the control group with both their preferred and non-preferred hands, demonstrating a mean difference of 12.3 and 17.9 seconds respectively. As the control group had performed within expected times compared to a populations study of 9HPT in healthy participants, the longer scores seen in the patient group demonstrate the level of upper of limb dysfunction. Of interest, the inter-hand difference between the mean 9HPT scores in the control group was 1.2 seconds, compared to an inter-hand difference of 6.8 seconds in the patient group. In a study of 9HPT in 206 pwMS, inter-hand asymmetry was identified as being common in progressive MS and more pronounced when compared to RRMS. The authors found an inter-hand difference of 7 seconds and 9 seconds in SPMS and PPMS respectively which is similar to our mean inter-hand difference of 6.8 seconds (Solaro *et al.*, 2019b). These findings in upper limb asymmetry in progressive MS underline the inherent difficulty in reporting the 9HPT score as a mean score from both hands, which overlooks the asymmetrical effect of the disease on physical functioning.

Furthermore, the presence or absence of sensory impairment in the upper limb, as qualified by the neurological examination, didn't have any impact on the correlation between the 9HPT score and EDSS. This lack of correlation

between the 9HPT and EDSS might be explained by the high degree of inter-hand asymmetry in the 9HPT scores seen in the patient group. In a recent study of 549 pwMS, the mean 9HPT score and EDSS were correlated, with the authors demonstrating that as the inter-hand asymmetry in the 9HPT score increases, usually in progressive disease, the correlation with the EDSS decreases. Therefore, different pwMS who have the same 9HPT score, will score differently on the EDSS. When the inter-hand difference is taken into account, the correlation of 9HPT with the EDSS improves, but even this becomes insignificant as the mean 9HPT increases (Solaro *et al.*, 2020). In summary, the 9HPT score correlates poorly with EDSS in the progressive MS population, highlighting the inability of the EDSS to adequately capture upper limb function as a part of its scoring framework.

3.5.3 The event detection kit as a measure of upper limb function

The EDK measured the reaction, reach and move times of the participants independently but concurrently with BIGKAT as described in section 3.3.2. The reaction time at the start of the trial, a measure of the time between the green light on the kit switching on and the patient starting to move their hand, was significantly longer for the patient group by 0.11s ($p<0.05$) compared to the control group. The increase in reaction time in pwMS has been linked to impaired processing speed and planning of movements, as illustrated in another kinematic assessment study of reaching profiles in pwMS, which showed a longer reaction time in a virtual simulation of reaching task (Wijeyaratnam *et al.*, 2022). The complexity of the motor task being planned for also has an effect on the reaction time to the start of a task, as shown in a study where pwMS demonstrated longer reaction times than controls,

specifically in motor tasks requiring a choice (Dana, Rafiee and Gholami, 2019). In our study, none of the participants reported cognitive impairment, which has been shown to have an impact on processing speed most commonly in pwMS, when it is present (Benedict *et al.*, 2020) The longer processing speed in pwMS even in the absence of self-report cognitive impairment independently predicts physical impairment and disease progression and thus is an important parameter to accurately measure as part of any motor planning task (Hechenberger *et al.*, 2022).

PwMS in our study demonstrated significantly longer times when reaching for the objects with the smaller grasp surface size. This was also seen in the control group, although the difference between the reach times of the grasp surface sizes was not as pronounced. These findings in the control group are supported by previous studies looking at the impact of the available surface area of an object for grasping on the movement time. The smaller size of an object's grasp surface area increased the movement time in healthy adults when reaching for the object (Zaal and Bootsma, 1993). More recently, a study in healthy adults shows that asymmetrical object contact surfaces also increased movement duration (Coats *et al.*, 2018). These studies provide evidence that adjustment in movement times based on object characteristics are a physiological response. Whilst our study replicated these changes, it showed that these differences in movement times increase in pwMS. Furthermore, the asymmetry in reach times seen in the pwMS with their preferred and non-preferred hand was not seen in the control group, again highlighting the pathological asymmetry seen in pwMS.

When moving the object toward the end position, on the EDK, the patient group took significantly longer than the control group to move the objects, which has also been seen in a study that used an instrumented version of the ARAT to measure the transport times of pwMS. They found that pwMS had an increase of up to 70% compared to healthy controls when moving objects as part of the ARAT protocol (Marteniuk *et al.*, 1990). In our study, the placement of the hole at the underside of the object meant that the participants need to place the object on the peg on the EDK without the visual feedback of seeing exactly how the base hole diameter was lined up with the peg. The EDK was unable to measure the exact time it took to place the object on the peg as the move time also incorporated the transport time of the object, but again the hand asymmetry in the pwMS was seen, with them taking significantly longer to move the object with their non-preferred hand compared to their preferred hand.

These results demonstrate that the EDK, being a portable piece of equipment can itself give a number of time parameters including reaction time, that are important markers of prognosis and monitoring of upper limb function in pwMS. In order to explore these movements in increased granularity the BIGKAT results provide some novel insights into the hand movements of pwMS in these reach and grasp trials.

3.5.4 BIGKAT as a kinematic tool to assess reach and grasp

The data collected concurrently with the EDK by BIGKAT demonstrated some significant differences between the control and patient group at baseline.

3.5.4.1 PwMS demonstrate slower wrist velocities when reaching and moving objects

The patient group demonstrated significantly lower peak wrist velocities than the control group both when reaching for objects and moving them. The control group had higher peak wrist velocities with their preferred hand compared to their non-preferred hand when reaching for objects, which wasn't seen in the patient group. Limb asynchrony with regards to peak velocities when reaching for objects has been shown previously in healthy adults, with the preferred hand demonstrating higher peak velocities (Marteniuk, Mackenzie and Baba, 1984). Another more recent study looking at centrally de-afferented patients have shown increased limb asymmetry in peak wrist velocities when reaching for objects in centrally deafferent patients compared to controls (Jackson *et al.*, 2000). Interestingly the loss of asymmetry between the preferred and non-preferred hands in peak wrist velocities in our patient group has not been shown before, which might seem to be contradictory to the asymmetry seen in in movement times as seen in the EDK. However, this may be explained by the significantly lower peak wrist velocities in the dominant hand itself in pwMS (bringing it more in line with the movement of the non-preferred hand), which then reduces the asymmetry that would be seen in healthy controls.

Similar results were seen when moving the object, with the patient group demonstrating a significantly lower peak wrist velocity than the control group. However, the inter-hand asymmetry seen in peak wrist velocity during the reaching movement in the control group was no longer evident during the move phase. Furthermore, the grasp surface size had no significant influence on the peak wrist velocity suggesting that once the object was grasped, the

grasping parameters had no influence on the peak wrist velocity when moving the object.

Further analysis of the velocity profiles showed that the control group spent a longer proportion of the time in the reach phase slowing down their hand when reaching for the objects with a smaller grasp surface size. This was not reflected in the patient group. Peak wrist velocity in healthy adults in reaching tasks is usually reached within the first 50% of the reach phase time, and the control group in our study demonstrated a deceleration period of 60 – 65% in the reach phase, replicating these findings (Paulignan *et al.*, 1990; Van Vliet *et al.*, 2013). The patient group also reached peak velocity with the first 50% of the reach phase, but they took significantly longer in the range of 65 - 70% in deceleration which has not been shown in kinematic studies before. Castiello et al. showed that in healthy adults, when reaching for a smaller object at the same distance, the time spent in wrist deceleration is longer, which is supported by the findings in our control group (Castiello, Bennett and Stelmach, 1993). This difference in deceleration profiles in response to objects with a smaller grasp surface size, seems to be lost in the pwMS in our study, which suggests that the online control of grasping is impaired in this group during the final phase of reaching (Camponogara and Volcic, 2019). Another possibility is that pwMS have a weaker pincer grip compared to healthy controls, as demonstrated in a longitudinal study using dynamometers (Newsome *et al.*, 2019). Therefore, when they approach all the objects in the reach phase of the trial, any advantage afforded by the larger grasp surface size is overcome by the level of impairment in grip strength.

3.5.4.2 Object pick-up and placement profiles are significantly affected in pwMS compared to controls

When measuring the object pick-up and placement times, it was hypothesised that the patient group would take significantly longer than the controls and this was borne out in the results. Whilst the control group took longer to pick up objects with a smaller grasp surface size, as expected and shown in other studies, the patient group took significantly longer with all the objects (Castiello, Bennett and Stelmach, 1993; Paulun *et al.*, 2016). This could be explained by the impairment in grip force control in pwMS demonstrated in a case-control study by Reilmann et al (2013). In this study, the authors found that pwMS demonstrated greater grip force variability when using a precision grip, which was correlated with the level of motor disability seen in the patient (Reilmann *et al.*, 2013).

During the object placement phase at the end of each trial, termed the hover phase, the patient group took significantly longer than the control group, and this was more pronounced for objects with the smaller base hole diameter. This part of the trial relied on visual and haptic feedback for the correct placement of the object on the peg. A study by Miall et al (2019) showed that loss of haptic feedback affects hand posture, although the study group were chronically deafferented patients (Miall *et al.*, 2019). The findings from this study can be extrapolated to pwMS as another case-control study by Ji Liang et al. (2009) showed that pwMS demonstrated more accurate grasp force control when allowed haptic feedback to grasp objects (Jiang *et al.*, 2009). In summary, we have shown that the impaired grip force control and haptic

feedback in pwMS leads to significantly longer times with object manipulation and placement.

3.5.4.3 PwMS demonstrate altered grip aperture profiles when reaching for objects

When measuring grip aperture during the reach phase of the trials, the control group demonstrated the expected grip aperture profiles, with a larger maximum grip aperture achieved when reaching for objects with a larger grasp surface size. This has been shown in studies in healthy adults where grip aperture, and more specifically maximum grip aperture, scales to the perceived object size (Linkenauger, Witt and Proffitt, 2011; Collier and Lawson, 2017). Interestingly, there was no significant difference in maximum grip aperture between the control and patient group, although both groups demonstrated a larger maximum grip aperture when reaching for objects with their preferred hands. This in contrast to some studies that have shown that a smaller maximum grip aperture is seen with the preferred hand and usually associated with greater precision (Grosskopf and Kuhtz-Buschbeck, 2006; Flindall, Doan and Gonzalez, 2014). Furthermore, in other neurological conditions, like Parkinson's disease (PD), maximum grip aperture is significantly smaller when reaching, although the scaling of aperture based on object size is similar to that of healthy controls (Rand *et al.*, 2006; Parma *et al.*, 2014). In people who have hemiparesis due to stroke, the grip aperture scaling based on object size is partially maintained but aperture size can be smaller compared to healthy controls (Michaelsen, Magdalon and Levin, 2009). The impairment of maximum grip aperture in chronic stroke and PD is likely due to the underlying pathophysiology in these distinct neurological

conditions, with a significantly larger portion of the parietal cortex affected in a hemiparetic stroke. In PD, the impairment of the dopaminergic pathway may likely play a significant role in grip aperture as a whole as shown in animal models (Bova *et al.*, 2020). In MS the location of the inflammatory insult in the cortex is important to the resulting functional deficit and it maybe that in our cohort, the MS participants didn't have a severe enough inflammatory burden affecting the neural correlates important in grasping and hence we were not able to identify significant differences at a group level (Turella and Lingnau, 2014).

The time to reach maximum grip aperture was also longer for participants with their preferred hand in the control groups. This is supported by a study in healthy adults which showed that there was earlier anticipatory control for the left non-preferred hand in grasp pre-shaping and a stronger transport–grasp linkage for the right preferred hand, leading to a later achievement of maximum grip aperture in the reach phase (Tretriluxana, Gordon and Winstein, 2008). In summary, although there was no significant difference in maximum grip aperture between the patient and control group in our study, the impact of handedness on grip aperture was demonstrated in the control group, but lost in the patient group.

Whilst time reach maximum grip aperture didn't show a difference in handedness in the MS group, the impact of handedness on some of the kinematic parameters like peak wrist velocity when reaching may be linked to the asymmetry seen at the cortical level in pwMS. Imaging of pwMS has shown that grey matter, also known as cortical volume, is significantly decreased in certain regions like the left fronto-temporal cortex and praecuneus, as well as

of anterior cingulate gyrus and of caudate nuclei bilaterally (Prinster *et al.*, 2006). However, there has not been many studies like this Prinster et al, looking at hemispheric differences in pwMS and the varied localisation of inflammation in the cortex may explain why some kinematic parameters in the MS group were affected by handedness as opposed to others which seemed to be affected in the control group. Another factor maybe that the functional neural networks involved in reach and grasp are themselves affected. Hemispheric asymmetry reduction in older adults (HAROLD) is a model which has been shown in older adults as a possible compensatory function for the deafferentation process in aging individuals (Cabeza, 2002). More recent functional imaging studies have shown that the HAROLD model captures only some of the age-related brain patterns observed in healthy aging. Instead, the CRUNCH (compensation-related utilisation of neural circuits hypothesis) model posits that elderly subjects recruit additional brain regions that do not necessarily belong to the contralateral hemisphere as much as they rely on additional strategies to solve cognitive problems in particular (Berlingeri *et al.*, 2013). This model maybe a factor in our control group and an additional confounder in our MS group when looking at the impact of handedness in the kinematic assessment. Furthermore, transcranial magnetic stimulation, has also shown that there is a degree of asymmetry in corticospinal excitability that also significantly predicted the severity of MS-related physical symptoms (Chaves *et al.*, 2019). Taken together these studies demonstrate that in pwMS, cortical volume and functional connectivity play an important role in determining the impact of handedness on upper limb function, in particular reach and grasp.

3.5.4.4 The correlation of kinematic parameters with the event detection kit and clinical outcome measures

Kinematic parameters recorded by BIGKAT correlated significantly with the EDK parameters, as described in section 3.3.4. This included the time parameters for the reach and move phase as recorded by the EDK and the corresponding reach and move phase times recorded by BIGKAT. Although BIGKAT was able to separate out the object pick-up and placement times to provide a more accurate reflection of the time that the hand is actually moving, these times correlated strongly with the time parameters from the EDK. Furthermore, the EDK parameters correlated with the peak wrist velocity in the reach phase and the deceleration phase in both reach and move phases as recorded by BIGKAT. The time parameters from the EDK also correlated with the time to pick-up and place objects as measured by BIGKAT. These correlations demonstrate that the reach and grasp profiles measured by BIGKAT are also reflected by the more basic linear time parameters captured by the EDK. Importantly, this means that the EDK by itself, as a more portable piece of equipment, may suffice as a measure of reach and grasp trials in pwMS. Measures like maximum grip aperture when reaching do not differ significantly between controls and pwMS and therefore, may not be of use as a measure in the clinical space. Whilst the granular kinematic data recorded by BIGKAT allows the detailed description of reach and grasp profiles for the first time in patients with progressive MS, the EDK may have a greater transferability to the clinic space in order to capture a wider population of pwMS in further studies of reach and grasp function.

Furthermore, the 9HPT showed significant correlation with all the kinematic measures recorded, except the wrist deceleration profiles. The correlations shown in section 3.3.5, demonstrate the validity of the BIGKAT and EDK parameters against the current gold standard upper limb measure, but provide significantly more detail in how the hand movement profiles are affected. Once again there was no correlation with maximum grip aperture or time to reach maximum grip aperture with the 9HPT, suggesting that grip aperture doesn't factor significantly in this cohort of pwMS as a confounder of performance on the 9HPT.

Section 3.3.7 also described the correlation between the EDSS and some of the BIGKAT parameters, namely the wrist profiles and object pick-up times. This correlation between kinematic parameters and EDSS has been shown in a case control study by Coghe et al. (2019) which showed that the EDSS is correlated significantly with hand to mouth and gait analysis (Coghe *et al.*, 2019). The difference between Coghe et al's study and ours is that they only included pwMS with an EDSS of between 1 to 6, which means that all their participants were ambulatory, with/without walking aids. Another recent study of 20 pwMS showed moderate-to-large correlations between the EDSS and kinematic assessment of hand to mouth movements, but once again the participants all scored between an EDSS of 2 to 6.5 (Corona *et al.*, 2018). To our knowledge, our study is the first to compare the performance of the EDSS at the higher end of the scale (5.0 to 7.5) against kinematic parameters of upper limb function. As shown in Figure 3.2, once the EDSS increases to higher than 5 (which was the cases for the all the pwMS in our study), the variation seen in upper limb function for a small increase in EDSS is significant.

Therefore, the correlations between the kinematic parameters and the EDSS in our study is not as strong.

3.5.4.5 Kinematic parameters also correlate with the PROs

When we compared the PROs in pwMS with the kinematic assessment parameters at baseline there was a significant association with the AMSQ-SF and object pick-up and move times as measured by the EDK. The ABILHAND didn't show any association with the kinematic assessment. One explanation might be the smaller sample size, especially in pwMS who reported a severe dysfunction in the PROs. The 9HPT also demonstrated some correlation to the AMSQ-SF demonstrating its validity as a measure of upper limb function as evidenced in the literature (Lamers *et al.*, 2014; Feys *et al.*, 2017)

3.6 Discussion of baseline results summary

The baseline results have demonstrated the wide variation in upper limb dysfunction in our cohort of pwMS. The control group demonstrated expected kinematic reach and grasp profiles in line with previous studies of healthy adults. In the patient group, the pwMS demonstrated increased reaction time which is a marker of cognitive impairment. We have shown novel aspects of upper limb dysfunction with slower peak wrist velocities, and significantly longer object pick-up and placement times. There is significant inter-hand asymmetry in pwMS, but in certain aspects of reaching, like the maximum grip aperture and time to reach maximum grip aperture, the expected asymmetry is absent. The kinematic parameters show a strong correlation amongst the parameters themselves and currently accepted clinical outcomes, namely the

9HPT. However, the kinematic parameters also show a significantly different reach and grasp profile in pwMS compared to healthy controls, namely in wrist velocities and object pick-up and placement times. The EDK, demonstrates strong correlation to the BIGKAT kinematic measures and provides a more portable method of measuring the important time parameters of reach and grasp trials that can be assessed in the clinical setting. The EDSS shows poor correlation to upper limb function (as measured by the 9HPT and kinematic assessment) in this cohort of people with progressive MS and lacks utility in delineating the impairment detected by the kinematic assessment.

Chapter 4 Follow-up Results and Discussion

4.1 Patient group follow-up details

The healthy volunteers who made up the control group were tested at one time point during the baseline assessment and did not have follow-up testing. All participants in the patient group were offered a follow-up assessment after six months, to complete the same clinical and kinematic protocol as the baseline assessment. Forty-one patients completed the follow-up assessments from the original cohort of forty-two. One patient's condition significantly worsened, such that they were unable to attend the study site to complete the follow-up assessment and therefore had to withdraw from the study.

The mean length of time between baseline and follow-up assessments was 6.8 months (S.D. 0.7 months). None of the patients reported any relapses or change in their treatment between the baseline and follow-up assessments. Five out of forty-two patients remained on disease modifying treatment with ocrelizumab and two out of forty-two patients remained on siponimod. Twenty-six out of forty-two patients remained on the randomised placebo-controlled MS-STAT2 trial during the course of the follow-up assessments.

4.2 Follow-up clinical outcome measures

The median EDSS during the follow-up assessment was 6.5 (range 5.0 - 7.5), unchanged from the median baseline EDSS of 6.5 (range 5.0 – 7.5). However, 11 out of 42 patients had a 0.5 increase in their EDSS score between the baseline and follow-up assessments. One patient had a 1.0 increase in their EDSS score between baseline and follow-up. The increase in these EDSS scores were due to a deterioration in walking distances with some patients

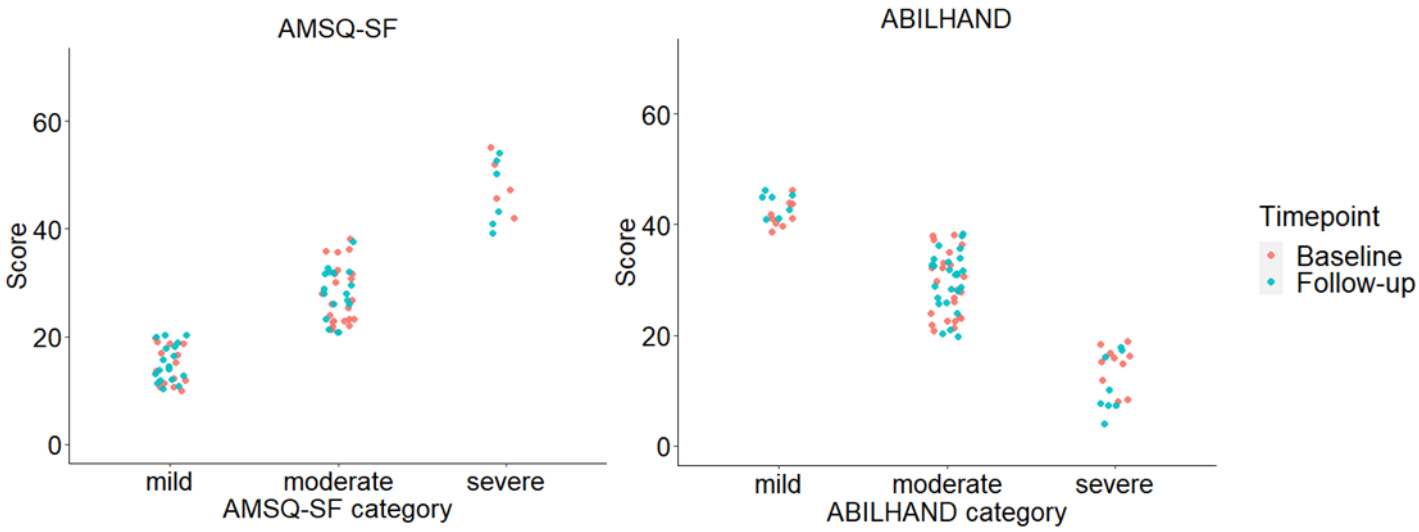
requiring two walking aids instead of one at baseline, or not being able to walk as far compared to the baseline timepoint. Thus, 12/42 (29%) patients demonstrated progression in their EDSS score. There was no change in any of the patients' handedness between baseline and follow-up. The mean time on the 9HPT during the follow-up assessment was 36.6 seconds (SD 13.5) compared to 36.6 seconds (SD 14.2) during the baseline assessment, showing very similar results after approximately six months. The mean 9HPT score for the preferred hand was 34.2 seconds (SD 14.1) at the six month follow-up compared to 33.6 seconds (SD 13.5) at baseline ($p = 0.84$). The mean 9HPT score for the non-preferred hand was 39.5 seconds (SD 16.8) during the follow-up assessment compared to 40.4 seconds (SD 16.8) at baseline ($p = 0.83$). Four out of 42 (10%) patients demonstrated a greater than 20% worsening in their 9HPT times at 6 month follow-up, which is deemed a clinical meaningful worsening in the test score as per established trial studies (Lublin *et al.*, 2016; Kapoor *et al.*, 2018).

4.3 Follow-up patient reported outcome measures

The patient reported outcomes (PROs) as measured by the ABILHAND and AMSQ-SF are illustrated in Figure 4.1. The median ABILHAND score at baseline was 28 (range 8 – 46) compared to the median score at follow-up of 31 (range 4 – 46), with no significant change ($p = 0.89$). However, five patients' scores deteriorated from the mild to moderate category on the scale, whilst two patients' scores deteriorated from moderate to severe at the follow-up timepoint. Four patients' scores improved from severe to moderate, and three patients' scores improved from moderate to mild categories during the follow-up timepoint.

The median AMSQ-SF score at baseline was 23 (range 10 – 55) compared to the median score at follow-up of 21 (range 10 – 54). There was no significant change between the median AMSQ-SF scores at the two timepoints (p = 0.79). Two patients' scores deteriorated from mild to moderate and another two patients' scores deteriorated from moderate to severe. Six patients' scores improved form moderate to mild categories and one patients' score improved from the severe to moderate category.

Figure 4.1 Scatterplots of patient reported outcome measures at baseline and follow-up timepoints



4.4 Follow-up kinematic measures

4.4.1 Follow-up trials data validation

The trials recorded for the kinematic assessment during the follow-up timepoints underwent the same data validation as described in Chapter 3.3.1. Each participant performed five reach and grasp trials for each condition and each participant had to complete eight unique conditions (4 objects x 2 hands). The total possible trials for each participant at the follow-up visit was 40 trials,

the same as the baseline visit. As there were 41 patients who completed follow-up assessments, the total number of trials possible was 1640 trials. Figure 4.2 shows the number of trials recorded and analysed after the validation process. The data validation and selection of trials for analysis at follow-up was identical to the process at the baseline timepoint outlined in section 3.3.1. BIGKAT recorded 1551/1640 (94.6%) trials and after validation in R studio 1026/1551 (66.2%) trials were included in the final analysis.

The main effects of the kinematic parameters between baseline and follow-up are outlined in Table 9. The interactions and individual factor comparisons are expanded upon in the following sections of this chapter.

Figure 4.2 Flowchart illustrating the number of follow-up trials collected and used in the analysis

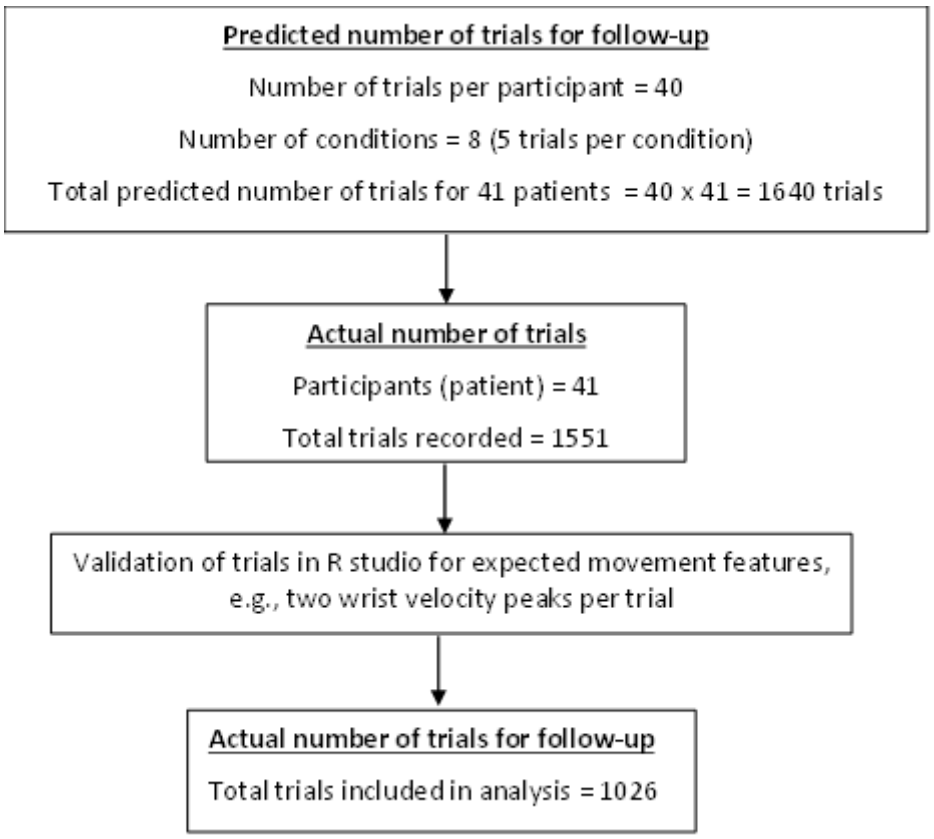


Table 9 Main effects of the kinematic parameters between the baseline and follow-up timepoints in the MS group

Dependant kinematic variable	F-value	d.f.	ηp2	p-value
Reaction time	0.35	1,80	0.00	0.555
Reach time	1.10	1,80	0.01	0.299
Move times	0.92	1,78	0.01	0.327
Time spent in reach phase	2.20	1,76	0.03	0.142
Time spent in move phase	0.18	1,78	0.00	0.672
Object pickup time	0.62	1,78	0.00	0.439
Object placement time	0.77	1,64	0.01	0.384
Maximum wrist velocity (reach phase)	0.06	1,77	0.00	0.812
Proportion of time in wrist deceleration (reach phase)	7.46	1,72	0.09	0.008
Maximum wrist velocity (move phase)	2.33	1,77	0.03	0.131
Proportion of time in wrist deceleration (move phase)	0.03	1,73	0.00	0.855
Maximum grip aperture	9.71	1,71	0.12	0.003
Proportion of time to reach maximum grip aperture	4.27	1,74	0.05	0.042

ηp2 effect size reported as partial Eta squared

4.4.2 Event detection kit kinematic measures

4.4.2.1 Reaction time, reach time and move time

Reaction time

There was no significant difference between the baseline and follow-up timepoints in the reaction time as measured by the event detection kit (EDK). There was no significant main effect of grasp surface size, base hole diameter or hand. There were no significant interactions.

Reach time

The reach time showed no significant difference between the baseline and follow-up timepoints. There were no significant interactions. There was a significant main effect of grasp surface size with patients demonstrating a significantly longer reach time with objects with the smaller grasp surface compared to the larger grasp surface size ($F(1,395) = 87.9$; $p<0.05$, $\eta p^2 = 0.18$). There was a significant main effect of base hole diameter, with patients taking longer in the reach phase with objects with the smaller base hole diameter compared to the larger base hole diameter ($F(1,396) = 4.80$; $p<0.05$, $\eta p^2 = 0.01$). There was also a significant main effect of hand with patients taking significantly longer with their non-preferred hand in the reach phase compared to their preferred hand ($F(1,401) = 18.2$; $p<0.05$, $\eta p^2 = 0.04$).

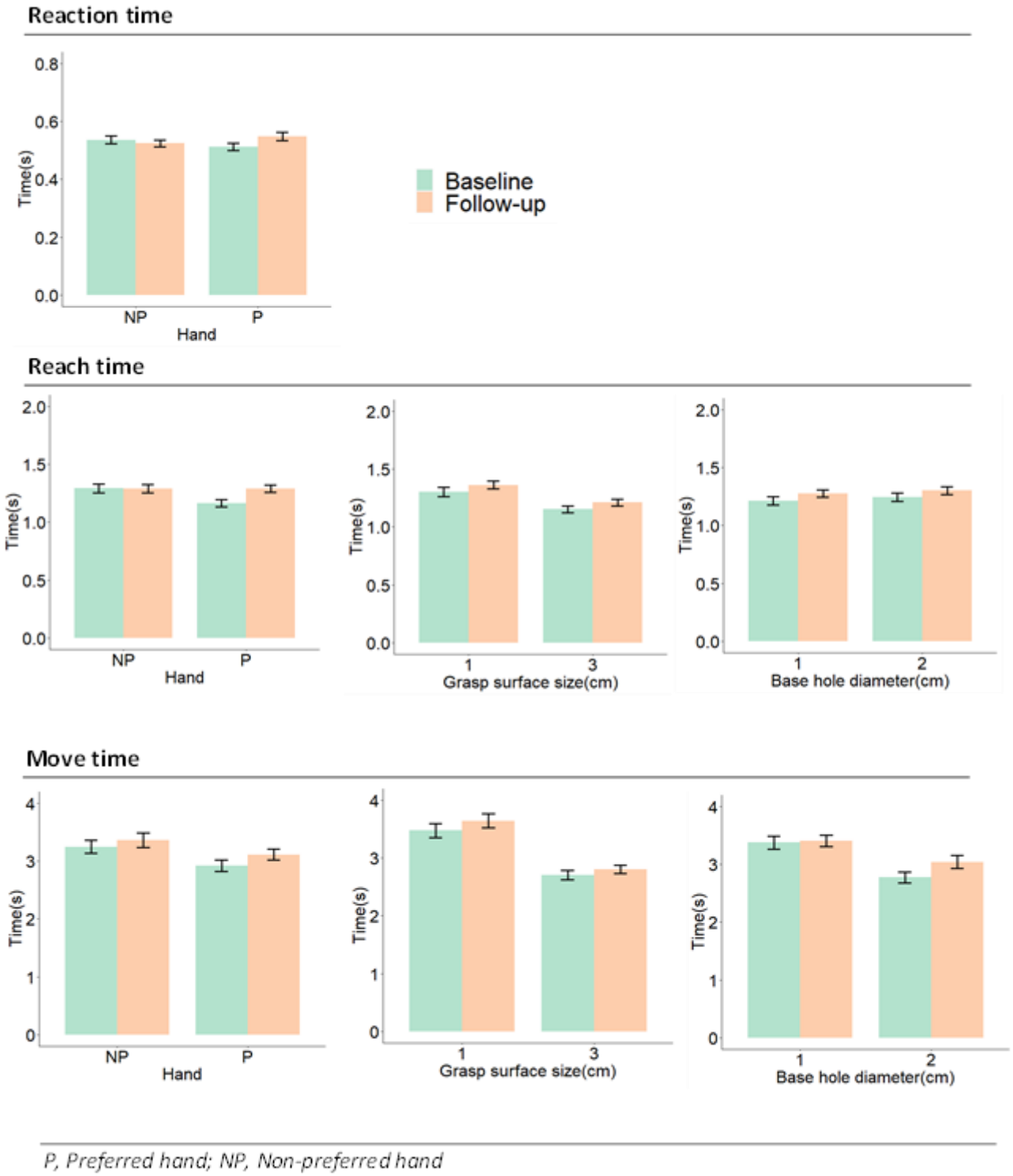
Move time

The move time as measured by the EDK, didn't show any significant difference between the baseline and follow-up time points. There was a significant interaction between grasp surface size and base hole diameter ($F(1,393) = 7.83$; $p<0.05$, $\eta p^2 = 0.02$). Pairwise testing at the level of the grasp surface size

showed that patients took significantly longer to transport the objects with the smaller grasp surface size compared to those with the larger grasp surface size ($p<0.05$). At the level of the base hole diameter, the patients took significant longer to transport objects with the smaller base hole diameter when the grasp surface size was larger ($p<0.05$). This difference wasn't seen in objects with the smaller grasp surface size. There was a significant main effect of grasp surface size with patients taking longer when moving the objects with the smaller grasp surface compared to the larger grasp surface size ($F(1,397) = 150$; $p<0.05$, $\eta p^2 = 0.28$). A significant main effect of base hole diameter was shown, with patients taking longer to move and place objects with the small base hole diameter compared to the large base hole diameter ($F(1,398) = 45.0$; $p<0.05$, $\eta p^2 = 0.10$). There was also a significant main effect of hand with patients taking longer to move objects with their non-preferred hand compared to their preferred hand ($F(1,410) = 29.8$; $p<0.05$, $\eta p^2 = 0.07$).

These results show that although there was no significant difference between baseline and follow-up timepoints, the grasp surface size of the object as well as the base hole diameter of the object had a significant impact on the time taken in the reach and move phases at both timepoints. Furthermore, patients took longer in both reach and move phases with their non-preferred hand compared to their preferred hand. These pattern of results were similar to those obtained at the baseline timepoint in the patient group as well. These results are illustrated in Figure 4.3.

Figure 4.3 Reaction, reach and move times as recorded by the event detection kit



P, Preferred hand; NP, Non-preferred hand

4.4.3 BIGKAT kinematic parameters

4.4.3.1 Peak wrist velocity when reaching and moving objects

Reach phase

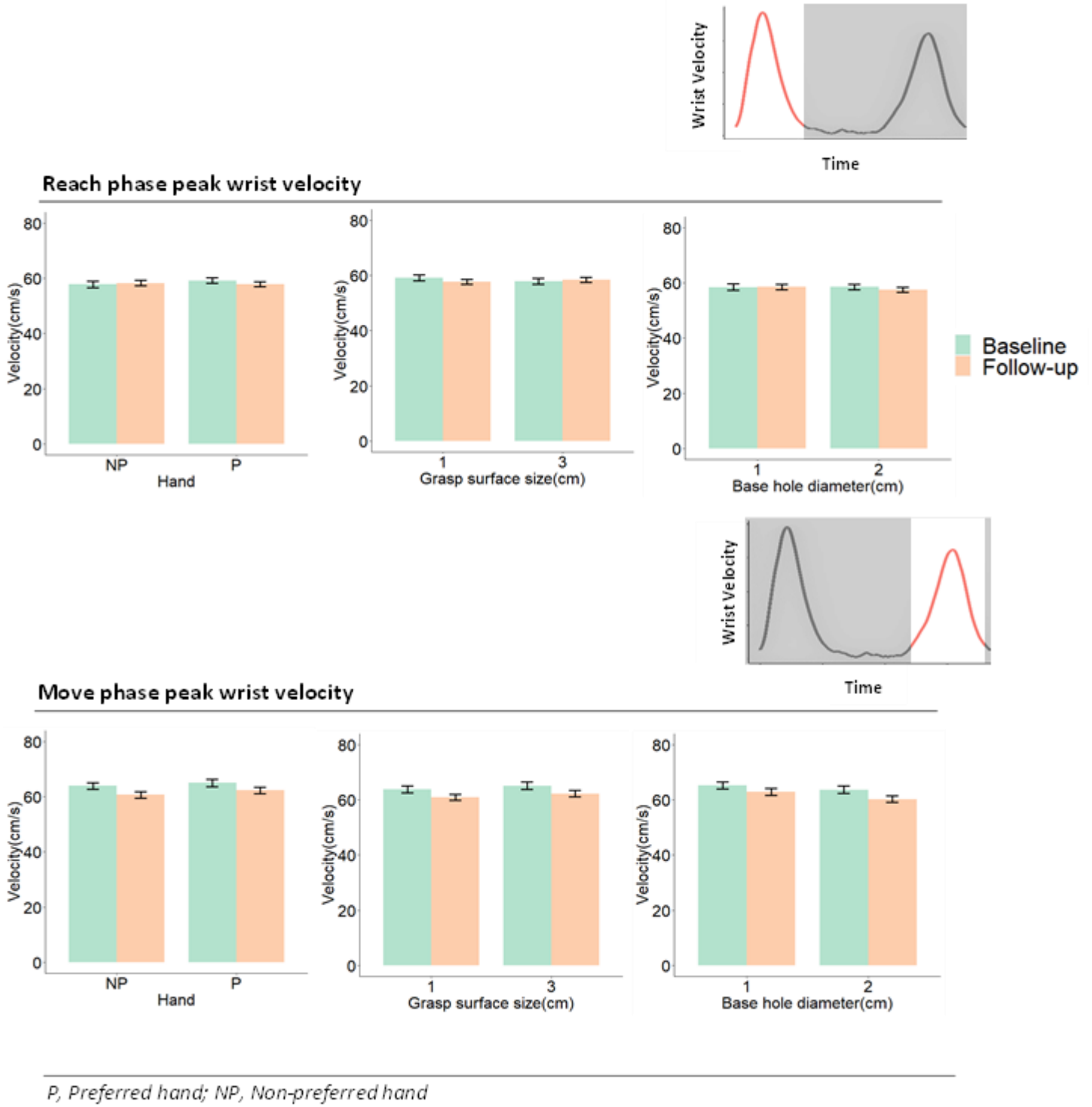
There was no significant difference in peak wrist velocities when patients were reaching for objects between the baseline and follow-up time points. There was no significant main effect of grasp surface size, base hole diameter or hand. There were no significant interactions.

Move phase

When moving objects there no significant difference in peak wrist velocities between baseline and follow-up time points either. There was a significant main effect of base hole diameter ($F(1,398) = 5.96$; $p<0.05$, $\eta p^2 = 0.01$), with patients demonstrating a slower maximum wrist velocity when moving objects with the larger base hole diameter compared to the smaller base hole diameter. There was also a main effect of hand ($F(1,410) = 7.62$; $p<0.05$, $\eta p^2 = 0.02$), with patients demonstrating a slower maximum wrist velocity when moving objects with their non-preferred hand compared to their preferred hand. There were no significant interactions and no other significant main effects detected.

These results show that patients' peak wrist velocities didn't change significantly between the baseline and follow-up timepoint. However, patients moved their hands slower when moving objects with their non-preferred hand as well as when moving objects with a larger base hole diameter, similar to the pattern of results seen in the baseline timepoint. These results are illustrated in Figure 4.4.

Figure 4.4 Peak wrist velocities when reaching for and moving objects



P, Preferred hand; NP, Non-preferred hand

4.4.3.2 Wrist deceleration during reach and move phase

The proportion of reach time during which the wrist was decelerating as the hand approached the object was measured during the follow-up assessment as well.

Reach phase

In the reach phase, wrist deceleration showed a significant interaction between timepoint and hand ($F(1,436) = 5.03$; $p<0.05$, $\eta p^2 = 0.01$). Pairwise testing at the level of the timepoint showed that patients spent a significantly longer proportion of time in deceleration when reaching during the follow-up time point compared to the baseline, but this was only the case for the preferred hand. At the level of the hand, patients spent a significantly longer proportion slowing down their hand with their non-preferred hand compared to the preferred hand, at the baseline timepoint only. This difference between hands was not seen in the follow-up time point. There was a significant main effect of timepoint ($F(1,72) = 7.46$; $p<0.05$, $\eta p^2 = 0.09$), with patients spending longer during the reach phase in deceleration in the follow-up timepoint compared to baseline. There was also a significant main effect of hand ($F(1,418) = 8.01$; $p<0.05$, $\eta p^2 = 0.02$), with patients spending a shorter amount of time decelerating with their preferred hand compared to their non-preferred hand.

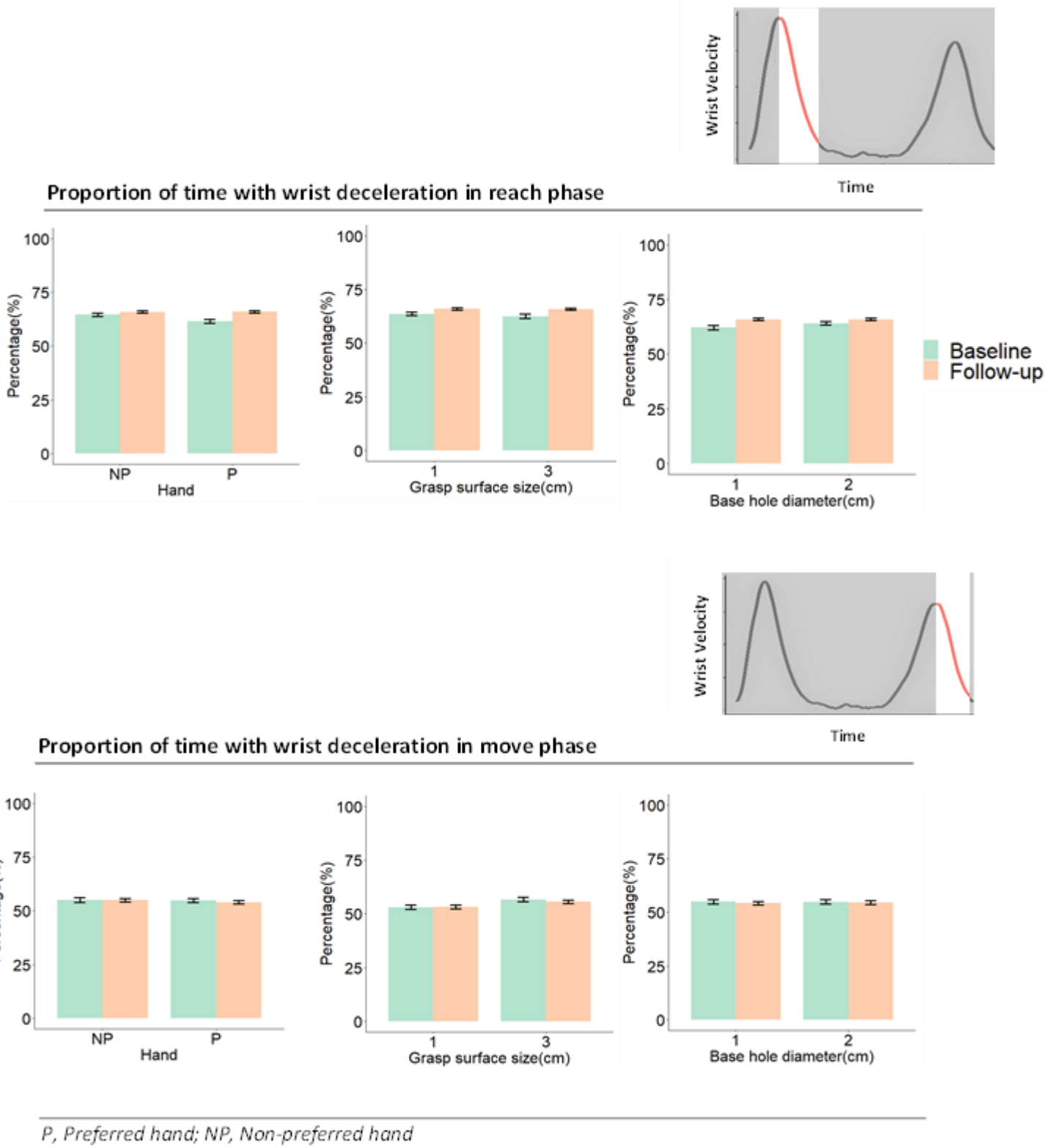
Move phase

When moving objects, there was no significant difference in wrist deceleration between the baseline and follow-up timepoints. There was a significant main effect of grasp surface size ($F(1,410) = 12.8$; $p<0.05$, $\eta p^2 = 0.03$) with patients

spending a shorter time in deceleration when moving objects with the smaller grasp surface size compared to the larger grasp surface size. There was no significant main effect of hand or base-hole diameter. There were no significant interactions.

These results show that patients spent significantly longer slowing down their hands when reaching for objects with their non-preferred hand during the follow-up timepoint compared to the baseline timepoint, suggesting a longer time spent planning the grasping action. This significant difference in deceleration times between baseline and follow-up time points was still maintained even when the four patients who showed progression in the 9HPT by an increase of more than 20% in their 9HPT scores were excluded. Patients also spent longer slowing down their hand when reaching for objects with a smaller grasp surface, highlighting the importance of grasping parameters when reaching for objects, seen in the baseline timepoint as well. These results are highlighted in Figure 4.5.

Figure 4.5 Proportion of the reach and move phase during which the wrist is decelerating



P, Preferred hand; NP, Non-preferred hand

4.4.3.3 Time spent in reach and move phases

Reach phase

There was no significant difference in the time taken during the reach phase between the baseline and follow-up time periods. There was no significant main effect of grasp surface size, base hole diameter or hand. There were no significant interactions.

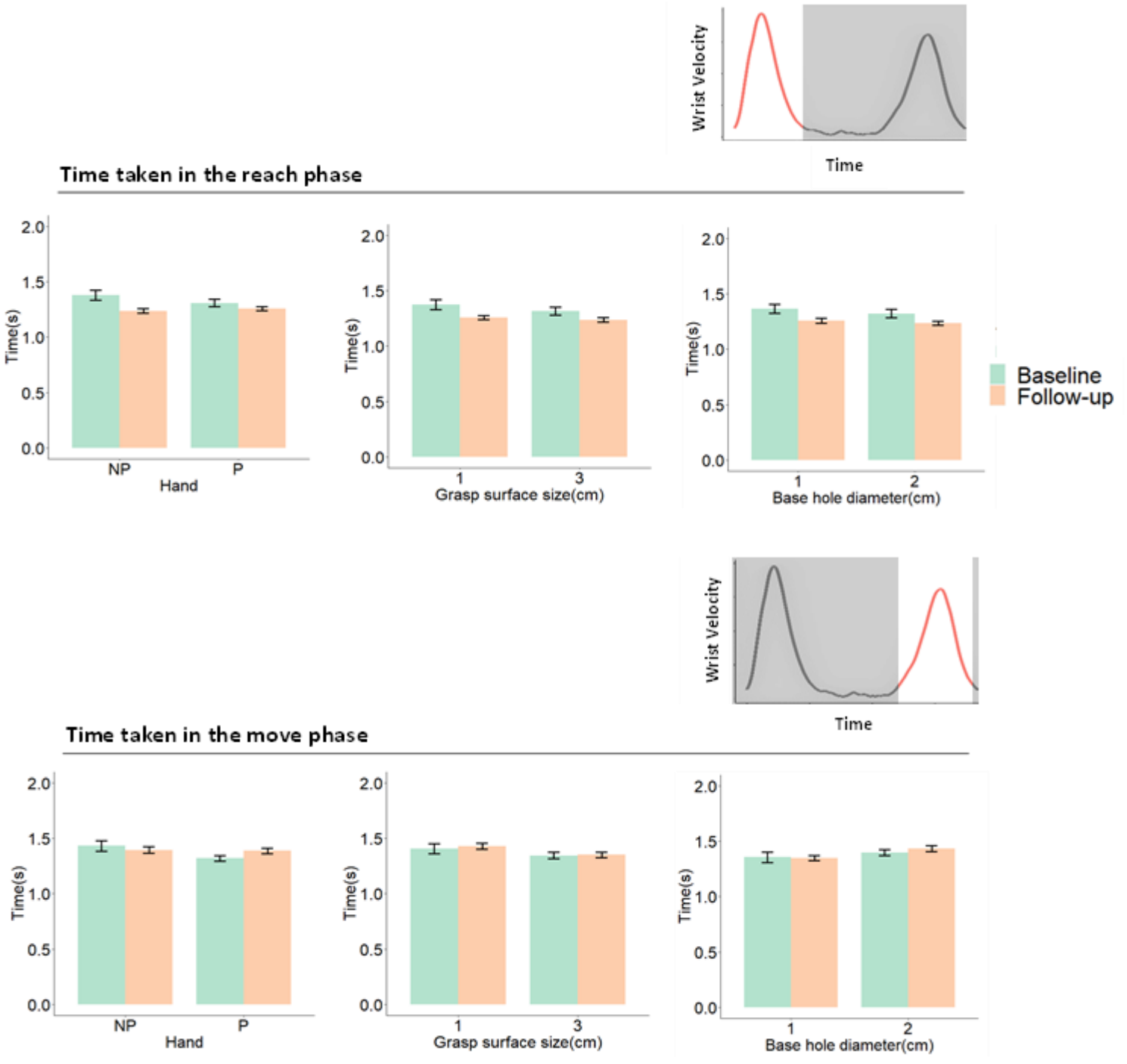
Move phase

In the move phase, there was no significant difference between the baseline and follow-up time periods. There was a significant main effect of grasp surface size ($F(1,405) = 8.25$; $p<0.05$, $\eta p^2 = 0.02$) with patients taking a significantly shorter time to move the objects with a larger grasp surface size compared to the smaller grasp surface size. There was a significant main effect of base hole diameter ($F(1,406) = 4.92$; $p<0.05$, $\eta p^2 = 0.01$) with patients taking a significantly shorter time to move objects with a smaller base hole diameter compared to the larger base hole diameter. There was also a significant main effect of hand ($F(1,427) = 8.26$; $p<0.05$, $\eta p^2 = 0.02$) with patients taking a significantly shorter time to move objects with their preferred hand compared to their non-preferred hand. There were no significant interactions noted.

These results show that the time spent moving in the reach and move phase did not change significantly between baseline and follow-up timepoints. However, patients took longer to move objects with a smaller grasp surface size and base hole diameter, confirming the difficulty with transporting objects

based on grasping parameters. Once again, this pattern of results was seen at baseline as well, demonstrating consistent findings in kinematics parameters that pwMS find more difficult. These results are illustrated in Figure 4.6.

Figure 4.6 Time taken in the reach and move phases as recorded by BIGKAT



P, Preferred hand; NP, Non-preferred hand

4.4.3.4 Time taken to pick-up and place objects

Object pick-up time

There was no significant difference in object pick-up times between baseline and follow-up time points. There was a significant main effect of grasp surface size ($F(1,405) = 165$; $p<0.05$, $\eta p^2 = 0.29$) with patients taking a significantly shorter amount of time to pick-up objects with a larger grasp surface size compared to the smaller grasp surface size. There was also a significant main effect of hand ($F(1,428) = 7.34$; $p<0.05$, $\eta p^2 = 0.02$) with patients taking significantly longer to pick-up objects with their non-preferred hand compared to their preferred hand. There was no main effect of base hole diameter and no significant interactions.

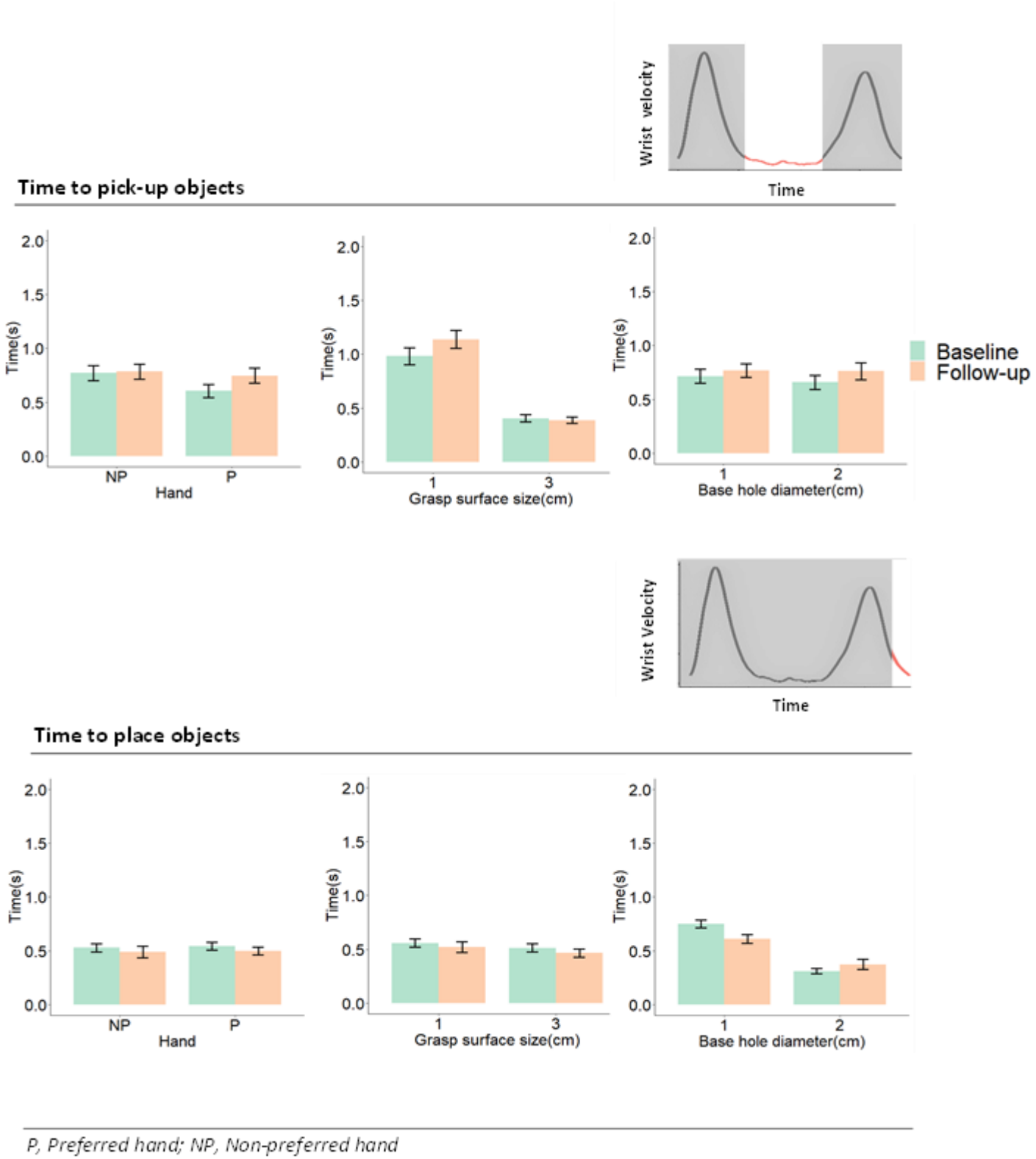
Time to place objects

The time taken to place objects showed a significant interaction between timepoint and base hole diameter ($F(1,408) = 6.91$; $p<0.05$, $\eta p^2 = 0.02$). Pairwise testing at the level of the base hole diameter showed that in objects with the smaller base hole diameter, patients took significantly longer to place the object at the follow-up time point compared to baseline ($p<0.05$). At the level of both the baseline and follow-up time points, pairwise testing showed that patients consistently took significantly longer to place objects with the smaller base hole diameter ($p<0.05$).There was also a significant interaction between grasp surface size and hand ($F(1,405) = 5.33$; $p<0.05$, $\eta p^2 = 0.01$). Pairwise testing at the level of grasp surface size, didn't show any different in object placement times between smaller and larger grasp surface sizes. At the level of the hand, patients took significantly longer to place objects with the larger grasp surface size with their non-preferred hand compared to the

preferred hand ($p<0.05$). There was a significant main effect of base hole diameter ($F(1,408) =76.7$; $p<0.05$, $\eta p^2 =0.16$) with patients taking significantly longer to place objects with a smaller base hole diameter ($p<0.05$). There were no other significant interactions or main effects.

These results show that patients took significantly longer to place objects with a smaller base hole diameter at follow-up compared to baseline. This significant difference was not maintained when the four patients who showed progression in the 9HPT at follow-up were excluded. Furthermore, similar to baseline results, grasping parameters were shown to significantly impact on the time taken to pick-up objects, whilst the smaller base hole diameter also significantly prolonged the time taken to place objects. Furthermore, the asymmetry of hand function was again demonstrated, with patients taking consistently longer to pick-up and place objects with their non-preferred hand. These results are illustrated in Figure 4.7

Figure 4.7 Time taken to pick up and place objects



P, Preferred hand; NP, Non-preferred hand

4.4.3.5 Maximum grip aperture and time taken to reach maximum grip aperture

Maximum grip aperture

Patients demonstrated a significantly smaller maximum grip aperture when reaching for objects during the follow-up timepoint when compared to the baseline timepoint. ($F(1,71) = 9.71$; $p<0.05$, $\eta p^2 = 0.12$). There was a main effect of grasp surface size on the maximum grip aperture, with patients demonstrating a significantly smaller maximum grip aperture when reaching for objects with a smaller grasp surface size ($F(1,389) = 32.1$; $p<0.05$, $\eta p^2 = 0.08$). There was also a main effect of hand on the maximum grip aperture, with patients showing a significantly smaller maximum grip aperture when reaching for objects with their non-preferred hand ($F(1,402) = 8.26$; $p<0.05$, $\eta p^2 = 0.02$). There was no significant main effect of base-hole diameter and no significant interactions.

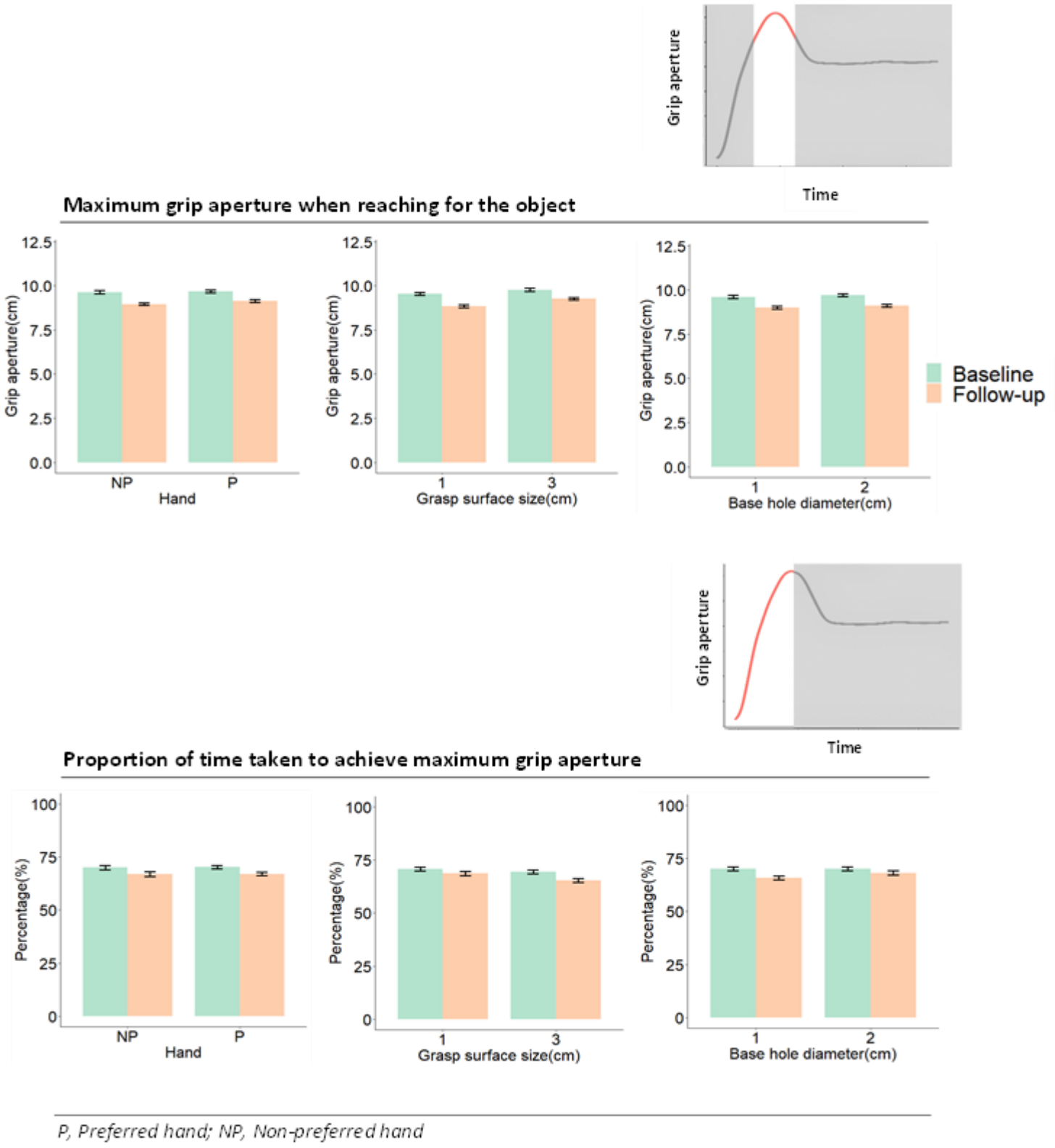
Time taken to reach maximum grip aperture

The proportion of time taken to reach maximum grip aperture was also recorded during the follow-up timepoint. There was a significant main effect of time point, with patients achieving maximum grip aperture sooner during the follow-up timepoint compared to baseline ($F(1,75) = 4.27$; $p<0.05$, $\eta p^2 = 0.05$). There was a significant main effect of grasp surface size ($F(1,401) = 9.35$; $p<0.05$, $\eta p^2 = 0.02$), demonstrated by the patients reaching maximum grip aperture significantly quicker when reaching for objects with a larger grasp surface size compared to a smaller grasp surface size. There was no main effect of hand or base hold diameter. There were no significant interactions.

These results show that patients opened their hands more quickly, but with a smaller maximum grip aperture, when reaching for objects during follow-up compared to baseline. This shows that they spent a longer proportion of time after achieving maximum grip aperture, in adjusting their grip aperture before grasping the object. Maximum grip aperture when reaching for objects with a larger grasp surface size, was larger and reached more quickly, demonstrating the importance of grasping parameters on grip aperture when reaching. The difference in maximum grip aperture and time to reach the maximum grip aperture between baseline and follow-up time points remained significant even when the four patients who had shown progression on the 9HPT by more than a 20% change, were excluded. This demonstrates that BIGKAT detected significant changes at a group level even when the 9HPT hadn't detected any statistically or clinically significant change. These results are illustrated in Figure 4.8.

However, it is difficult to identify the clinical significance in the change in grip aperture between baseline and follow-up. Patients were still able to pick up the objects in the same way, the subtle but significant changes seen here might be a practice effect although it was on average 7 months between baseline and follow-up assessment. The change in grip aperture in pwMS longitudinally has not been studied before, so a longer follow-up period might clarify in the changes seen here are 6 months are sustained at 12 months for example.

Figure 4.8 Maximum grip aperture and time taken to reach maximum grip aperture



P, Preferred hand; NP, Non-preferred hand

4.5 Follow-up results summary

Forty one out of forty two patients completed the follow-up assessment at an average of 6.8 months (SD 0.7) after the baseline assessment. There was no significant difference between the EDSS, 9HPT scores and patient outcome measures between the baseline and follow-up assessment. But 29% of patients demonstrated progression in their EDSS score and 10% of patients showed progression in 9HPT scores.

PwMS demonstrated similar results in the reaction, reach and move times in the follow-up assessment when compared to the baseline assessment, as measured by the EDK. However, patients spent significantly longer slowing down their hand when reaching for objects during the follow-up timepoint compared to baseline. Also, they took longer to place objects during the follow-up time point compared to baseline. Furthermore, patients demonstrated a smaller maximum grip aperture and took longer to achieve this aperture, during the follow-up time point compared to baseline, as measured by BIGKAT. As well as the significant difference between baseline and follow-up in some kinematic parameters detected by BIGKAT, there remained a significant impact of the grasp surface size on time spent in the reach phase, with quicker times recorded with objects with a smaller grasp surface size compared to the larger grasp surface size. PwMS spent significantly longer moving and placing objects with the smaller base-hole diameter compared to objects with the larger base hole diameter. PwMS demonstrated significantly longer times in the reach and move phase when using their non-preferred hand rather than their preferred hand. These follow-up results were similar to the patterns seen during the baseline assessment.

4.6 Discussion of follow-up results

The follow-up of the patient group allowed the kinematic assessment protocol to be repeated to identify any changes in the upper limb function of the pwMS compared to their baseline assessment. The results in this follow-up chapter are novel, as no previous study has used kinematic techniques to assess changes in upper limb function in the progressive MS population.

4.6.1 Determining the length of follow-up to identify progression in progressive MS

Randomised clinical trials of disease modifying treatments have used 'confirmed disability worsening', measured as an increase in EDSS over a three to six month period, as an acceptable clinical measure of disability accrual (Sharmin *et al.*, 2022). A progression event is usually defined by an increase of ≥1.5 EDSS steps from a baseline score of <1.0, an increase of ≥1.0 EDSS steps from a baseline score of between 1.0 – 5.5, or 0.5 steps from a baseline score ≥6.0 (Meca-Lallana, Berenguer-Ruiz, *et al.*, 2021a). The accuracy of progression determination increases with the follow-up period with a sensitivity of 70% at 3 months compared to 89% at 24 months according to one large cohort study (Kalincik *et al.*, 2015). In this study, the authors used different criteria of progression to assess the proportion of progression events that were sustained on follow-up, at 3 or 6 months. The main reason why progression in the EDSS might not be sustained is because the patient might have had a relapse, leading an increase in their EDSS step score, which then resolves back to their baseline score, once the relapse resolves after a few weeks. We used six months as the follow-up interval in the patient group as it has been used in most MS treatment trials, and by the treatment regulator

NHS England, as the most common period of follow-up to assess changes in outcome measures and confirm disability progression (NHS, 2018; Meca-Lallana, Berenguer-Ruiz, *et al.*, 2021b). We also specifically asked all the patients at baseline and follow-up whether they had suffered from symptoms suggestive of a relapse, in order to account for this confounder in the EDSS progression, and none of the patients reported a relapse at baseline or follow-up.

4.6.2 Changes in disability progression measured by the EDSS, 9HPT and patient reported outcome measures

Twelve out of 42 (29%) pwMS in the patient group demonstrated at least a 0.5 point increase in their EDSS over the 6 month follow-up period, which is accepted as the minimal increase in EDSS score to confirm disability progression in pwMS who have a baseline EDSS of 5.5 or more (Healy *et al.*, 2021). This rate of progression is higher than that seen in natural history cohort studies looking at disability progression in SPMS and PPMS cohorts. In a natural history study of 208 people with SPMS, confirmed disability progression occurred in 38% of patients over 24 months (Klinsing, Yalachkov and Foerch, 2022). In PPMS, the progression rate is higher with approximately 64% of patients demonstrating confirmed disability progression at 24 months (Koch *et al.*, 2017). However, the SARS-COV-2 pandemic has had a significant impact on the psychological and physical functioning of pwMS and a cohort study of 225 people with both SPMS and PPMS demonstrated a disability progression rate of 19% over just 4 months of lockdown (Vercellino *et al.*, 2022). In addition, demographic factors like male sex and older age at diagnosis as well as historic relapse activity have been shown to be important

factors in determining progression (Degenhardt *et al.*, 2009). Our cohort of 42 was not powered enough to detect confounding factors on progression rates as measured by the EDSS.

The mean 9HPT scores for both the preferred and non-preferred hands did not show any significant worsening over the 6 month follow-up period. Progression as measured in the placebo arms of large trials in people with progressive MS has shown that the 9HPT scores worsens in about 41% of patients over a course of 36 months (Lublin *et al.*, 2016; Kapoor *et al.*, 2018). This progression is defined by at least a 20% worsening in average 9HPT scores. In our cohort, 4/42 (10%) of patients demonstrated a greater than 20% worsening in their 9HPT times at 6 month follow-up. Therefore, progression as measured by the EDSS showed more events compared to the 9HPT. One reason may be that the new EDSS score was not confirmed at 3 months after the 6 month interval which is agreed as the time point for which disability progression is confirmed if the same score is obtained (Lorscheider *et al.*, 2016). Furthermore, the EDSS also shows the higher rate of improvement in follow-up studies compared to the 9HPT when the increase in the score seen is actually reversed when examined at 3 months following the initial assessment (Koch *et al.*, 2021). This might be explained by the high levels of inter-rater and intra-rater variability seen in administering the EDSS (Cohen *et al.*, 2021).

With regards to PROs there was no significant difference between the mean scores in both the ABILHAND and AMSQ-SF PROs at baseline and follow-up. This suggests that the patients' perceptions of their hand function did not significantly change over the 6 month follow-up period at a group level.

However, some of the patients did have a change in their scores in the ABILHAND and AMSQ-SF enough to change their score on the severity category. Interestingly, a few patients reported an improvement in their upper limb function between baseline and follow-up timepoints. The inherent difficulty with PROs is the suitability of the sample to the measurement by the PROs to prevent ceiling and floor effects. Whilst the ABILHAND and AMSQ-SF have been validated in pwMS, the identification of clinically meaningful change in both these PROs for pwMS has yet to be validated. This arises from difficulties at either end of these scales where a small change in the score, might be more significant than a large change in the score towards the centre of the scale. In addition, statistically significant change might not be clinically meaningful change in PROs and vice versa (Barrett *et al.*, 2013). Keeping this in mind, the wide range in the ABILHAND and AMSQ-SF scores as illustrated in Figure 4.1 demonstrate the range of upper limb dysfunction in the patients both at baseline and follow-up.

4.6.3 Changes in kinematic parameters measured by the EDK and BIGKAT as a measure of disability progression

In the baseline results in Section 3.3.4 – 3.3.6, we have shown that the EDK and BIGKAT parameters are significantly correlated to the established clinical outcome measures like 9HPT and also linked to PROs. Whilst few kinematic studies in the literature have looked at upper limb function in pwMS, there is an even greater dearth of studies following up pwMS with the use of kinematic analysis, with just one study looking at the improvement in upper limb spasticity using kinematic tools after the use of Nabiximols, a cannabinoid mouth spray (Pau *et al.*, 2022a). In the follow-up analysis as described in this

chapter, we were able to assess for any significant changes in the kinematic parameters over time and presented some novel findings.

Wrist deceleration in the reach and move trials was one parameter measured by BIGKAT where a significant difference was noted between baseline and follow-up, with patients taking a significantly longer proportion of the time in the reach phase of the trial slowing down their wrist in follow-up compared to baseline. It has been shown previously that wrist deceleration time increases as the object size available for grasping decreases which we have shown in the baseline results, but what we have demonstrated here is that wrist deceleration seems to change more significantly than other parameters over a relatively short follow-up (Marteniuk *et al.*, 1990).

The time taken to place objects was also significant longer in the follow-up timepoint compared to baseline, although there was no significant difference between timepoints in the time taken to pick-up objects. Once again, the objects with a smaller grasp surface size and base hole diameter took longer to pick-up and place respectively. As in the baseline results, these findings are supported by previous studies looking at the grasping impairment in pwMS which show altered grip force and variability of the pincer grip in this population (Iyengar *et al.*, 2009; Jo *et al.*, 2014).

BIGKAT also detected a significant change in maximum grip aperture between baseline and follow-up timepoints, with patients opening their hands quicker and achieving a smaller maximum grip aperture at follow-up compared to baseline. This is seen in studies of healthy adults as well which show that the grip surface available for grasping affects maximum grip aperture (Verheij, Brenner and Smeets, 2014). Our finding that pwMS demonstrate similar grip

aperture profiles to healthy controls is novel and has not been quantified previously in upper limb studies.

Importantly, when the four patients who had shown progression on the 9HPT at follow-up compared to baseline, suggested by an increase of more than 20% in their follow-up 9HPT times, were excluded from the analysis, the change in BIIGKAT parameters remained significant. The remaining patients still demonstrated a significant change in their wrist deceleration time, maximum grip aperture and time to reach maximum grip aperture at follow-up compared to baseline. This shows that the significant changes seen between baseline and follow-up in the kinematic parameters were not driven by just these 4 patients. It also highlights the ability of BIGKAT to detect subtle but significant changes at follow-up at a group level, which were not picked up by the time parameters of the 9HPT scores. The 29% who progressed in the EDSS scores from baseline to follow-up, had progressed due to deterioration in their ambulation. As previously described in Table 2, an EDSS score of more than 5.5 is measured primarily by ambulation score. Therefore, in our cohort the progression determined by the EDSS would have had no bearing on any progression in upper limb function.

We saw similar results with time parameters as measured by BIGKAT between baseline and follow-up timepoints, where the object manipulation times are able to be selected and accounted for, thus providing a more specific time on when the patient's hand is actually moving, as we had set a velocity threshold of 5cm/s as described previously in the methods chapter.

Hand preference was also a significant factor in wrist velocities measured by BIGKAT with patients demonstrating slower wrist velocities when moving the

objects with their non-preferred hand compared to their preferred hand. Interestingly, in the baseline results the hand asymmetry was seen more evidently in the reach phase compared to the move phase in the patient group. This could be because the worsening in hand function in the reach phase whilst not statistically significant may have been sufficient to eliminate any main effects on hand asymmetry when measured during the follow-up assessment.

The time parameters of the reaction, reach and move times, measured by the EDK didn't show any significant differences in the patients over the 6 months follow-up period, but demonstrated that object grasp surface size and base hole diameter affect grasping parameters similar to the pattern seen at baseline. The significance of hand asymmetry was again highlighted with patients performing the reach and grasp trials much quicker with their preferred hand in our study. This level of asymmetry in upper limb function was also seen at the baseline timepoint and has been seen with more traditional outcome measures like the 9HPT (Solaro *et al.*, 2020).

In summary, the EDK and BIGKAT were reliable in finding similar patterns seen in the patient group at baseline and follow-up assessment as well. However, BIGKAT was also able to detect significant changes in specific kinematic parameters over a period of 6 months, namely detecting a longer wrist deceleration time when reaching, longer object placement time, smaller maximum grip aperture and a quicker time to achieve this grip aperture. This suggests BIGKAT might be more sensitive at detecting changes earlier in aspects of reach and grasp compared to the EDK.

Only one other study has looked at follow-up kinematic assessment of upper limb spasticity in a cohort of pwMS, after treatment with Nabiximols. In this study, Pau el al. assessed the hand to mouth movements of 13 pwMS after 4 weeks of treatment with Nabiximol and found significant improvement in hand to mouth times as measured by kinematic techniques (Pau *et al.*, 2022a). However, unlike our study, the authors of this study did not factor in hand asymmetry.

4.6.4 The clinical utility and feasibility of the EDK and BIGKAT

Kinematic assessment tools have usually been employed in a lab based setting when researching upper limb function in pwMS as well as other neurological disorders (Schwarz, Christoph M Kanzler, *et al.*, 2019; Villepinte *et al.*, 2021). Some kinematic studies of pwMS especially measuring gait, have more recently been employed in the clinical or home setting (Coghe *et al.*, 2019; Montalban *et al.*, 2021; Pau *et al.*, 2021). In people with progressive MS, their limited ambulation prevents them from attending the lab based environment regularly which usually means additional visits to the hospital or location where the assessment takes place. Therefore, this means that any kinematic measures need to be able to be tested in a clinical space if they are to be of clinical use. With this in mind, we have identified the need to develop a relatively portable kinematic system to measure upper limb function. Whilst BIGKAT had already been used in the lab, its size and portability as illustrated in the Methods chapter (Figure 2.3), allowed it to be moved and set up in clinical rooms. One limitation was the 3D camera software that needed the cameras to be calibrated ideally once the equipment was moved to a new location or room. The EDK on the other hand, as illustrated in the Methods

chapter Figure 2.4, was designed specifically as an easily portable piece of equipment that could record its own parameters independently of BIGKAT. This portability of both BIGKAT and the EDK allowed the administration of the kinematic assessments throughout the SARS-COV-2 pandemic in a vulnerable patient population, as adjustments could be made to transport the equipment so that patients could attend the local hospital for ease of access, rather than a lab-based environment.

As we have shown in the baseline results, many of the kinematic parameters recorded by BIGKAT are significantly correlated with the time parameters as recorded by the EDK. Whilst BIGKAT allows the detailed analysis of the trajectory of the hand in 3D space with the use of the infra-red markers, the EDK provides a relatively limited measure of reaction, reach and move times. However, we were able to demonstrate significant effects of object parameters on the EDK measures and going forward the EDK itself might be suitable as a sole measure of the upper limb function. Whilst we have shown wrist velocities are significantly affected in pwMS, these measures mirror the performance on the EDK. In our follow-up analysis, BIGKAT has demonstrated a greater sensitivity than the EDK in detecting changes in kinematic parameters in pwMS over a relatively short time interval of six months. This highlights its advantage as a possible outcome measure in short term treatment or rehabilitation interventions to detect early change.

The clinical utility of kinematic measures is in providing granular data on discrete upper limb movements that would otherwise not be detected and may be implicated in other aspect of functioning in pwMS. As shown in the recent study of Pau el al., time parameters of hand to mouth movements can be

shown with kinematic measures to demonstrate a significant change after a clinical intervention. In our study, we demonstrated that the reaction time as measured by the EDK was significantly increased in the patient group compared to healthy controls in the baseline results. In a study by Reicker et al.,(2007) a computerised test of information processing demonstrated significantly longer reaction times in pwMS who demonstrated subtle cognitive deficits compared to healthy controls (Reicker *et al.*, 2007). In our study, the patient group demonstrated longer reaction times despite not reporting any cognitive dysfunction at inclusion, although we did not screen for cognitive deficits with a validated cognitive tool like the Symbol Digit Modalities test (Strober *et al.*, 2019). These time parameters like the reaction, reach and move times are all lost when administering traditional upper limb outcome measures like the 9HPT without the scope for adjusting the 9HPT to incorporate these measurements.

The clinical utility of the EDK is also inherent in its ability to be adjusted for different object parameters and reaching distances based on the size of the board. It also has the ability for possible assessment of both hands in bimanual tasks, which as we have shown in the baseline and follow-up timepoints, is a significant factor in upper limb function.

One of the limitations of kinematic analysis is in the software and hardware requirements demonstrated in studies utilising these protocols. In our study, we specifically used relatively easily assembled hardware with minimal computing requirements as explained the Methods chapter. The use of open source software like R and Python to develop our kinematic assessment protocol allows for convenient sharing and reproducibility of the assessment

protocol and results analysis which can be automated offline to produce near instantaneous clinically meaningful parameters.

In summary, we have shown in this study that the portability of BIGKAT and to a greater extent the EDK itself has allowed the administration of this novel kinematic assessment in pwMS and healthy controls in a clinical based setting and has the potential to be expanded and used in other clinical and research settings to track progression, as well as response to interventions.

4.7 Discussion of follow-up results summary

The analysis of the follow-up results in this chapter has demonstrated a statistically significant change between baseline and follow-up timepoints in specific kinematic parameters including object placement time, wrist deceleration time, maximum grip aperture and time to reach the maximum grip aperture. The EDK and BIGKAT kinematic measures demonstrate consistent intra-group differences at follow-up with grasp surface size and base hole diameter having an important effect of the time to pick-up, move and place objects. The follow-up results in this chapter have also reproduced the baseline timepoint findings regarding the importance of hand preference in pwMS when performing reach and grasp tasks.

The portability of the EDK and BIGKAT equipment lends itself to the clinical feasibility of this kinematic assessment, as it allows the administration of the reach and grasp trials in a clinical setting or in an environment more accessible to the participant. The EDK itself has demonstrated significant correlation with most of the BIGKAT parameters and is able to extract important time

parameters like reaction, reach and move times, independently of BIGKAT, further increasing its clinical feasibility.

The ability of BIGKAT and EDK to reproduce this assessment at a relatively short follow-up interval as shown in this chapter allows for the deployment of these assessment protocols in further studies focusing on progression or intervention in pwMS.

Chapter 5 Conclusions

5.1 Study summary and contribution to current literature

The aim of this thesis was to characterise upper limb function in people with multiple sclerosis (pwMS). We have developed a kinematic assessment protocol that includes BIGKAT, a tool to assess movement in 3D space, and combined it with a custom built event detection kit (EDK). We have deployed this kinematic assessment protocol in a sample of healthy controls and in a sample of people with progressive MS. We have followed-up the pwMS in our study over a six month time period to collect longitudinal data on upper limb function. This study has delivered a number of findings, which add to the current literature of upper limb function in pwMS and others which are novel results not previously reported in pwMS.

In people with progressive MS, including both PPMS and SPMS, we have shown that upper limb function is not well-captured with existing clinical outcome measures such as the EDSS (Chapter 3, Figure 3.2). The 9HPT on the other hand, shows some correlation with patient reported outcome measures of upper limb function (PROs) in pwMS in our study, as reported in the literature (Lamers *et al.*, 2014).

The reaction time as measured by the event detection kit (EDK) demonstrated a significant difference between the patient and control group at baseline, despite no self-report of cognitive impairment in our patient sample. This finding has been seen in one previous study, which proposed the use of reaction time as a surrogate marker for cognitive processing speed and thus as an identifier of subtle cognitive impairment in pwMS (Reicker *et al.*, 2007).

In this study Reicker et al. tested the time taken for pwMS to respond to stimuli on a computer screen in a set of tasks testing choice and semantic fluency, and found that pwMS took significantly longer in these tasks compared to healthy controls.

BIGKAT demonstrated that pwMS have lower wrist velocities when reaching for and moving objects on the EDK, compared to healthy controls at baseline. Wrist velocities in pwMS was also affected by the object parameters namely the grasp surface size and base hole diameter. Whilst it is known that wrist velocities can be affected by object characteristics when grasping, even in healthy adults, we have shown for the first time the significant reduction in wrist velocities seen in pwMS when reaching and grasping (Grosskopf and Kuhtz-Buschbeck, 2006).

We have shown that object grasp surface size and base hole diameter significantly affected the amount of time pwMS took to pick-up and place the objects respectively. Object pick-up and placement times were significantly longer in pwMS than healthy controls at baseline. Whilst previous studies have investigated the grasping action of pwMS and demonstrated the pathological variability of grip forces in this population, we have shown for the first time that the grasp surface size of objects significantly affected object pick-up times, even more so than would be expected in healthy controls (Krishnan, De Freitas and Jaric, 2008a; Reilmann *et al.*, 2013).

Grip aperture in healthy adults has been shown to vary based on object characteristics, like object size (Mon-Williams and Tresilian, 2001). We have demonstrated for the first time that pwMS did not show a significant difference

in their maximum grip aperture profiles when reaching for objects compared to healthy controls at baseline. This is in contrast to other neurological conditions like PD, where maximum grip aperture when reaching is significantly reduced compared to healthy controls (Rand *et al.*, 2006).

We have demonstrated that pwMS perform significantly worse with their non-preferred hand compared to their preferred hand when reaching for and grasping objects, and movements with the former were also affected by the grasp surface size of the objects. PwMS took significantly longer in the reach and move phases of the non-preferred hand trials and this difference was more pronounced than the inter-hand difference seen in the control group at baseline. This asymmetry in hand function in pwMS has been demonstrated in studies looking at the upper limb function in people with advanced MS (Bonzano *et al.*, 2013; Solaro *et al.*, 2019b).

We have also shown that the EDK and BIGKAT kinematic parameters correlated strongly with the 9HPT times at baseline, although the information on upper limb performance provided by the kinematic parameters goes beyond the simple time scores recorded by the 9HPT. We have also shown that the severity as measured by the AMSQ-SF PRO in particular had a main effect on select kinematic parameters at baseline, like the time taken to move and place objects.

In our follow-up time point, we were able to use BIGKAT to detect significant differences in some of the measured kinematics parameters in pwMS, namely, longer wrist deceleration time when reaching, longer object placement time, smaller maximum grip aperture and a quicker time to achieve this grip

aperture. Whilst the EDK didn't detect any significant differences between the two timepoints on a group level, the sensitivity of BIGKAT in detecting changes at follow-up compared to baseline highlights its potential role as a marker of early deterioration in upper limb function. The portability of BIGKAT and more so the EDK offers a role for the use of kinematics in the clinical space and not just as part of research trials. The reach and grasp trials test a highly conserved fundamental aspect of upper limb function and we have shown that the kinematic analysis of these movements provide clinically correlated but more nuanced aspects of upper limb function that are not detected with conventional clinical outcome measures. This longitudinal measurement of upper limb function using kinematics has only been illustrated in one other study before focusing on upper limb spasticity in pwMS (Pau *et al.*, 2022b).

This ability to measure parameters of upper limb function over time will have an important role in clinical trials and interventional studies of progressive MS where the study participants are usually limited with their mobility and rely on hand function to maintain their activities of daily living (Lamers and Feys, 2014; Close *et al.*, 2020)

5.2 Research limitations

Over the course of conducting this study and analysing the results, there have been a number of limitations that have become apparent and they are addressed here in the context of how they might have impacted on the results and suggestions for how they might be resolved in future research.

5.2.1 Study participants

When recruiting to the study, we aimed to recruit age and sex matched controls to complete the kinematic assessment protocol alongside our patient group. Despite having a similar proportion of male to female participants in the patient and control group, our control group was significantly older than the patient group. We recruited most of our control group from a healthy aging research cohort at the University of Leeds. Volunteers registered their details to be kept informed of research studies looking for healthy participants. Most of the members of this group took part in studies focusing on older adults. As recruitment for this study took place during the first and second peaks of the SARS-CoV-2 pandemic, despite getting ethical approval from the Health Research Authority (HRA) to recruit healthy volunteers, we had difficulty in identifying willing volunteers. The kinematic assessment protocol involved attending a clinical space for the study visit and it is likely that people were hesitant about attending hospital sites due to risk of exposure to the virus. In order to minimise the risk of exposure to the virus for the study participants, the trust protocols on personal protective equipment, including facemasks, gloves and aprons were followed by the researcher. Furthermore, the clinical space allowed safe distancing of the participants when they attended for the study visits and appointments were spread out to give time for wiping down the clinic room and equipment between study participants.

Despite the lack of age matching, we were able to show that our control group performed within the accepted norms for healthy controls of their age group in the clinical measures like the 9HPT. Furthermore, despite being significantly older we were able to show a significant difference in the majority of kinematic

parameters between the patient and control group (the latter performing better than the former), highlighting the severity of upper limb dysfunction in our patient sample. In a control cohort that was age matched to our patient cohort, the controls would have been younger, likely producing a more profound difference in the kinematic assessment performance between the patients and controls than we have seen.

5.2.2 Lack of cognitive battery to assess unreported cognitive dysfunction

During the analysis of the baseline results, as described chapter 3, we identified significant differences between our patient and control groups in kinematics parameters (e.g. reaction time) which have been linked to cognitive processing speed in pwMS (Reicker *et al.*, 2007). This suggested that some of our patient group might have sub-clinical cognitive dysfunction that we had not accounted for at baseline. As part of our recruitment, one of our exclusion criteria was the lack of any reported cognitive impairment as we were aware that moderate to severe cognitive impairment affects upper limb function in pwMS (Yozbatiran *et al.*, 2006). However, once we realised the significant difference in reaction times between the control and patient group, mild or sub-clinical cognitive dysfunction might have been a confounder in our patient group. As outlined in Chapter 1, studies looking at the neural correlates of grasping have identified distinct dorsal and ventral streams for processing visual information, with the ventral temporal and occipital cortex essential to semantic object identification and dorsal occipital and parietal cortex critical for physical interaction with objects (Turella and Lingnau, 2014). Whether cognitive impairment in pwMS disrupts the interconnectivity of these streams

is not yet studied. Whilst we may infer that the increased reaction time in the kinematic assessment in the MS group was a marker of cognitive impairment, the use of an established cognitive screening test, concurrently would help established the extent of these impairments, as kinematic techniques have not been used before to identify cognitive impairment in pwMS. A change to the protocol to include a cognitive screening tool might have detected a clinically meaningful level of cognitive dysfunction but this would have resulted in an ethical review of the protocol as we would have to accommodate the clinical follow-up and management of the patients in whom we detected any cognitive impairment during the course of the study.

On the other hand, the simplistic aspect of the reach and grasp trials compared to other current clinical measures of upper limb function like the action research arm test (ARAT), likely meant that any impact from mild cognitive impairment will have been limited. Future studies of this nature will need to factor in a cognitive screening tool like the symbol digit modalities test (SDMT) to identify any mild cognitive impairment in participants.

5.2.3 Follow-up time interval might not have allowed for progression to be adequately captured.

We identified some significant changes in the kinematic parameters in our patient group between the baseline and follow-up timepoints. The follow-up time interval of 6 months, might be a reason why we did not see further changes in kinematic parameters or a significant change in the clinical measures on a group level. A natural history study of PPMS has shown that patients take an average of 1 year to progress from an EDSS of 5.0 to 6.0 but

an average of 5 years to progress from an EDSS of 6.0 to 7.0 (Harding *et al.*, 2015). In SPMS, the presence of relapses and the uncertainty in identifying the exact time of transition from RRMS to SPMS, makes it difficult to establish the natural history of this subtype of MS (Cree *et al.*, 2021). Another large cohort study in pwMS found that disability outcomes based on 3 to 6 month confirmed disability progression using the EDSS overestimate the accumulation of permanent disability by up to 30% (Kalincik *et al.*, 2015). However, less work has been done on how pwMS develop upper limb disability overtime and most research relies on cross-sectional data of upper limb function (Solaro *et al.*, 2019a). Therefore, whilst BIGKAT has shown the potential to detect changes at a group level even at 6 months, another follow-up timepoint at 12 months and/or 24 months, will likely provide additional information on how upper limb function changes over time.

5.2.4 Lack of the control group for the follow-up timepoint

We were able to compare the patient group to healthy controls for the baseline time point. However, we did not follow-up the control group at 6 months. The main reason, was that the 6 month follow-up of the control group was due around the same time as the SARS-CoV-2 cases were rising again in the local community. As a result, a number of the healthy volunteers were reluctant to re-attend for follow-up and those that were willing to attend, wanted to wait until they had received their SARS-CoV-2 booster vaccination which would have delayed the follow-up by a few months after the 6 month time point. Given the relatively short timepoint for follow-up of 6 months, we presumed that there would not have been a significant change in the control group over six months, as they had performed within population mean scores for their age at baseline

on outcomes measures like the 9HPT. There was no reason to assume that they would have had a change in their kinematic parameters, but without the follow-up data, this is an assumption. However, the patient group demonstrated similar intra-group patterns on the kinematic assessment during follow-up, suggesting that the kinematic assessment protocol delivers reliable data on re-testing. The statistical analysis in Chapter 4 for the follow-up data was adjusted accordingly, to allow valid conclusions to be drawn without a control group.

5.3 Future research directions

The results from this study provide novel insights into upper limb function in pwMS as described in the earlier section 5.1. The kinematic assessment protocol developed during this study can be employed in future research studies to obtain further new insights into many aspects of upper limb function in pwMS.

5.3.1 The impact of cognitive impairment and vision on upper limb function in pwMS

We have shown in the baseline results in chapter 3, that the patient group, had a significantly longer reaction time to the start of the reach and grasp trials and this was captured by the EDK. Cognitive processing speed as previously mentioned earlier in this chapter is a factor in reaction time in pwMS (Reicker *et al.*, 2007). By removing the exclusion criteria of cognitive impairment, a sample of pwMS who have reported cognitive impairment could be recruited. Patients with asymptomatic cognitive impairment could also be recruited if a suitable screening test like the SDMT detected cognitive dysfunction. Once on

study, these participants would have their cognitive performance quantified by the SDMT which has been shown to be a valid measure of cognitive impairment, specifically attention, in pwMS (Benedict *et al.*, 2017; Strober *et al.*, 2019). Additional cognitive tests could be administered in addition to the SDMT to provide a comprehensive overview of cognitive function in this patient group, for example, the Paced Auditory Serial Addition Test, which is a measure of processing speed (Meca-Lallana, Gascón-Giménez, *et al.*, 2021). The performance of these pwMS with cognitive impairment on the kinematic assessment protocol could then be compared to pwMS who do not report cognitive impairment and a sample of healthy controls. This cross-sectional study would be able to evaluate how cognitive impairment impacts on upper limb function in pwMS.

In the same way, pwMS who have visual impairment can be assessed to identify the impact of vision on upper limb function. Binocular vision has long been known to be an important factor in prehensile task in healthy adults (Servos, Goodale and Jakobson, 1992; Gnanaseelan, Gonzalez and Niechwiej-Szwedo, 2014). A kinematic study, measuring movement time and hand velocities in people with visual impairment has shown that impaired vision can impact on task times and accuracy (Timmis and Pardhan, 2012). Optic neuritis, inflammation of the optic nerve, is the presenting feature of MS in approximately 15 - 20% of patients and occurs in about 50% of pwMS at some time during the course of their illness, although good visual recovery is seen in 90% of pwMS (Frohman *et al.*, 2005; Brodsky *et al.*, 2008). The significant prevalence of visual impairment in pwMS, due to optic neuritis, makes it another factor that can potentially impact on upper limb function. The

kinematic assessment protocol we have developed can be adapted to be delivered in pwMS who report visual impairment or have previously had optic neuritis, in order to evaluate how impaired vision can impact on prehensile tasks in this population.

5.3.2 Evaluating the performance of bimanual tasks in pwMS

The kinematic assessment protocol used in this study, allowed an assessment of unimanual tasks in the study participants. However, a significant number of upper limb tasks in daily life require the co-ordinated involvement of both hands. The kinematics of goal oriented bimanual tasks have been well studied, both in health and in neurological conditions like stroke (Kazennikov, Perrig and Wiesendanger, 2002; Gulde *et al.*, 2019; Kim and Kang, 2020). However, there is little evidence in the literature about the impact of MS on bimanual activities as quantified by kinematics, with a couple of studies that have looked at this focusing of grip forces and hand position in bimanual tasks (Gorniak *et al.*, 2014; Ballardini *et al.*, 2019). The baseline and follow-up data in our study confirmed the significant hand asymmetry seen in people with progressive MS and furthermore we were able to quantify the inter-hand differences as the object parameters changed. BIGKAT and EDK can be developed to analyse the movements of both hands in simple preset bimanual tasks in order to evaluate the impact of upper limb dysfunction on bimanual activities in pwMS. One way this can be done is with the use of objects that require bimanual manipulation or transport, e.g. larger objects. Whilst still located on the table-top on an EDK these objects will require the participant to manipulate the objects with both hands each with their own IREDs. This will allow a more in-depth characterisation of any limb asymmetry seen in unimanual tasks and

how this might be affected in bimanual tasks as done in other neurological conditions like stroke (Duff *et al.*, 2022).

5.3.3 The move toward markerless motion capture

In our study we used infra-red markers (IREDs), which were attached to the participants' fingers to allow BIGKAT to track and capture the markers, and therefore the hand, in 3D space. However, attachment of markers and wires to the hands, whilst small, may impact on how participants move their hands, compared to if they didn't have such markers attached. Furthermore, we had to exclude invalid trials predominantly because BIGKAT required the IREDs to be in full view in most of the recorded frames to provide accurate velocity and aperture graphs. Techniques of video capture that do not rely on such IRED markers provide a natural solution to the difficulty we had in motion capture in this study. There has been a lot of work on markerless motion capture in a number of different areas like sport and medicine, some of which are more accurate than others (Martinez *et al.*, 2018; Lahkar *et al.*, 2022; Wade *et al.*, 2022). An example of a recent development in markerless motion capture has been DeepLabCut, which is a markerless position estimation software based on transfer learning with deep neural networks that require some training data (Mathis *et al.*, 2018). Preliminary work done with DeepLabCut in our lab showed that there were some reliability concerns with the accuracy of the markerless motion capture, suggesting this model may need more work before it can be incorporated reliably in the current kinematics assessment protocol that we have developed. However, the deployment of a markerless kinematics assessment protocol can provide a number of opportunities in capturing upper limb function in pwMS without the constraints of physical markers.

5.4 Thesis summary

Upper limb dysfunction is common in pwMS, especially in the progressive subtypes of PPMS and SPMS. Current clinical outcome measures used in pwMS (like the EDSS) focus on ambulation as the score increases. Other measures like the 9HPT have been, to date, the gold standard test of upper limb function in pwMS. However, the 9HPT provides a summative score of a preset task, with no further information on performance during the task, whilst also giving a mean of both hands. This underappreciates the nuance of inter-hand asymmetry in pwMS, which we have demonstrated in this study.

Prehension is the motor behaviour of reaching and grasping which is the fundamental action of most upper limb activities in everyday life. The neural correlates of prehension and the upper limb movements involved have been extensively studied in healthy adults and in some neurological diseases. Analysis of simple reach and grasp tasks is an ideal method of testing upper limb function in a given population. The use of kinematic techniques allows the capture of movement in real time and space and a handful of studies in pwMS have looked at upper limb function using these techniques. These few kinematic studies in pwMS have shown in general that pwMS move their hands slower, with less accuracy and demonstrate weaker grip forces than healthy controls. An important limitation of these studies in pwMS is the lack of an accurate description of the MS subtype and relapses activity of the participants. Furthermore, whilst the equipment in these studies address conserved parameters of prehension like hand to mouth movements and grip forces, the novelty of the EDK and BIGKAT in our study is in its ability to be scaled up to capture more complex tasks involving uni-manual and bimanual

object manipulation (Krishnan, De Freitas and Jaric, 2008b; Coghe *et al.*, 2019).

We have developed a kinematic assessment protocol delivered using BIGKAT and the EDK in a sample of people with progressive MS and healthy controls. We have demonstrated that pwMS demonstrated longer reaction times, reach times and took longer to move objects between pre-defined positions, compared to controls. There was no difference between the maximum grip aperture when reaching between pwMS and controls, but the time to reach maximum grip aperture was quicker for pwMS. PwMS took longer to pick up objects after arriving at them, and spent more time on the placement of objects. PwMS had lower peak wrist velocities when reaching and moving objects. In pwMS, object reach and movement times correlated with their performance on the 9HPT, which was significantly longer than the control group. There was no correlation between upper limb performance on the kinematic assessment kit and EDSS score in pwMS. PwMS who reported severe upper limb dysfunction in the patient reported outcomes demonstrated longer reach and grasp times and smaller peak velocities. PwMS demonstrated significant inter-hand asymmetry in the reach and grasp trials compared to the controls

We collected follow-up data at 6 months in the pwMS in our study and demonstrated a significant change in specific kinematic parameters between baseline and follow-up timepoints, suggesting the utility of BIGKAT in being able to pick-up changes earlier than clinical measures the 9HPT and EDSS at a group level. Once clinically meaningful changes have been quantified and validated in these measures, BIGKAT may well provide utility in picking up

changes at an individual level too. The portability of BIGKAT and the EDK, allowed it to be used in the clinical space and similar patterns in performance of pwMS seen at baseline and follow-up timepoints highlights its reliability as a clinically feasible outcome measure. The kinematic assessment of upper limb function in this study has provided novel insights into the upper limb function of people with progressive MS. Simple modifications to this kinematic assessment protocol can expand its use in the evaluation of upper limb dysfunction in the natural history, treatment or rehabilitation of pwMS.

Appendices

Appendix 1 Patient baseline case report form

Demographic Information		
Subject Initials		
Subject ID		
Age (at baseline) / years		
Gender		
Past Medical History		
Concurrent medication conditions	Current Medication History	
	Allergies:	
Social History		
Employment		
Smoking		
Multiple Sclerosis History		
Date of first symptoms (year)		
Date of MS diagnosis (year)		
Date of progressive MS diagnosis (year)		
Years since MS diagnosis		
MS subtype (PPMS/RRMS)		
Previous MS DMT/s and dates of treatment		
Details of any MS relapses in the previous 3 months:		

EXPANDED DISABILITY STATUS SCALE						
1. VISUAL FUNCTIONS						
	OD (R)	OS (L)			OD (R)	OS (L)
Visual Acuity (corrected)			Scotoma			
Visual fields			Disc pallor*			
			Functional system score^			
2. BRAINSTEM FUNCTIONS						
Extraocular movements impairment			Hearing loss			
Nystagmus			Dysarthria			
Trigeminal damage			Dysphagia			
Facial weakness			Other cranial nerve functions			
			Functional system score			
3. PYRAMIDAL FUNCTIONS						
REFLEXES	R	><	L		R	L
Biceps				Knee flexors		
Triceps				Knee extensors		
Brachioradialis				Plantar flexion		
Knee				Dorsiflexion		
Ankle				Pronation*		
Plantar response				Downward drift*		
Palmomental reflex*				Sinking*		
LIMB STRENGTH		R	L	SPASTICITY		
Deltoids				Arms		
Biceps				Legs		
Triceps				Gait		
Wrist/finger flexors						
Wrist/finger extensors						
Hip flexors				Functional system score		
4. CEREBELLAR FUNCTIONS						
Head tremor				Tandem walking		
Truncal ataxia				Gait ataxia		
		R	L	Romberg test		
Tremor/dysmetria UE				Other, e. g. rebound		
Tremor/dysmetria LE						
Rapid alternating movements UE impairment						
Rapid alternating movements LE impairment						
				Functional system score		
5. SENSORY FUNCTIONS						
SENSORY EXAM		R	L		R	L
Superficial sensation UE				Position sense UE		
Superficial sensation trunk				Position sense LE		
Superficial sensation LE				Lhermitte's sign*		
Vibration sense UE				Paraesthesia UE*		
Vibration sense LE				Paraesthesia trunk*		
				Paraesthesia LE*		
				Functional system score		

EXPANDED DISABILITY STATUS SCALE continued				
6. BOWEL/ BLADDER FUNCTIONS				
Urinary hesitancy/retention		Bowel dysfunction		
Urinary urgency/incontinence		Sexual dysfunction*		
Bladder catheterisation		Functional system score^		
7. CEREBRAL FUNCTIONS				
Depression*		Decrease in mentation		
Euphoria*		Fatigue*		
		Functional system score		
8. AMBULATION				
Walking range as reported				
metres				
In mins				
Distance able to walk without rest or assistance		Requires constant assistance to walk 100m		
≥ 100m but < 200m		Unilateral assistance (in metres)		
≥ 200m but < 300m		Cane/crutch		
≥ 300m but < 500m		Other		
≥ 500m but not unrestricted		Bilateral assistance (in metre)		
Unrestricted		Canes/crutches		
Actual distance (obligatory up to 500 m if possible) metres		Other		
		Assistance by another person (in metres)		
SYNOPSIS OF FS SCORES				
1. VISUAL^		*= Optional		
2. BRAINSTEM		^=converted FS score		
3. PYRAMIDAL				
4. CEREBELLAR				
5. SENSORY				
6. BOWEL /BLADDER^				
7. CEREBRAL				
EDSS STEP				

NINE HOLE PEG TEST		
Dominant Hand (circle)	Left / Right	
Dominant hand trials	Time (seconds)	*Comment if unable to complete trial*
Trial 1		
Trial 2		
Non-dominant hand trials	Time (seconds)	
Trial 1		
Trial 2		

ABILHAND QUESTIONNAIRE					
		Easy	**Difficult**	**Impossible**	**Not sure**
1	Wrapping up gifts				
2	Unwrapping a chocolate bar				
3	Filing one's nails				
4	Spreading butter on a slice of bread				
5	Cutting meat				
6	Buttoning up trousers				
7	Opening a screw-topped jar				
8	Peeling potatoes with a knife				
9	Pulling up the zipper of trousers				
10	Sharpening a pencil				
11	Threading a needle				
12	Fastening a snap (jacket, bag, ...)				
13	Washing one's hands				
14	Tearing open a pack of chips				
15	Buttoning up a shirt				
16	Taking the cap off a bottle				
17	Fastening the zipper of a jacket				
18	Cutting one's nails				
19	Hammering a nail				
20	Opening mail				
21	Peeling onions				
22	Squeezing toothpaste on a toothbrush				
23	Shelling hazel nuts				
	Totals in each column				

ABILHAND SCORE =

AMSQ-SF10 QUESTIONNAIRE							
During the past two weeks, to what extent has MS ...		**Not at all**	**A little**	**Moderately**	**Quite a bit**	**Extremely**	**No longer able to**
1	Limited your ability to tie shoelaces?						
2	Limited your ability to hold a full plate?						
3	Limited your ability to pour from a bottle into a glass?						
4	Limited your ability to cut off a piece of paper with a pair of scissors?						
5	Limited your ability to fasten buttons?						
6	Limited your ability to pick up coins from the table?						
7	Limited your ability to zip up a coat?						
8	Limited your ability to wash your hands?						
9	Limited your ability to cut something with a knife?						
10	Limited your ability to put toothpaste on a toothbrush?						
	Totals in each column						

AMSQ-SF10 SCORE =

Appendix 2 Control baseline case report form

Demographic Information		
Subject Initials		
Subject ID		
Age (at baseline) / years		
Gender		
Past Medical History		
Concurrent medication conditions	Current Medication History	
	Allergies:	
Social History		
Employment		
Smoking		

NINE HOLE PEG TEST		
Dominant Hand (circle)	Left / Right	
Dominant hand trials	Time (seconds)	*Comment if unable to complete trial*
Trial 1		
Trial 2		
Non-dominant hand trials	Time (seconds)	
Trial 1		
Trial 2		

Appendix 3 Patient follow-up case report form

Demographic Information		
Subject Initials		
Subject ID		
Details of any significant medical issues since the last assessment:		
Details of any MS relapses since the last assessment:		

EXPANDED DISABILITY STATUS SCALE						
9. VISUAL FUNCTIONS						
	OD (R)	OS (L)			OD (R)	OS (L)
Visual Acuity (corrected)			Scotoma			
Visual fields			Disc pallor*			
			Functional system score^			
10. BRAINSTEM FUNCTIONS						
Extraocular movements impairment			Hearing loss			
Nystagmus			Dysarthria			
Trigeminal damage			Dysphagia			
Facial weakness			Other cranial nerve functions			
			Functional system score			
11. PYRAMIDAL FUNCTIONS						
REFLEXES	R	><	L		R	L
Biceps				Knee flexors		
Triceps				Knee extensors		
Brachioradialis				Plantar flexion		
Knee				Dorsiflexion		
Ankle				Pronation*		
Plantar response				Downward drift*		
Palmomental reflex*				Sinking*		
LIMB STRENGTH		R	L	SPASTICITY		
Deltoids				Arms		
Biceps				Legs		
Triceps				Gait		
Wrist/finger flexors						
Wrist/finger extensors						
Hip flexors				Functional system score		
12. CEREBELLAR FUNCTIONS						
Head tremor				Tandem walking		
Truncal ataxia				Gait ataxia		
		R	L	Romberg test		
Tremor/dysmetria UE				Other, e. g. rebound		
Tremor/dysmetria LE						
Rapid alternating movements UE impairment						
Rapid alternating movements LE impairment						
				Functional system score		
13. SENSORY FUNCTIONS						
SENSORY EXAM		R	L		R	L
Superficial sensation UE				Position sense UE		
Superficial sensation trunk				Position sense LE		
Superficial sensation LE				Lhermitte's sign*		
Vibration sense UE				Paraesthesia UE*		
Vibration sense LE				Paraesthesia trunk*		
				Paraesthesia LE*		
				Functional system score		

EXPANDED DISABILITY STATUS SCALE continued				
14. BOWEL/ BLADDER FUNCTIONS				
Urinary hesitancy/retention		Bowel dysfunction		
Urinary urgency/incontinence		Sexual dysfunction*		
Bladder catheterisation		Functional system score^		
15. CEREBRAL FUNCTIONS				
Depression*		Decrease in mentation		
Euphoria*		Fatigue*		
		Functional system score		
16. AMBULATION				
Walking range as reported				
metres				
In mins				
Distance able to walk without rest or assistance		Requires constant assistance to walk 100m		
≥ 100m but < 200m		Unilateral assistance (in metres)		
≥ 200m but < 300m		Cane/crutch		
≥ 300m but < 500m		Other		
≥ 500m but not unrestricted		Bilateral assistance (in metre)		
Unrestricted		Canes/crutches		
Actual distance (obligatory up to 500 m if possible) metres		Other		
		Assistance by another person (in metres)		
SYNOPSIS OF FS SCORES				
8. VISUAL^		*= Optional		
9. BRAINSTEM		^=converted FS score		
10. PYRAMIDAL				
11. CEREBELLAR				
12. SENSORY				
13. BOWEL /BLADDER^				
14. CEREBRAL				
EDSS STEP				

NINE HOLE PEG TEST		
Dominant Hand (circle)	Left / Right	
Dominant hand trials	Time (seconds)	*Comment if unable to complete trial*
Trial 1		
Trial 2		
Non-dominant hand trials	Time (seconds)	
Trial 1		
Trial 2		

ABILHAND QUESTIONNAIRE					
		Easy	**Difficult**	**Impossible**	**Not sure**
1	Wrapping up gifts				
2	Unwrapping a chocolate bar				
3	Filing one's nails				
4	Spreading butter on a slice of bread				
5	Cutting meat				
6	Buttoning up trousers				
7	Opening a screw-topped jar				
8	Peeling potatoes with a knife				
9	Pulling up the zipper of trousers				
10	Sharpening a pencil				
11	Threading a needle				
12	Fastening a snap (jacket, bag, ...)				
13	Washing one's hands				
14	Tearing open a pack of chips				
15	Buttoning up a shirt				
16	Taking the cap off a bottle				
17	Fastening the zipper of a jacket				
18	Cutting one's nails				
19	Hammering a nail				
20	Opening mail				
21	Peeling onions				
22	Squeezing toothpaste on a toothbrush				
23	Shelling hazel nuts				
	Totals in each column				

ABILHAND SCORE =

AMSQ-SF10 QUESTIONNAIRE							
During the past two weeks, to what extent has MS ...		**Not at all**	**A little**	**Moderately**	**Quite a bit**	**Extremely**	**No longer able to**
1	Limited your ability to tie shoelaces?						
2	Limited your ability to hold a full plate?						
3	Limited your ability to pour from a bottle into a glass?						
4	Limited your ability to cut off a piece of paper with a pair of scissors?						
5	Limited your ability to fasten buttons?						
6	Limited your ability to pick up coins from the table?						
7	Limited your ability to zip up a coat?						
8	Limited your ability to wash your hands?						
9	Limited your ability to cut something with a knife?						
10	Limited your ability to put toothpaste on a toothbrush?						
	Totals in each column						

AMSQ-SF10 SCORE =

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