THE FEASIBILITY OF KINARM-BASED ASSESSMENT OF NEUROLOGICAL IMPAIRMENT IN PRIMARY BRAIN TUMOUR PATIENTS

by

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Abstract

This thesis investigated the feasibility of using Kinarm-based neurological assessment in primary brain tumour patients, a clinical population with a high incidence of neurological impairment. Current clinical assessment methods are limited by the low resolution and subjective nature of the clinical examination. Moreover, these tools are timeconsuming and prone to floor and ceiling effects due to their narrow scale. Interactive robots such as the Kinarm offer multi-dimensional neurological assessment and utilize quantitative and continuous outcome measures. The Kinarm therefore provides a more robust, objective, and quantifiable approach to assessing a broad range of sensory, motor, and cognitive functions in individuals with primary brain tumours.

Brain tumour patients were recruited from the neurosurgery clinics at Kingston General Hospital and Hotel Dieu. Feasibility was defined as successful study recruitment, high data capture rates, tolerable levels of fatigue, and identification of impairment by Kinarm assessment and correlation with an existing assessment tool (RBANS). Our assessment protocol included a traditional assessment (RBANS), a fatigue inventory (BFI), and a robot-based assessment (Kinarm).

In a cohort of 16 brain tumour participants, we found that Kinarm-based assessment was capable of assessing neurological functioning. The robot identified impairment in at least one neurological domain in the majority of brain tumour participants (81.5%). Using Pearson correlation coefficients, concurrent validity was established between several Kinarm tasks and RBANS domains. Kinarm assessment also demonstrated that brain tumour participants often exhibited multiple deficits across a broad range of cognitive, sensory, and motor tasks, thus revealing a pattern of global neurological impairment. This finding was supported by strong and significant Kinarm inter-task correlations. Fatigue

assessments showed mild levels of fatigue and data capture rates were high suggesting Kinarm-based assessment was tolerable. Participant recruitment rate however was low and resulted in our small sample size.

In conclusion, we provide evidence that the Kinarm may be a feasible neurological assessment tool in brain tumour patients and may be used in future studies investigating neurological impairment in this population and the impact of novel therapeutic interventions.

Co-Authorship

The research present within this thesis was conducted by Jack Lott under the cosupervision of Dr. Stephen Scott and Dr Douglas James Cook

Dr. Stephen Scott and Dr Douglas James Cook provided guidance on all aspects of this thesis including data analysis, data presentation and manuscript preparation.

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List of Abbreviations

ALS Amyotrophic Lateral Sclerosis

APM Arm Position Matching

BOB Ball on Bar

BFI Brief Fatigue Inventory

CNS Central Nervous System

DSM-V Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

EOR Extent of Resection

FDR False Discovery Rate

GBM Glioblastoma

GTR Gross Total Resection

HRQOL Health Related Quality of Life

ICP Intracranial pressure

IDH Isocitrate dehydrogenase

Kinarm Kinesiological Instrument for Normal and Altered Reaching Movements

KST Kinarm Standard Tasks

MGMT O-6-methylguanine-DNA methyltransferase

MMSE Mini-Mental State Examination

MoCA Montreal Cognitive Assessment

MRI Magnetic Resonance Imaging

MS Multiple Sclerosis

OH Object Hit

OHA Object Hit and Avoid
PAL Paired Associates Learning

RBANS Repeatable Battery for the Assessment of Neuropsychological Status

RVGR Reverse Visually Guided Reaching

TMA Trail Making A

TMB Trail Making B

VGR Visually Guided Reaching

WHO World Health Organization

Chapter 1 Introduction

1.1 Prevalence, Classification, and Survival

Primary central nervous system (CNS) neoplasms are a heterogenous group of tumours arising from cells of the CNS (Lapointe et al., 2018). These tumors can arise within structures surrounded by the skull and spinal column, such as the brain, cranial nerves, spinal cord, and meninges. In Canada, there are an estimated 40,000 individuals living with CNS tumours and the average annual age-standardized incidence rate for all primary CNS tumours is 21.05 per 100,000 (Walker et al., 2022). Primary brain tumours account for 85% to 90% of all primary CNS tumours. This group of tumours arise from the brain parenchyma and its surrounding structures and can be classified as either malignant or nonmalignant. Within primary brain tumours, neuroepithelial tissue tumours are amongst the most common, representing 33.6% of all primary brain tumours and 83.2% of malignant tumours (Ostrom et al., 2022). Most notable amongst neuroepithelial tissue tumors are adult-type diffuse gliomas which can be further categorized histologically as astrocytomas, oligodendrogliomas, and glioblastomas (GBM) (Louis et al., 2021). Glioblastoma accounts for the majority of gliomas as well as half of malignant primary brain tumours. The majority of malignant primary brain tumours are located within the frontal, temporal, parietal, and occipital lobes with prevalence of 24.4%, 17.5%, 10.4%, and 2.6% respectively (Ostrom et al., 2022). Tumours of the meninges are the second most common primary brain tumour and the most common non-malignant tumour. The most prevalent histology amongst these tumours is meningioma with the majority of them occurring in the cerebral meninges (Walker et al., 2022).

In addition to histology and cells of origin, tumours can also be classified according to molecular features and biomarkers - the most critical of these being enzyme-related gene mutations and DNA alterations. Isocitrate dehydrogenase (IDH) enzymes contribute to critical metabolic processes that maintain cellular homeostasis (Han et al., 2020). Mutations in the IDH1 and IDH2 genes are believed to be the starting point for the development of many gliomas and determine a specific pathway for cancerous progression (Turkalp et al., 2014). Specifically, these mutations are thought to fundamentally alter enzyme function, leading to the production of 2- hydroxyglutarate, a possible oncometabolite. In GBM, mutations in IDH indicate a more favorable disease prognosis, associated with greater median survival (Cohen et al., 2013). One DNA alteration that can be used to differentiate primary brain tumours is the heterozygosity of chromosome 1 and 19. Gliomas of specific types, such as oligodendroglioma, display notable deletions in chromosome 1's short arm (1p) and chromosome 19's long arm (19q). In general, 1p/19q co-deletion is associated with a positive response to radiation and chemotherapy (Ostrom et al., 2022). Another relevant DNA alteration in primary brain tumours is an elevation in methylation levels within the promoter region of the O-6-methylguanine-DNA methyltransferase (MGMT) gene. Being a DNA repair protein, it is postulated that MGMT enhances the responsiveness to alkylating chemotherapies utilized for glioma treatment, subsequently leading to enhanced survival rates particularly among GBM patients (Ostrom et al., 2022).

Primary brain tumours may also be classified based on an assigned CNS World Health Organization (WHO) grade ranging from 1 (low grade) to 4 (high grade). These grades are applied within tumour types and combine traditional understanding of tumour histology

with more recently discovered molecular markers. The objective of these grades is to convey information regarding tumour behaviour and prognosis. As an example, IDHmutant astrocytoma can be classified from CNS WHO grade 2 to 4 while meningioma extends only from CNS WHO grade 1 to 3 (Louis et al., 2021).

Given the heterogeneity in tumour histology, molecular features, biomarkers, and grade, survival rates amongst primary brain tumour patients are varied. Moreover, survival time following the diagnosis of primary brain tumours is significantly influenced by demographic factors such as age at diagnosis, gender, racial background, and ethnicity (Ostrom et al., 2022). In general, malignant primary brain and other CNS tumours have a lower survival rate with a 1-year survival rate of 49.7% and a 5-year of 23.0% (Walker et al., 2022). For non-malignant primary CNS tumours, these rates increase to a 1-year survival rate of 90.3% and 5-year survival rate of 83.7%. When comparing survival of specific tumour pathologies, median survival is lowest for high grade glioblastoma (8 months) and higher for lower grade oligodendroglioma (199 months) as well as meningioma (>96 months) (Ostrom et al., 2022; Walker et al., 2022).

1.2 Clinical Presentation

The clinical presentation of primary brain tumours can be characterized by focal and generalized signs and symptoms. Focal symptoms are most common in the initial stages of disease and are caused by the destruction or compression of tissue within the specific anatomical location of the tumour (Perkins & Liu, 2016; Butowski, 2015). Clinical focal signs are varied and depend on tumour location. Supratentorial tumors can result in a combination of motor or sensory impairments, visual field deficits, and language

impairments. Infratentorial tumors may cause dysfunction in cranial nerves, autonomic functions, and cerebellar functions (Behin et al., 2003; Lapointe et al., 2018).

Generalized symptoms occur with disease progression due to increased tumour size and infiltration within brain parenchyma (Lapointe et al., 2018). Generalized symptoms may be associated with elevated intracranial pressure (ICP), which can arise from cerebral edema, vasogenic edema, cerebrospinal fluid flow obstruction, or venous flow obstruction. Symptoms that are a result of increased ICP include nausea, headache, vomiting, imbalance, fatigue, and impaired vision (Butowski, 2015). Headaches are especially pertinent as they are the first symptom presented upon diagnosis in 23.5% of primary brain tumour patients and are present in 53% of the population at some point in the disease course (Perkins & Liu, 2016; Alther et al., 2020). Although the experience of headache can vary, commonly reported types include tension-type and migraine (Hadidchi et al., 2019). Seizures are another prevalent generalized symptom and are a major cause of morbidity in brain tumour patients (Lee et al., 2010). The histologic subtype of brain tumour as well as location influences the incidence of seizures at presentation. Approximately 90% of patients with low-grade tumours experience seizures compared to 35% of high grade GBM patients. Moreover, temporal lobe tumours are more than twice as likely to be associated with seizures than tumours in other locations (Butowski, 2015). Fatigue is also a highly prevalent and distressing symptom that occurs in >80% of brain tumour patients (Hofman et al., 2007). It can have both a direct and indirect impact on patients' well-being through its association with depression, anxiety, and sleep disturbances. Fatigue is of particular interest in research settings as it may prevent patients from undergoing extensive assessment or therapeutic intervention.

Upon clinical presentation of focal and generalized symptoms, diagnostic neuroimaging and histopathology are used to confirm the diagnosis of a primary brain tumour (Lapointe et al., 2018). Cranial computed tomography and magnetic resonance imaging (MRI) play a crucial role in the initial diagnosis of brain tumors. Standard T1- and T2-weighted MRIs demonstrate high sensitivity in detecting brain tumors and provide valuable information about tumor size and location, as well as secondary phenomena like mass effect, hemorrhage, edema, and elevated ICP (Jacobs et al., 2005). This information along with tumour location and histology is pertinent when developing the treatment plan.

1.3 Treatment of Brain Tumours

Surgery is the most common treatment for primary brain tumours and is often used in conjunction with radiotherapy and chemotherapy. The current gold standard for surgical resections of primary brain tumours is awake surgery combined with intraoperative direct electrical stimulation and intraoperative neuromonitoring (Kelm et al., 2017). These precise monitoring techniques allow for surgical resection that aims to remove as much of the tumour as possible while sparing healthy eloquent brain tissue. The radicality or extent of resection (EOR) of primary brain tumours is a topic of long-standing controversy in neurosurgery as a lack of Level I evidence has limited certainty in assessing its effect on functional status and survival (Hentschel & Sawaya, 2003; Hardesty & Sanai, 2012). However, recent evidence elucidates the role of EOR in survival amongst primary brain tumour patients. Significant removal of a tumour or Gross Total Resection (GTR) has been associated with increased survival across a wide range of primary brain tumour patients. In the case of high-grade GBM, resection of >98% tumour volume is associated with an increased median survival of 8.8 to 13.4 months in patients while in low-grade tumours

EOR has shown an increase in mean survival from 61.1 to 90 months (Hervey-Jumper & Berger, 2016). Given this association between EOR and patient survival, supramaximal resection is a re-emerging technique in the surgical treatment of primary brain tumours. Supramaximal resection can be accomplished by resecting a large margin surrounding the tumour or performing a formal lobectomy. In cases where the lesions are limited to a single lobe, an anatomical lobectomy is typically performed (Shah et., 2020). Similar to GTR, supramaximal resections may lead to increased median survival for GBM and other primary brain tumours.

While greater tumor resection may lead to improved survival, it is essential to consider the potential risk of functional loss and neurological impairment associated with radical removal (Sanai & Berger, 2009). Approximately 92% of glioma patients present with cognitive or mood impairments, and after surgery, 55% of patients demonstrate cognitive impairments (Hervey-Jumper & Berger, 2016). Given this risk of neurological morbidity, tumour resection must be balanced with the preservation of neurological functioning and in turn, quality of life. Moreover, understanding the functioning of the brain region to be resected is critical to limit potential neurological impairment during and after surgery (Sanai & Berger, 2009).

1.4 Effects of Brain Tumours on Neurological Function

Impairments in neurocognition are observed in up to 90% of primary brain tumour patients (Tucha et al., 2000). These impairments can be caused by the tumour itself through the disruption of both local and distant brain networks which can vary depending on several factors: (1) mass effect caused by the compression and displacement of healthy brain tissue from tumour growth, (2) surrounding edema caused by tumour volume and increase

cerebrospinal fluid resulting in increased ICP and reduced cerebral blood flow, and (3) direct tissue damage in critical brain regions (Parsons & Dietrich, 2021; Esquenazi et al., 2017). Moreover, adjuvant therapies such as chemotherapy and radiotherapy as well as medications often prescribed to primary brain tumour patients (e.g., anti-epileptics, antiinflammatory therapies) may exacerbate neurological impairment caused by the tumour (Morshed et al., 2021).

Neurological function may also be impacted by surgical intervention although resection can both positively and negatively affect patients' functioning. In a cohort of high-grade glioma patients, Taphoorn & Klein showed that at a median follow-up of 5 weeks after surgery, 59% of patients were cognitively impaired in at least one neurological domain but when compared to baseline, 49% showed improvement, while 23 % declined (Taphoorn & Klein, 2004). These results suggest that patients' post-operative outcomes are highly variable and likely depend on the tumour location as well as its potential mass effect and associated edema. Surgery therefore has the potential to both recover as well as further disrupt healthy brain functioning in primary brain tumour patients.

Sensorimotor functioning is one area in which primary brain tumour patients often experience neurological deficits over the disease course. Specifically in high-grade glioma, recent studies indicate that >70% of patients exhibit sensorimotor impairment (Amidei & Kushner, 2015). The greatest determinant of sensorimotor impairment is tumour location and the anatomic location affected. This creates a broad range of possible deficits that vary significantly by patient given the heterogeneity of tumour location within the population. Some of the most common sensorimotor impairments among primary brain tumour patients include ataxia, gait impairment, spasticity, and unilateral or bilateral weakness (Kushner &

Amidei, 2015). The presence of such sensorimotor impairments is significant as these deficits contribute to a decline in functional status amongst primary brain tumour patients which in addition to motor deficits themselves, is a predictor of median survival.

Neurocognitive function is another area in which primary brain tumour patients often experience impairment. Patients may experience deficits across several Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) cognitive domains including executive functioning, perceptual motor, language, learning and memory, and complex attention (American Psychiatric Association, 2013). Which of these domains become impaired varies greatly depending on tumour location and the anatomic regions affected by mass effect and associated edema. The most commonly affected cognitive domains are memory and executive functioning, often attributed to the predominant occurrence of primary brain tumors in adults within the frontal and temporal lobes (Noll et al., 2019). Moreover, patients with tumours of the left hemisphere predominantly present with deficits in language while those of the right hemisphere experience deficits in visual perception (Scheibel et al., 1996). Tumour histology, malignancy and grade may also influence the extent of cognitive impairment. Specifically, patients with low grade gliomas most frequently exhibit impairment on measures of learning and memory, attention, and executive function (Racine et al., 2015; Noll et al., 2015). While patients with high grade gliomas also show significant rates of impairment in these domains, they commonly experience additional cognitive deficits in language and processing speed. Regardless of tumour grade, neurocognitive impairment is often progressive as tumour infiltration increases and exacerbates the disruption of brain regions and networks (Chandana et al., 2008).

1.5 Effect of Brain Tumours on Health-Related Quality of Life

Brain tumour patients experience a significant decrease in health-related quality of life (HRQOL) and functional status when compared to age-, sex-, and education-matched controls (Aaronson et al., 2011). This decrease in HRQOL can be attributed to local and generalized symptoms such as headaches, seizures, and fatigue, sensorimotor dysfunction, and cognitive impairment all of which greatly impact patients' participation in daily living, ability to work, and social interaction. Importantly, HRQOL can change with disease diagnosis and progression. When compared to baseline, both low- and high-grade glioma patients show an apparent correlation between tumour progression and deterioration of HRQOL (Sagberg et al., 2016). Moreover, HRQOL has also been shown to fluctuate with surgical intervention having the potential for both positive and negative changes depending on whether resection leads to symptom relief or exacerbation. In GBM patients, Jakola et al., reported that deterioration in HRQOL occurs in about half of the patients postoperatively (Jakola et al., 2011a). Perhaps most importantly, HRQOL has been shown to be an independent predictor of survival in primary brain tumour patients giving it great prognostic value (Quinten et al., 2009). This considered, clinicians should evaluate treatments intended to prolong survival and weigh them with the potentially negative consequences of neurological impairment, decreased HQOL, and in turn, patient wellbeing (Jakola et al., 2011b).

1.6 Current Clinical Assessment Methods and their Limitations

The assessment of neurological deficits and impairments caused by brain tumours provides clinicians with important information regarding patient prognosis, HRQOL, and overall brain function. However, in this population, there is a lack of consensus on the most appropriate assessment tool to employ. This is due to the delicate balance between

specificity, sensitivity, and brevity that must be considered in order to feasibly attain valid and meaningful information (Dwan et al., 2015).

Brief cognitive screening tools are designed to be easily tolerated, time efficient, have the potential to be delivered in an acute setting, and provide a global evaluation of cognitive function. These factors are important when considering the potential demand on patients' stamina, clinicians' limited availability, and the cost of detailed assessments in research. A widely administered brief cognitive assessment tool is the Mini-Mental State Examination (MMSE) (Cockrell & Folstein, 1988). Originally designed to detect gross cognitive impairment, the assessment takes 5-10 minutes to complete and includes scales of orientation, registration, recall, attention and calculation, naming, comprehension, language, and visual construction. Although the MMSE is practical and convenient for assessing cognitive functioning in brain tumor patients, it is not recognized as a validated tool; it has shown to be insensitive to subtle clinical and focal impairments in the population (Wefel et al., 2016). Moreover, the MMSE is limited in scope as it evaluates only attention functioning and neglects to assess other domains frequently affected by brain tumours such as executive function, processing speed, and working memory (Carlson et al., 2022). Another brief cognitive screening tool often used in primary brain cancer patients is the Montreal Cognitive Assessment (MoCA). Similar to the MMSE, the tool is a 10-minute test aimed at assessing patients' cognitive functioning using numeric scales across 8 domains: attention, memory, executive function, visuoconstruction, language, conceptual thinking, and orientation (Nasreddine et al., 2005). In the field of primary brain tumours, the MoCA is generally favored over the MMSE for its greater sensitivity in detecting cognitive impairment (Robinson et al., 2015). Olson et al., found that while 80% of patients

were categorized as impaired by the MoCA, only 30% were deemed cognitively impaired by the MMSE (Olson et al., 2008). However, despite its superiority over the MMSE, there remains concern regarding the sensitivity of the MOCA when compared to complete neuropsychological assessment (Robinson et al., 2015). Brief cognitive screening tools as a collective are prone to floor and ceiling effects due to their narrow scale and are limited by low resolution.

The alternative to brief cognitive screening tools is formal neuropsychological evaluation which offers more sensitive and specific assessment of cognitive function in primary brain tumour patients (Carlson et al., 2022). These exams are carried out by a neuropsychologist and include a comprehensive battery of assessments that can be tailored to assess specific cognitive domains depending on the tumour location and presenting symptoms. When compared to brief assessment tools, Robinson et al., found that in a sample of primary brain tumour patients, only 30.4% were identified as cognitively impaired by the MoCA while neuropsychological examination found 69.6% of patients were impaired on at least one domain specific cognitive test and, of these, 75% were impaired in at least two cognitive domains (Robinson et al., 2015). Despite their increased sensitivity, neuropsychological evaluations pose their own challenges. The exams are lengthy ranging from 2-8 hours making it difficult for brain tumour patients to complete and are restricted to psychologist use and administration. This combined means that these evaluations are often inaccessible to patients and are not feasible for use in clinical practice and large clinical trials (Olson et al., 2008).

As a compromise between brief cognitive assessment tools and extensive

neuropsychological examinations, shorter batteries (20-30 minutes) have been developed to assess cognitive functioning (Dwan et al., 2015). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a standardized cognitive screening battery used to identify cognitive impairment in a broad range of clinical populations. The battery consists of 12 subtests that assess 5 DSM-V cognitive domains: immediate memory, visuospatial constructional, language, attention, and delayed memory (Randolph et al., 1998). The test produces 5 corresponding index scores as well as a total scale score allowing for a clinically valuable assessment of abilities across cognitive domains and the production of a global measure of cognitive functioning. The feasibility and validity of the RBANS to assess cognitive functioning in brain tumour patients has recently been investigated. In a cohort of 82 low-grade and high-grade glioma patients, Loughan et al., found the RBANS consistently identified significant impairments across all domain indices compared to the standardization reference group (Loughan et al.,2019). However, similar to brief cognitive assessment tools, the RBANS is prone to floor and ceiling effects given the abbreviated format of its subtests making it potentially unable to detect subtle clinical impairments in cognitive functioning (Lageman et al., 2010).

A common weakness among brief cognitive screening tools, neuropsychological assessment, and abbreviated batteries such as the RBANS is that they are relatively one dimensional. While they extensively assess neurocognitive function across many cognitive domains, they lack methods to assess motor and sensory function. This is significant as neurological impairment in primary brain tumour patients is multidimensional and spans across cognitive, motor, and sensory domains. A more robust assessment method would be one that maintains an assessment of cognitive function but adds tests that assess

sensorimotor function. This in turn would provide a more comprehensive understanding of neurological functioning in brain tumour patients.

1.7 Computer-Based and Robotic-Based Assessment

To promote the systematic assessment of neurocognitive functioning in primary brain tumour patients, computer-based cognitive assessments have been developed. These tools are designed to be more accessible, easy to administer and score, and overall, more efficient than traditional testing methods. One of such tools is NeuroCogFX, a computerbased battery which has been employed in brain cancer populations (Hoffermann et al., 2017). NeuroCogFX is comprised of 6 subtests which are performed in a standard order: digit span, 2-back test, reaction time, verbal memory, figural memory, and word fluency. These subtests aim to assess 5 important cognitive domains: psychomotor speed, attention/executive functions and visual working memory, verbal memory and word fluency, verbal short-term memory, and figural memory (Fliessbach et al., 2010). Performance is standardized to a group of 242 healthy controls to evaluate impairment/function. In retrospective studies of NeuroCogFX in brain tumour patients, the tool showed highly significant and strong correlations with established cognitive tests thus validating its use in this population. However, while NeuroCogFX may be more accessible and efficient than traditional testing methods, it still suffers from similar weaknesses; most notably, floor and ceiling effects as well as inadequate assessment of executive functioning. Similar tools to NeuroCogFX have more recently been developed in app-based formats. These too have shown feasibility and validity amongst primary brain tumour patients but have failed to overcome the same weaknesses (Butenschoen et al., 2022). This is largely

because they consist of simply computerized or digital formats of existing cognitive batteries/tests rather than novel methods of assessment that may be more robust.

The limited application of robotic technologies in primary brain tumours patients has been concentrated on physical rehabilitation and gait training. Compared with conventional physiotherapy robot-based rehabilitation allows for a greater number of treatment cycles, reduces burden on physical therapists and clinicians, and may ultimately lead to a more significant improvement in patient function (Jung et al., 2018). In a recent case series of primary brain tumour patients, Jung et al., investigated the use of an endeffector type robot used for lower-limb rehabilitation. Their results validated the robot as an effective tool in rehabilitating gait disturbances in brain tumour patients, and when compared to traditional physical therapy, showed and more significant improvement in gait speed, mobility, and functional ambulation (Jung et al., 2018). Although not related to assessment, this application of robotic technology demonstrates the potential for the application of robotics in brain tumour patients.

1.8 Kinarm-Based Assessment

Robotic technology has yet to be applied to the assessment of neurological functioning in primary brain tumours but has the potential to perform assessment with a high level of validity compared to current clinical standards. In contrast to current methods and tools, robotic technology uses continuous, real-time, high-resolution, and quantitative information on cognitive, sensory, and motor functioning (Scott & Dukelow, 2011). This allows for standardized comparisons among patients, minimized floor and ceiling effects, and overall, a more robust and objective approach to assessing neurological functioning.

One specific robotic system in this field is the Kinesiological Instrument for Normal and Altered Reaching Movements (Kinarm) (Scott, 1999). The Kinarm End-Point (EP) device positions the participant seated and offers two handles to grasp. The device allows unrestricted movement in the horizontal plane and is equipped with integrated virtual reality systems that provide visual feedback of the hand and spatial objects. Kinarm platforms comprise a set of behavioral tasks known as Kinarm Standard Tests™ (KSTs), designed to measure various domains of function, including motor, sensory, and cognitive. During task performance, the robotic system captures real-time information that describes the spatial and temporal parameters of the participant's performance. A standardized measure of performance (task score), corrected for age, sex, and handedness, is generated for each task based on performance in a large cohort of healthy individuals. (Scott et al., 2022; for full details, see Kinarm Standard Tests™ Summary). The Kinarm has been previously validated in several clinical populations including, but not limited to stroke, concussion, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) (Dukelow et al., 2010; Whitten et al., 2018; Simmatis et al., 2020a; Simmatis et al., 2019). Given its successful applications across a broad range of neurological conditions, the Kinarm has strong potential to be applied as a neurological assessment tool in brain tumour patients.

1.9 Purpose of Thesis

The purpose of this thesis is to investigate the feasibility and application of Kinarmbased assessment in primary brain tumour patients, a novel clinical population to which the robot has yet to be applied. Compared to traditional assessment tools, the Kinarm offers multi-dimensional neurological assessment and utilizes quantitative and continuous outcome measures. These factors allow the Kinarm to offer a more robust, objective, and

quantifiable approach to assessing a broad range of sensory, motor, and cognitive functions and which may ultimately improve our understanding of the precise nature and degree of neurological impairment caused by brain tumours.

A more comprehensive understanding of neurological functioning and impairment in this clinical population would offer several important opportunities as well as future directions. 1) It would allow clinicians to better predict neurological impairment in patients caused by the tumour itself and by therapeutic interventions such as surgical resection. This would inform a discussion with the patient on the implications of such interventions on neurological functioning. 2) Quantifying neurological impairments in specific cognitive, sensory, and motor domains would facilitate personalized and targeted rehabilitation to help maintain a patient's HRQOL and functional status. 3) Longitudinal monitoring could assess changes in neurological functioning and inform on tumour progression. 4) The validation of a robotic assessment device such as the Kinarm in this patient population would establish it as an assessment tool in clinical trials that investigate the neurological outcomes of different neuro-oncology treatments and therapies. The aim of this thesis is to examine the feasibility of Kinarm-based assessment in primary brain tumour patients. The specific objectives are a) to investigate the ability of Kinarm-based assessment to identify neurological impairments in our cohort primary brain tumour patients, b) to compare the results from the RBANS cognitive assessment to the results obtained using the Kinarm, and c) to investigate fatigue and the tolerability of Kinarm-based assessment in this clinical population.

Chapter 2 Methods

2.1 Study Characteristics

2.1.1 Study Design, Location, Participants, and Data Acquisition

This feasibility study was performed at an academic teaching hospital. Adult primary brain tumour patients were recruited from the neurosurgery clinic at Kingston General Hospital and Hotel Dieu. Inclusion criteria were: (1) diagnosis of primary brain tumour abstracted from clinical reports, (2) the ability to understand clinical and robotic assessment instructions, and (3) ≥18 years of age. Information regarding the number of eligible patients approached, the number of patients who consented participate, and the number of patients who completed the assessment in its entirety was recorded. Patients were asked to provide informed consent as well as information on demographics, handedness, and highest education level prior to assessment. Tumour pathology, location, and characteristics were abstracted from clinic reports. The study was approved by Queen's University and Affiliated Hospitals Health Sciences Research Ethics Board.

2.1.2 Definition of Feasibility

Feasibility will be defined by several parameters: (1) successful patient enrollment (defined as a recruitment rate >2 patient/month), (2) high Kinarm data capture rates (>90%), (3) Brief Fatigue Inventory (BFI) Scores that do not suggest problematic fatigue, and (4) identification of neurological impairment via Kinarm assessment and correlation with an existing clinical tool (RBANS).

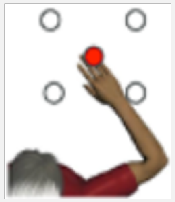
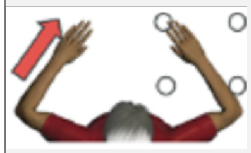
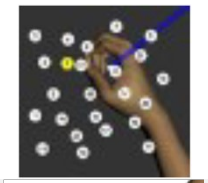
2.2 Kinarm-Based Assessment

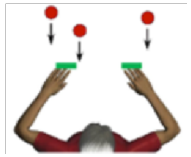
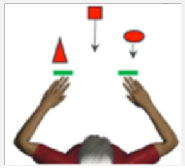
Patients completed robotic assessment on the Kinarm EP robot. The Kinarm EP device positions the participant seated and offers two handles to grasp. Figure 2.1

demonstrates how the device allows unrestricted movement in the horizontal plane and is equipped with integrated virtual reality systems that provide visual feedback of the hand and spatial objects. Kinarm Standard Tests™ were used to quantify sensory, motor, and cognitive functions associated with the upper limbs. The 9 standard tests employed in this study assessed different neurocognitive domains including perceptual-motor, complex attention, executive function, learning, and memory. A list of the 9 tasks and brief descriptions of each are provided in in Table 2.1 and summarized in Figure 2.2.

Figure 2.1: Depiction of Kinarm End-Point robotic device setup used in the study
Adapted from Kinarm.com.

Table 2.1: Summary of Kinarm tasks, task descriptions, related DSM-V domains, and brain region assessed

Task	Demonstration	Task Components/Task Description	Related DSM-V Domain	Brain Region Assessed
Visually Guided Reaching (VGR)		Subject starts at initial central target and then moves quickly and accurately to a peripheral target that appear. Measures visuomotor capabilities and multi-joint coordination (Coderre et al., 2010).	Perceptual-Motor	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
Reverse Visually Guided Reaching (RVGR)		Subject starts at initial central target and then reaches to peripheral targets that appear. Movement of the white circle representing hand position is mirror reversed relative to the central target. Assesses attention, inhibitory control, and cognitive control of visuomotor skills (Tippett & Sergio, 2006).	Perceptual-Motor, Complex Attention, Executive Function	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
Arm Position Matching (APM)		Robot moves one of the subject's arms to a given position, and the subject is instructed to move their other arm to a mirror-matched position. Measures a subject's proprioceptive capabilities (Dukelow et al., 2010).	Perceptual-Motor	Frontal Lobe, Cerebellum, Parietal Lobe
Trail Making A & B (TMA & TMB)		Subject must trace through sequence of targets numbered 1 to 25 as quickly as possible (Trail A). Subject must trace through an alternating alpha-numeric sequence of targets (Trail B). Assesses task switching (Bowie & Harvey, 2006; Corrigan & Hinkeldey, 1987).	Complex Attention, Executive Function	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
Ball on Bar (BoB)		Virtual bar is presented in between the subject's hands and a virtual ball is placed on the bar. Subject must move the ball on the bar into presented targets as quickly and accurately as possible. Assesses bimanual coordination and visuomotor skills (Lowrey et al., 2014).	Perceptual-Motor	Frontal Lobe, Occipital Lobe, Cerebellum, Basal Ganglia

Object Hit (OH)		Virtual paddles appear at the subject's fingertips. Subject is instructed to use these paddles to hit and push away balls that fall from the top of the screen. Speed and frequency of balls dropped increases as task progresses. Assesses visuomotor skills and spatial skills (Tyryshkin et al., 2014).	Perceptual-Motor, Complex Attention	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
Object Hit & Avoid (OHA)		At start, subject is shown 2 target shapes which the subject is instructed to memorize as the only shapes to hit during the task; they are instructed to avoid all other shapes or distractors. Speed and frequency of objects dropped increases as task progresses Assesses spatial attention, rapid motor selection and inhibition control (Bourke et al., 2016).	Perceptual-Motor, Complex Attention, Executive Function	Frontal Lobe, Occipital Lobe, Parietal Lobe, Cerebellum, Basal Ganglia
Paired Associate Learning (PAL)		Images are shown in spatial locations and then hidden. Upon presentation of an image, subject must indicate the spatial location of the hidden image. Assesses memory.	Learning and Memory	Frontal Lobe, Occipital Lobe, Temporal Lobe, Parietal Lobe, Cerebellum, Basal Ganglia

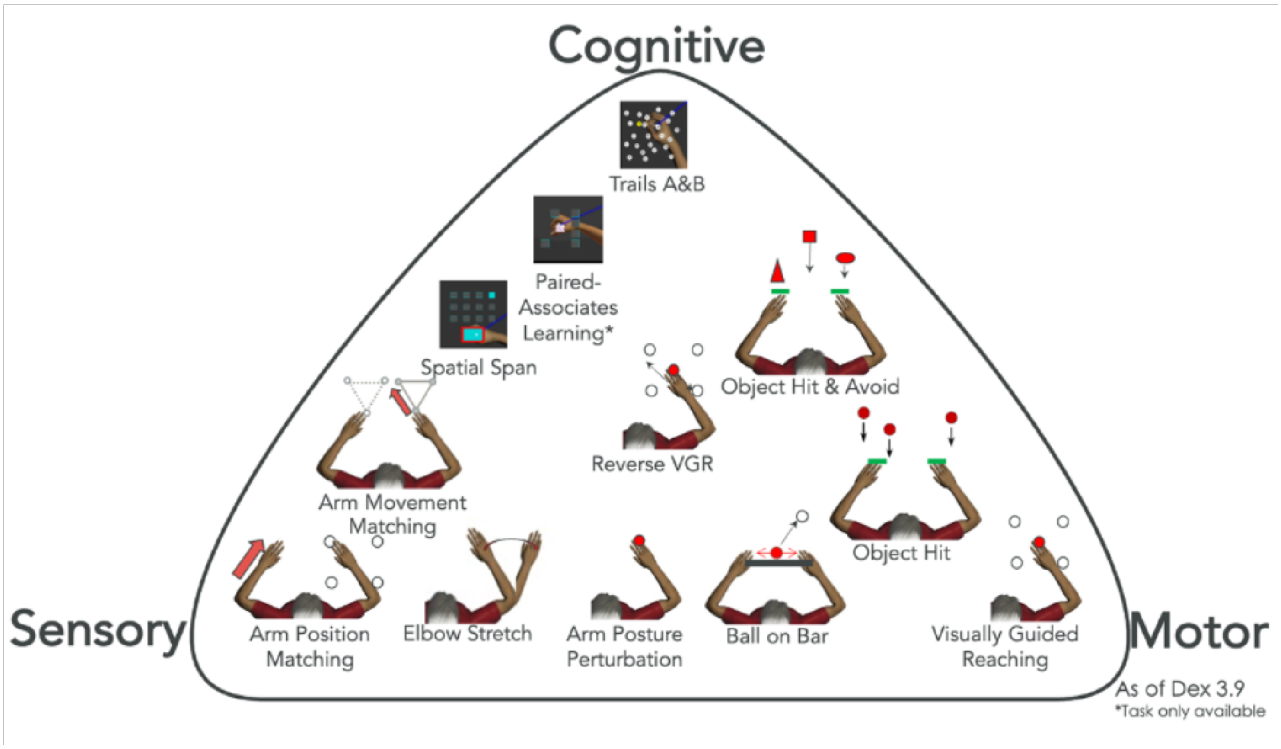


Figure 2.2 Summary of Kinarm Standard Tasks by cognitive, sensory, and motor domains

For each task, a unique set of parameters quantify a participant's performance. Examples of these parameters include reaction time, initial direction angle, return time, and visual reaction. To provide comparable measures of performance, raw parameter values are converted to Z-scores. All Kinarm Standard Tasks have a consistent methodology for developing the normal models used to calculate parameter Z-scores based on a large cohort of healthy control participants and considering age, sex, and handedness effects (Scott et al., 2022; for full details, see Kinarm Standard Tests™ Summary). Parameter Z-scores are then aggregated using the root-mean square and normalized using Box-Cox equations to produce Z-Task Scores. These standardized values can then be used to calculate a task score which provides a global measure of a subject's performance for a given standard task. Task scores are always positive; a score of 0 denotes best performance and increasing

values represent poorer performance. Task scores <1.96 (representing the 95th percentile) are considered within the typical normal range while those >1.96 are outside of the typical normal range and are thus considered impaired. A participant's level of impairment on a given task can be visualized in Kinarm standard task reports which display summaries of performance as well as task score.

2.3 RBANS Assessment

The RBANS has been shown to have utility as an assessment tool in primary brain tumour patients and therefore acted as the standard clinical assessment tool to which Kinarm assessment was compared. The RBANS generates an index score for each of the 5 domains assessed, as well as a total scale score. Normative information based on performance in healthy adults is used to calculate index and total scale scores which are also corrected by age. Table 2.2 provides a list of the RBANS domains, the tasks involved in each domain, and corresponding the DSM-V related neurocognitive domains. For index scores, RBANS traditionally employs a normative range of 85-115 (1 SD) with scores <85 indicating significant impairment. This categorizes 16% of the population as impaired. We have set a more stringent threshold, defining impairment as performance outside of the 95th percentile, reflected in index scores greater than or equal to 75(1.65 SD). This allows for direct comparison between Kinarm and RBANS and ensures a higher degree of certainty that scores represent true impairment.

Table 2.2: Summary of RBANS domain, task descriptions, corresponding DSM-V domain, and brain region assessed

Task/Domain	Task Components/Task Description	Related DSM-V Neurocognitive Domain	Brain Region Assessed
Immediate Memory	List Learning: List of 10 unrelated words is read aloud. Subject is asked to recall words immediately after. This is repeated 4 times with the same word list. Story Memory: A 12 item story is read to the subject. They are asked to recall as many details from the story as possible. This is repeated 2 times with the same story.	Learning and Memory	Temporal Lobe
Visuospatial	Figure Copy: Subject is provided with a complex figure to copy. Line Orientation: Subject is asked to identify the angles of 2 intersecting lines based on reference figure provided.	Perceptual-Motor, Complex Attention	Parietal-Occipital Lobe
Language	Picture Naming: Subject is shown 10 pictures and asked to name each. Semantic Fluency: Subject is given 60 seconds to name as many items related to the prompt as possible	Language	Frontal Lobe, Temporal Lobe (Dominant Hemisphere)
Attention	Digit Span: Subject is asked to repeat sequences of numbers. Sequences increase with correct response (up to 9). Symbol Coding: Subjects are given a list of symbols and asked to match them to their corresponding number according to a legend provided.	Complex Attention	Frontal Lobe, Temporal Lobe (Dominant Hemisphere)

Delayed Memory	List Recall: Subject is asked to recall as many of the words from the 10 word list previously provided. List Recognition: Subject is asked to identify which words were previously provided in the form of Yes or No response. Story Recall: Subject is asked to recall as many details from the previously provided story as possible. Figure Recall: Subject is asked to draw/recall as much of the complex figure previously copied.	Learning and Memory	Temporal Lobe
Total Scale Score	Summary of index scores. Representative of global performance on the RBANS	Learning and Memory, Perceptual-Motor, Complex Attention, Language	Whole Brain

2.4 Brief Fatigue Inventory

The BFI is used to assess fatigue severity and its impact on a patient's life (Mendoza et al., 1999). This tool was employed in the study as brain tumour patients are known to suffer from excessive fatigue which may limit their ability to complete long evaluations. The BFI consists of 9 items, each measured on a scale of 0-10 (0 being minimum/no fatigue, 10 being maximum fatigue). The reported fatigue measurements for the 9 items are then averaged to create a mean/total BFI score for each patient. Mild impairment is defined as a total score ranging from 1-3, moderate 4-6, and severe fatigue is defined by a total score of 1-7 (Mendoza et al., 1999).

2.5 Statistical Analysis Plan

All analyses and figures were conducted in Matlab R2023a. First, the distributions of impairment across the Kinarm tasks and across the RBANS domains were identified and summarized. Kinarm tasks assessing both hands individually were divided into contralesional and ipsilesional assessments as per the location of the tumour. Next, a more detailed view of impairments in each assessment was presented by participant. Cumulative distribution curves were then constructed for Kinarm task to demonstrate population performance across tasks. To assess the relationships between the RBANS, the Kinarm and the BFI, Pearson correlations were conducted using a confidence level of 95%, corresponding to a p-value of 0.05. All p- values from these correlations were corrected for multiple comparisons using the False Discovery Rate (FDR) correction.

Chapter 3 Results

3.1 Feasibility

The study consort diagram is shown in Figure 3.1. In total, 26 patients were approached to take part in the study between June 2021 and May 2023. Twenty of these patients consented to participate in the study and underwent the assessment protocol. Of the 20 participants, 16 were included in data analysis and four were excluded. One participant was excluded for brain infection, and 3 were excluded for diagnoses of arteriovenous malformation rather than brain tumour. Thus, our final sample size was 16 brain tumour participants, at an enrolment rate of 0.7 participants/month. This was lower than our target of 2 participants/month.

Feasibility was also defined by high data capture which relied on high assessment completion and task tolerability. The full assessment took approximately 90 minutes to complete, with the RBANS taking 30 minutes to complete and the Kinarm taking 60 minutes to complete. In our sample of 16, 13 participants had complete data sets, while 3 participants had partial data sets. Within these 3 participants, only 1 was missing RBANS assessment as they were assessed using a different protocol. Kinarm data capture rates averaged 94.8% and ranged from 81.3% to 100% depending on the task. Reasons for incomplete Kinarm assessment included, task not yet been added to protocol, participant with limited time due to hospital transport services, and participant unwilling to finish assessment.

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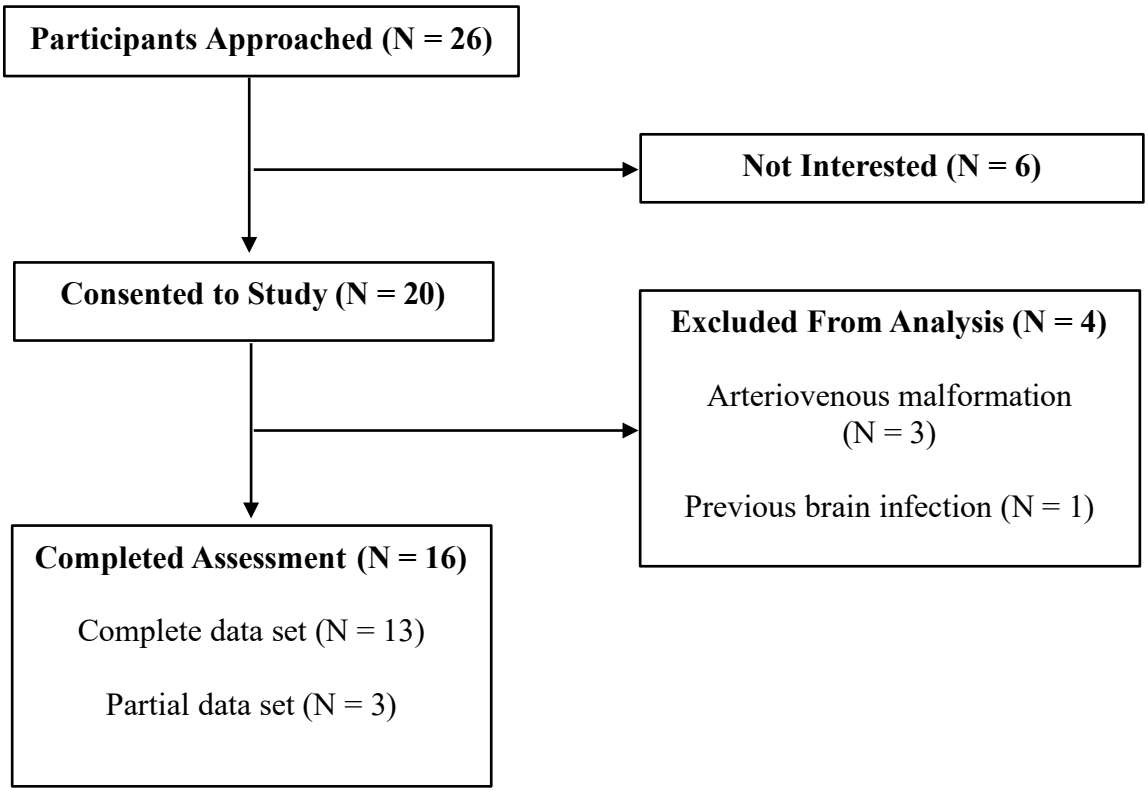

Figure 3.1: Consort diagram for brain tumour patient recruitment

3.2 Demographics and Clinical Characteristics

Participant demographics are displayed in Table 3.1 and summarized in Table 3.2. The majority of participants were male (81.3%), right-handed (81.3%), and listed College as their highest level of education. The median age of participants was 53 and ranged from 30 to 81. In regard to tumour characteristics, there was significant heterogeneity in participants' diagnoses. Tumour location was defined by laterality and lobe with 37.5% of participants exhibiting a tumour on the left side of the brain and 62.5% of participants exhibiting a tumour on the right side. Tumours were most commonly found in the frontal lobe. Tumour histology ranged from meningioma to glioblastoma, including astrocytoma, and oligodendroglioma with grades ranging from low-grade or Grade 2 up to high-grade or Grade 4.

Table 3.1: Participant demographics including age, sex, handedness, and clinical diagnosis

PARTICIPANT (P)	AGE	SEX	HANDEDNESS	DIAGNOSIS
P1	60	F	R	Right Temporal glioma (Low Grade)
P2	64	M	L	Left Parietal glioblastoma (Grade 4)
P4	48	M	R	Right frontal astrocytoma (Grade 2)
P5	40	M	L	Left insula and temporal astrocytoma (Grade 2)
P8	43	M	R	Left frontal oligodendroglioma (Grade 2)
P9	74	M	R	Right occipital glioblastoma (Grade 4)
P10	30	M	R	Left frontal glioma (Low Grade)
P11	53	M	R	Right temporal parietal glioblastoma (Grade 4)
P12	41	M	R	Left frontal oligodendroglioma (Grade 2)
P13	80	F	R	Right frontal meningioma
P17	78	M	R	Left temporal glioblastoma (Grade 4)
P18	81	M	R	Left frontal glioma (High Grade)
P19	49	M	R	Right angular gyrus glioblastoma (Grade 4)
P20	70	M	L	Left parietal oligodendroglioma (Grade 2)
P21	44	M	R	Left frontal oligodendroglioma (Grade 2)
P24	53	F	R	Left parahippocampal glioma (Low Grade)

Table 3.2: Summary of participant demographics and diagnoses

Age, years (median, range) Sex (N, %)	53 (30 – 81)
Male	13 (81.3%)
Female	3 (18.7%)
Handedness (N, %)	
Right	13 (81.3%)
Left	3 (18.7%)
Highest Level of Education (N, %)	
Grade 10	1 (6.3%)
Grade 12	3 (18.8%)
Trade School	1 (6.3%)
College	9 (56.3%)
University	1 (6.3%)
Professional School	1 (6.3%)
Diagnosis	
Left (N, %)	10 (62.5%)
Right (N, %)	6 (37.5%)
Meningioma (N, %)	1 (6.3%)
Astrocytoma (N, %)	2 (12.5%)
Oligodendroglioma (N, %)	4 (25%)
Other Glioma (N, %)	4 (25%)
Glioblastoma	5 (31.3%)
Grade 2 (N, %)	6 (37.5)
Low Grade (N, %)	3 (18.8%)
Grade 4 (N, %)	5 (31.3%)
High Grade (N, %)	1 (6.3%)
Unknown (N, %)	1 (6.3%)

3.3 Kinarm Assessment

Kinarm assessment was performed in all 16 participants to evaluate cognitive, sensory, and motor functioning. Kinarm standard task reports were generated for each participant to summarize performance and calculate task score. Figure 3.2 displays

examples of task reports from Participant 2 (P2) for VGR (A), RVGR (B), and OH (C). As displayed by the bolded task scores, this participant exhibited impairment in 3 out of 4 of the example tasks. Comparing a task in which they exhibited impairment (RVGR) with one they did not exhibit impairment (VGR), we can see noticeable differences in the hand tracings recorded when reaching for peripheral targets. Potential impairment can also be observed in P2 on the OH task. With the coloured cells indicating a successfully hit target and white cells representing a missed target, P2 showed more missed targets when reaching to hit objects with their right arm (red) and opposed to their left arm (blue).

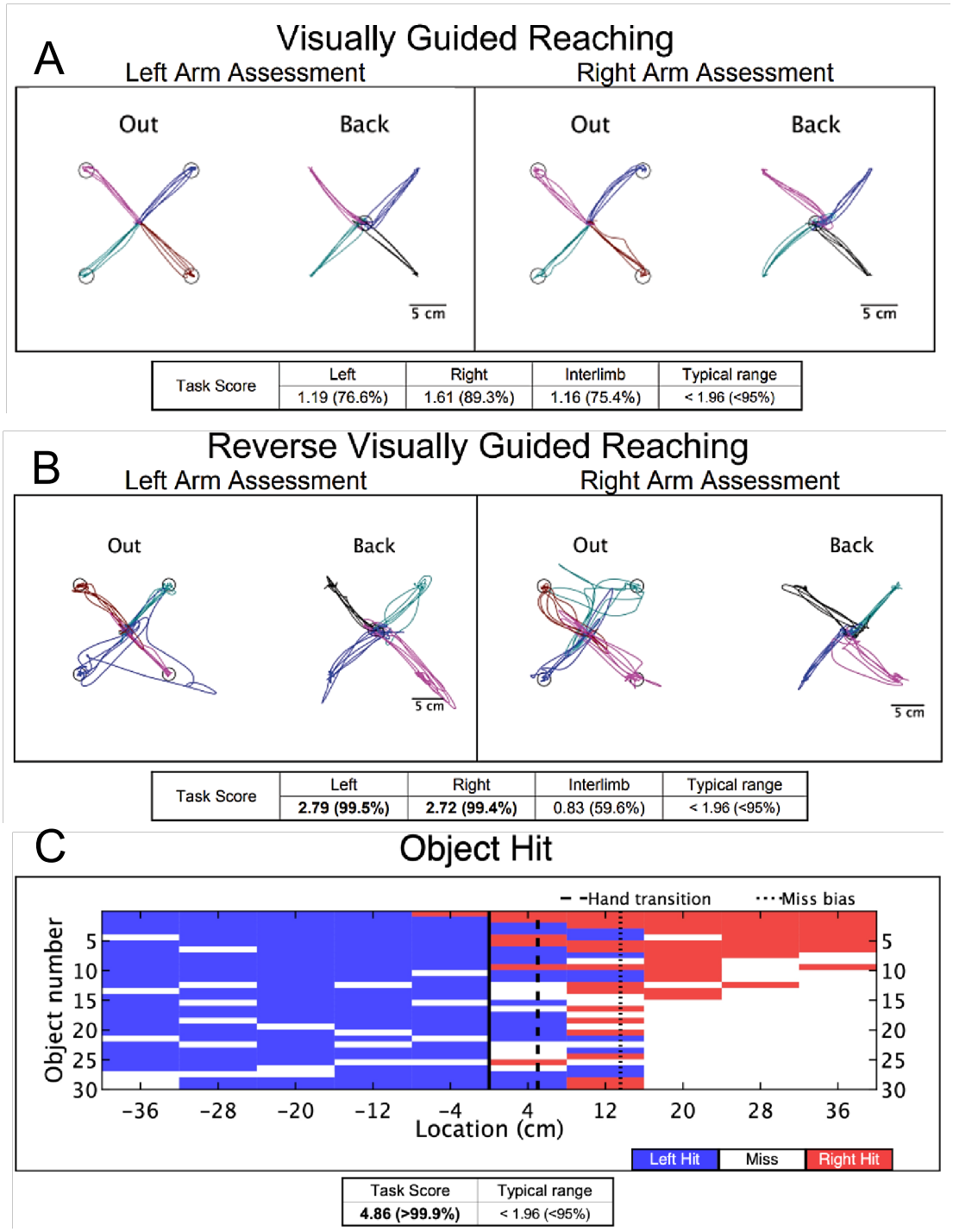

Figure 3.2: Example task reports summarizing performance of P2 on 3 tasks.

A. Task report for VGR. Hand trajectories depict reaching to peripheral targets. Unimpaired task score is provided below. **B** Task report for RVGR. Hand trajectories depict reaching to peripheral targets. Impaired task score is provided below. **C.** Task report for OH. Workspace is divided into left (blue) and right (red). Coloured cells

indicated hits complete. White cells indicate objects missed. Impaired task score is provided below.

Figures 3.3 and 3.4 display Kinarm performance for the 16 brain tumour participants. Figure 3.3 shows task scores as a scatterplot, separating participants' scores by Kinarm task (BoB, OH, OHA, APM, VGR, RVGR, TMA, TMB, PAL). Three tasks assessed both hands independently (VGR, RVGR, and APM) and were stratified by hand being assessed in respect to lesion laterality - contralesional (C) versus ipsilesional (I). Of the 16 patients included, several did not complete the entire suite of robotic tasks leaving some tasks with 13 (BoB), 14 (OH, OHA), and 15 (APM, PAL) complete participant datasets. Two thresholds of impairment are displayed. The red line placed at a score of 1.96 defines impairment as performance outside of the 95th percentile, defining 5% of the population as impaired while the blue line placed at a score of 1.41 classifies ~16% of the population as impaired and therefore reflects the threshold traditionally employed with RBANS. We included this to demonstrate the impact of a less stringent threshold on impairment detection. As seen in Figure 3.3, all Kinarm tasks identified impairment in at least 1 participant, with RVGR, TMA, OH, and OHA tasks showing impairment in the greatest number of participants. When comparing the stringency of the two thresholds, only ipsilesional VGR showed no difference in the frequency of impairment detection. A complete summary of Kinarm impairments by task as well as a comparison between thresholds can be seen in Table 3.3.

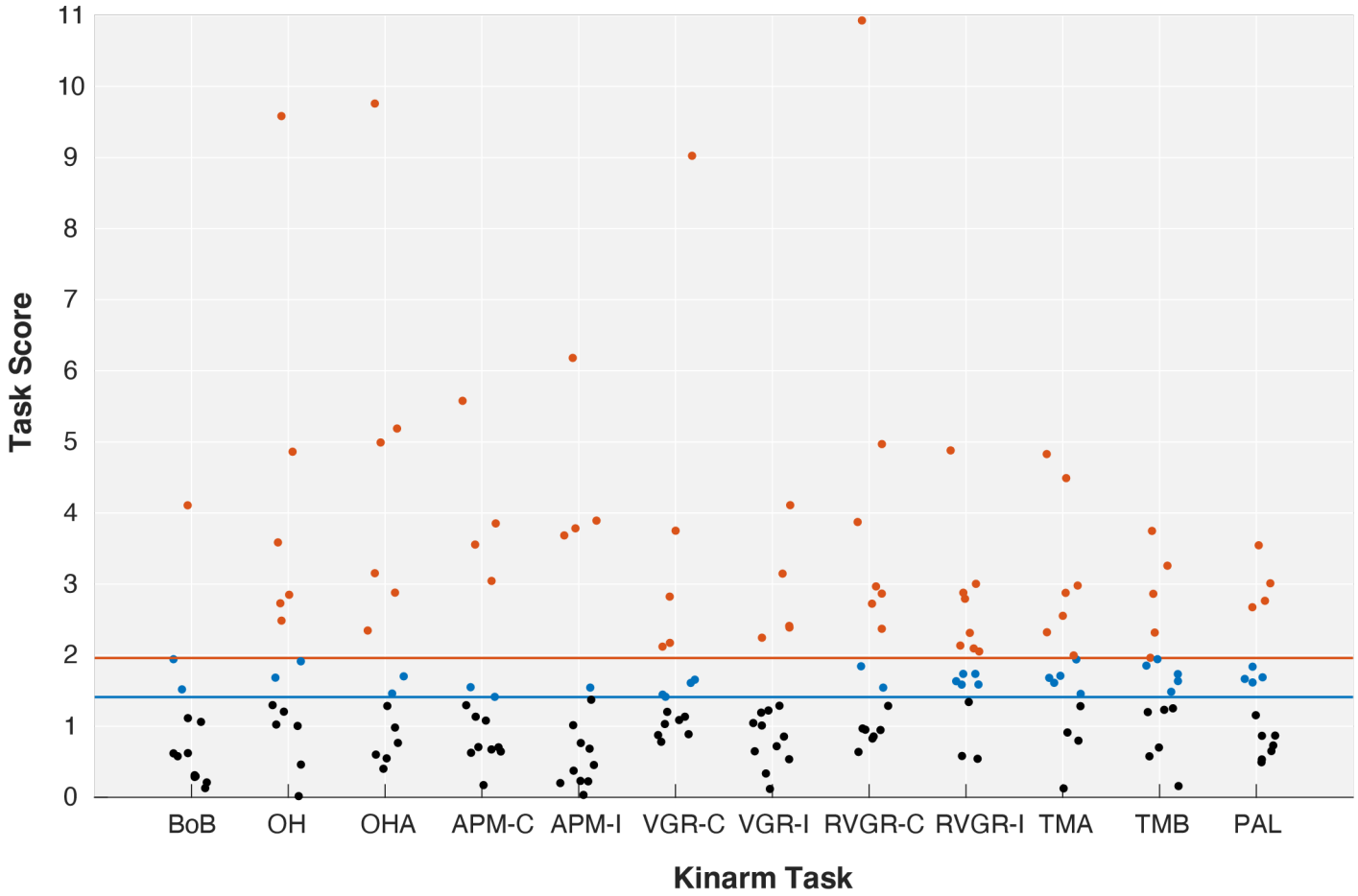

Figure 3.3: Scatter plot of Kinarm task scores

Kinarm tasks are displayed on x-axis and task scores on the y-axis. Impairment thresholds are displayed at 1.96 (on or above red line) and at 1.41 (one or above blue lone). Red points are those defined as impaired by threshold of 1.96, blue points are those defined as impaired by threshold of 1.41 and 1.96, black points are not defined as impaired.

Table 3.3: Summary of impairments detected by the Kinarm

Kinarm Task	Impairment Rate - 1.96 Threshold	Impairment Rate - 1.41 Threshold
BoB	1/13 (7.7%)	3/13 (23.1%)
OH	6/14 (42.9%)	8/14 (57.1%)
OHA	6/14 (42.9%)	8/14 (57.1%)
Contralesional - APM	2/15 (13.3%)	6/14 (42.9%)
Ipsilesional - APM	4/15 (26.7%)	5/15 (33.3%)
Contralesional - VGR	5/16 (44%)	9/16 (56.3%)
Ipsilesional - VGR	5/16 (44%)	5/16 (44%)
Contralesional - RVGR	7/16 (43.8%)	9/16 (56.3%)
Ipsilesional - RVGR	8/16 (50%)	13/16 (81.3%)
TMA	7/16 (43.8%)	12/16 (75%)
TMB	5/16 (44%)	10/16 (62.5%)
PAL	3/15 (20%)	7/15 (46.7%)

Figure 3.4 provides a more detailed view of impairment detected by Kinarm using the 95% impairment threshold. Individual participant's performances across the 12 robotic tasks are displayed. As shown, Kinarm reported 13/16 (81.3%) participants to be impaired in at least one task. The task most commonly reported to be impaired was ipsilesional RVGR (8/16) and the least common was BoB for which 1/13 participants exhibited impairment. Participants also showed varying levels of impairment with some participants showing no impairment across tasks and others showing impairment on up to 11 tasks.

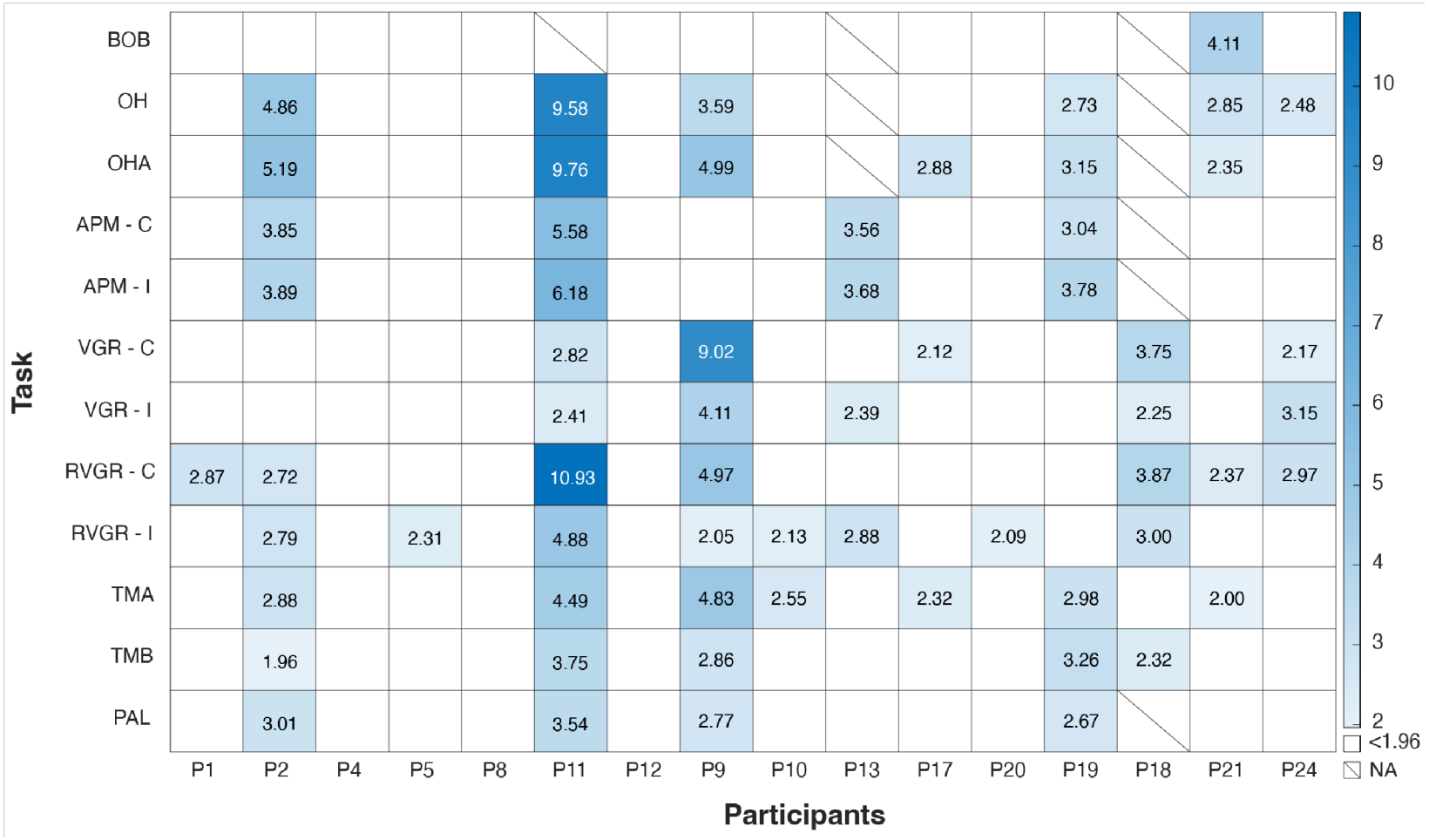

Figure 3.4: Kinarm task scores for participants across all robotic tasks

Participants are listed on the x-axis with Kinarm tasks on the y-axis. Task scores reaching the impairment threshold are displayed while those below the threshold are left white. Increasing colour intensity corresponds to increased task score and more impaired performance. Tasks not completed by a participant are crossed out (NA).

Figure 3.5 presents cumulative distributions of Kinarm performance for brain tumour participants across all robotic tasks (blue lines). This data is compared to the distribution of a theoretical healthy control population (black lines) derived from the means and standard deviations of healthy individuals. The threshold of impairment for a task score (1.96) is denoted by the vertical dashed red line. The intersections between a population line with the vertical red lines represent the percentage of individuals that are defined as impaired. For a theoretical healthy control cohort, this point is 5%. When comparing this to brain tumour participants, we find that a greater percentage of participants are deemed impaired and thus fall beyond the threshold of impairment. We also find that below the threshold of impairment, there are systematic shifts in the distributions of performances on all tasks. These two observations may be highlighted by the distributions of TMA, contralesional RVGR, OH, and OHA performances which showed the greatest percentage of participants as impaired and large shifts to the right below the impairment threshold.

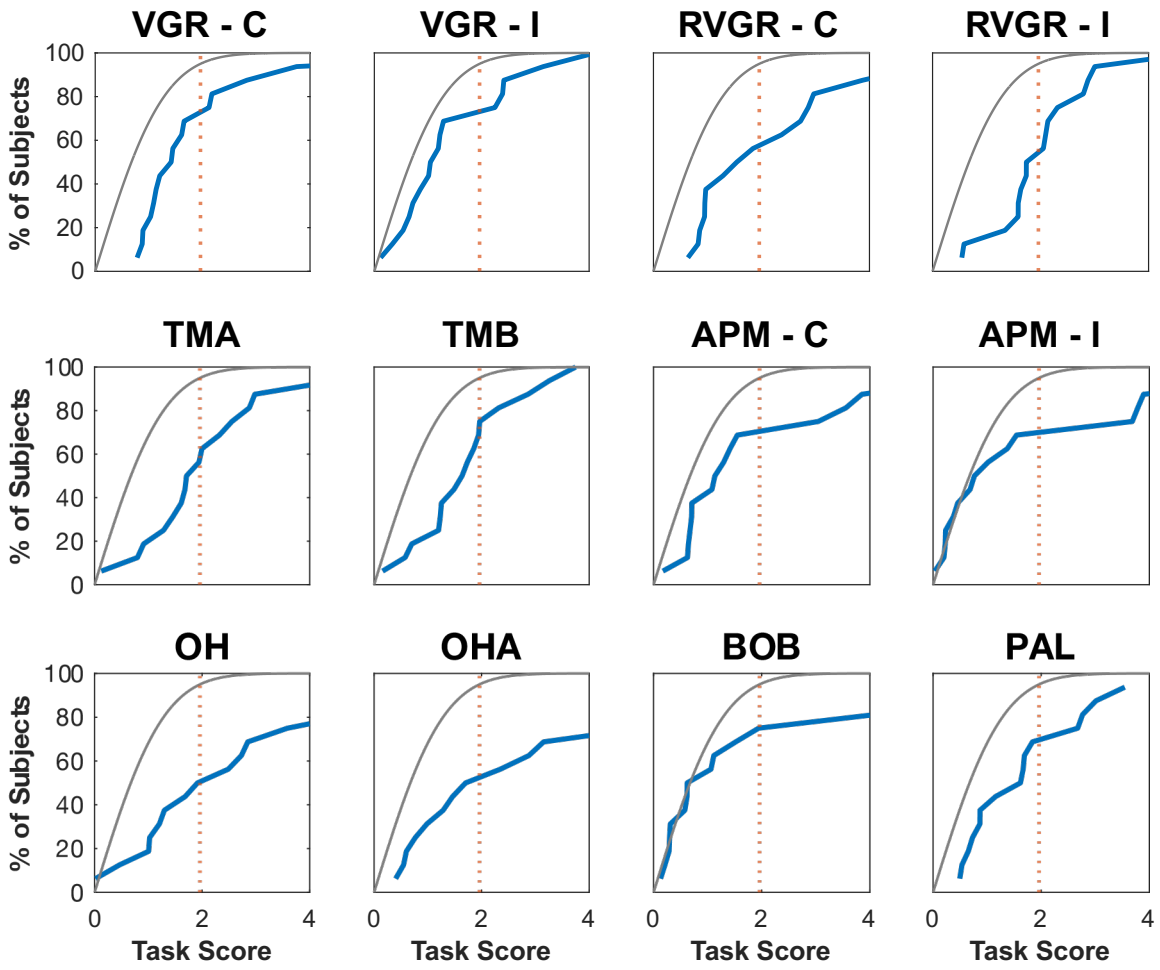

Figure 3.5: Cumulative distributions of Kinarm performance

Brain tumour participant performances are represented by blue lines. Theoretical healthy control distributions are shown by the black line. The dashed red lined represents a threshold of impairment at 1.96 (performance outside the 95th percentile

3.4 RBANS Assessment

Figures 3.6 and 3.7 display RBANS performance for 15 brain tumour participants. One participant (P11) is not shown as they did not complete RBANS at the time of preoperative assessment. Figure 3.6 shows scores as a scatterplot, separating participants' scores by the DSM-V related cognitive domains assessed (immediate memory, visuospatial constructional, language, attention, and delayed memory) as well as total scale score. Two thresholds of impairment are displayed; the red line placed at a score of 75 defines impairment as performance outside of the 95th percentile while the blue line placed at a score of 85 defines impairment as 1 SD away from the average score of 100. The latter is the threshold traditionally employed with RBANS and classifies ~16% of a healthy population as impaired. We have chosen to include the more stringent threshold to match that used by the Kinarm which defines impairment as performance outside of the 95th percentile. Notably, total scale score, which provides a global assessment of neurocognition, was deemed to be impaired in 2/15 (13.3%) of participants using a threshold of 75 while 7/15 (46.7%) were defined as impaired using a threshold of 85. Moreover, delayed memory, immediate memory, and visuospatial constructional were domains with high recorded rates of impairment according to both thresholds of impairment. A complete summary of RBANS impairments by domain as well as a comparison between thresholds can be seen in Table 3.4.

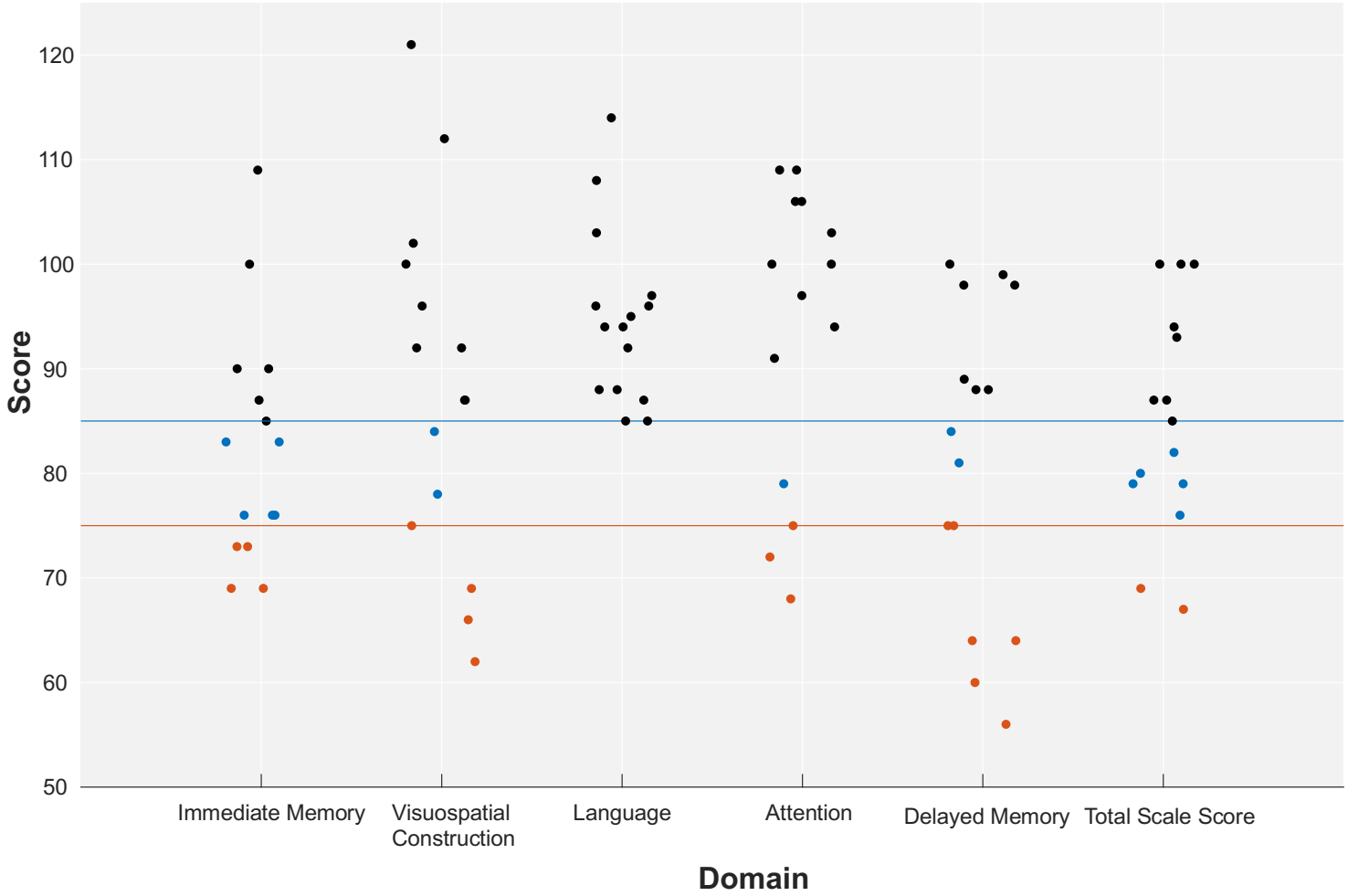

Figure 3.6: Scatter plot of RBANS scores

RBANS domains are displayed on x-axis and scores on the y-axis. Impairment thresholds are displayed at 75 (on or above red line) and at 85 (above blue line). Red points are those defined as impaired by threshold of 75, blue points are those defined as impaired by threshold of 85 and 75, black points are not defined as impaired.

Table 3.4: Summary of impairments detected by the RBANS RBANS Score

Impairment Rate - 75	Impairment Rate - 85 Threshold	Threshold
Immediate Memory	4/15 (26.7%)	9/15 (60%)
Visuospatial Construction	4/15 (26.7%)	6/15 (40%)
Language	0/15 (0%)	0/15 (0%)
Attention	3/15 (20%)	4/15 (26.7%)
Delayed Memory	6/15 (40%)	8/15 (53.3%)
Total Scale Score	2/15 (13.3%)	7/15 (46.7%)

Figure 3.7 provides a more detailed view of impairment detected by RBANS using a 95% impairment threshold (score of 75), displaying each individual participant's performances across the 5 neurocognitive domains assessed as well as total scale score. As shown, RBANS reported 10/15 (66.6%) participants to be impaired in at least one domain. The domain most commonly reported to be impaired was delayed memory (6/15) and the least common was language for which 0 participants exhibited impairment. Participants also showed varying levels of impairment with some participants showing no impairment across the 6 scores and others showing impairment in up to 4/6 domains.

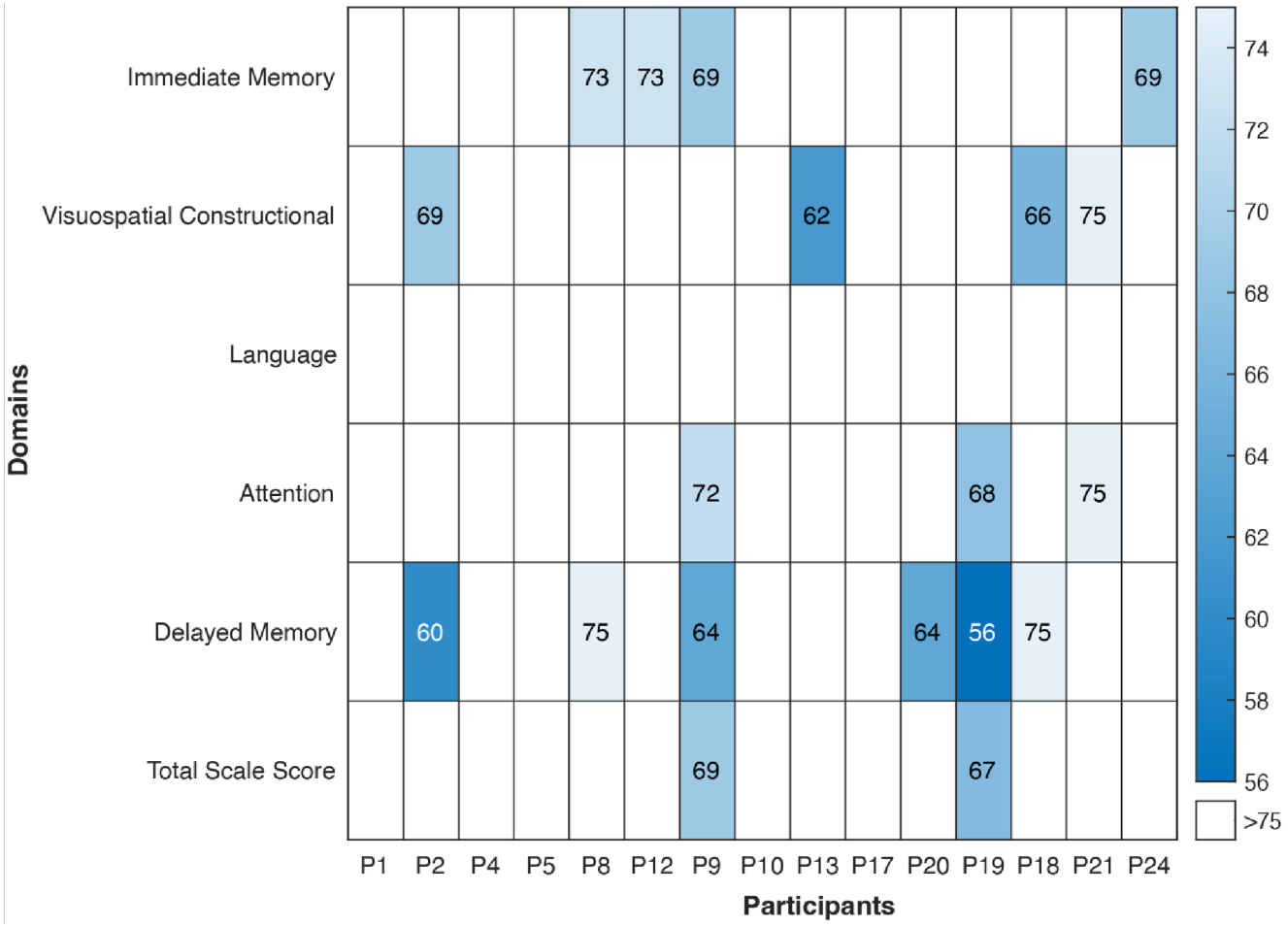

Figure 3.7: RBANS scores for participants across all domains

Participants are listed on the x-axis with RBANS domains on the y-axis. Scores reaching the impairment threshold are displayed while those above the threshold are left white. Increasing colour intensity corresponds to decreased domain score and more impaired performance.

3.5 Fatigue Assessment

Table 3.5 displays mean BFI scores in brain tumour participants. These scores are averages of 9 items included on the BFI which assesses several dimensions of fatigue. Fatigue assessment was completed for 13/16 participants. The remaining 3 participants did not complete fatigue assessment either due to limited time or the BFI had yet to be added to the assessment protocol. Total BFI score was then stratified into 4 different categories: not fatigued (0-1), mildly fatigued (1-3), moderately fatigued (4-7) and severely fatigued (7-10). Table 3.5 summarizes the categorization of fatigue scores in each participant showing that 8/13 participants were mildly fatigued, 4/13 participants were moderately fatigued, and only 1/13 participants was severely fatigued.

Table 3.5: Mean BFI scores and fatigue classification

Participant (P)	Mean BFI Score	Level of Fatigue
P2	8.0	Severe
P4	2.2	Mild
P5	4.7	Moderate
P8	5.6	Moderate
P9	6.1	Moderate
P10	3.7	Mild
P12	1.2	Mild
P17	1.6	Mild
P18	3.3	Mild
P19	2.3	Mild
P20	1.2	Mild
P21	1.0	Mild
P24	6.2	Moderate

3.6 Correlations Between the Kinarm, the RBANS, and the BFI

Table 3.6 displays a matrix of Pearson correlation coefficients and their corresponding p-value significances for Kinarm Z-Task Scores, RBAN domains, and BFI Score. All p-values have been corrected for multiple comparisons using the FDR correction. Correlation values with significant p-values ($p = <0.05$) are highlighted in red (indicating a significant positive relationship) and in blue (indicating a significant inverse relationship). There is an inverse relationship between Kinarm and RBANS performance as an increase in Kinarm task score represents increasing impairment while in RBANS increasing levels of impairment are reflected in decreased scores. The area outlined in black highlights the relationships between RBANS and Kinarm performance.

Figure 3.8 displays a visualization of the statistically significant relationships between assessments. There were 28 significant positive relationships between Kinarm tasks (illustrated in red), with OH and OHA tasks being the most commonly involved. There were 8 significant relationships between Kinarm tasks and RBANS domains (illustrated in blue): OH and visuospatial construction ($r = -0.84$ $p = 0.005$), OHA and total scale score ($r = -0.70$ $p = 0.039$), contralesional APM and visuospatial construction ($r = 0.77$ $p = 0.010$), contralesional APM and total scale score ($r = -0.67$ $p = 0.048$), ipsilesional APM and visuospatial construction ($r = -0.73$ $p = 0.024$), ipsilesional RVGR and visuospatial constructional ($r = -0.66$ $p = 0.039$), PAL and delayed memory ($r = -0.72$ $p = 0.026$), and PAL and total scale score ($r = -0.71$ $p = 0.029$). Notably, the only RBANS domains to be correlated with each other were delayed memory and total scale score. The BFI was not correlated with Kinarm nor RBANS performance.

Table 3.6: Pearson correlations between the Kinarm, RBANS, and BFI

Pearson correlation coefficients (*r*) and FDR corrected p-values between the Kinarm, RBANS, and BFI. Significant positive correlations are bolded in red and significant negative correlations in blue. The outlined black area compared Kinarm tasks to RBANS domains.

		BOB	OH	OHA	APM - C	APM - I	VGR - C	VGR - I	RVGR - C	RVGR - I	TMA	TMB	PAL	Immediate Memory	Visuospatial Construction	Language	Attention	Delayed Memory	Total Scale Score	BFI
BOB	*r*	1																		
	p-value	1																		
OH	*r*	0.345	1																	
	p-value	0.410	1																	
OHA	*r*	0.283	**0.930**	1																
	p-value	0.499	<0.001	1																
APM - C	*r*	0.118	**0.931**	**0.901**	1															
	p-value	0.843	<0.001	<0.001	1															
APM - I	*r*	0.057	**0.888**	**0.884**	**0.973**	1														
	p-value	0.981	<0.001	<0.001	<0.001	1														
VGR - C	*r*	0.369	0.375	0.481	0.166	0.182	1													
	p-value	0.380	0.348	0.219	0.715	0.680	1													
VGR - I	*r*	0.187	0.446	0.493	0.391	0.322	**0.744**	1												
	p-value	0.703	0.272	0.211	0.329	0.410	0.010	1												
RVGR - C	*r*	0.393	**0.881**	**0.844**	**0.662**	0.618	0.504	0.486	1											
	p-value	0.345	<0.001	0.003	0.039	0.064	0.160	0.175	1											
RVGR - I	*r*	-0.014	**0.710**	**0.717**	**0.758**	**0.735**	0.196	0.290	**0.747**	1										
	p-value	1	0.028	0.026	0.010	0.015	0.639	0.426	0.010	1										
TMA	*r*	0.395	**0.747**	**0.785**	0.362	0.405	**0.647**	0.284	**0.682**	0.324	1									
	p-value	0.345	0.017	0.010	0.348	0.312	0.039	0.433	0.026	0.385	1									
TMB	*r*	0.391	**0.833**	**0.788**	0.458	0.497	0.525	0.277	**0.678**	0.284	**0.886**	1								
	p-value	0.345	0.004	0.010	0.227	0.182	0.137	0.444	0.026	0.433	<0.001	1								
PAL	*r*	0.321	**0.797**	**0.817**	0.621	0.578	0.485	0.397	**0.672**	0.441	**0.757**	**0.781**	1							
	p-value	0.433	0.008	0.005	0.063	0.096	0.199	0.322	0.036	0.260	0.010	0.008	1							
Immediate Memory	*r*	0.253	0.108	-0.139	0.076	0.142	-0.365	-0.540	-0.102	0.261	-0.184	-0.197	-0.221	1						
	p-value	0.564	0.856	0.794	0.923	0.774	0.348	0.138	0.852	0.499	0.680	0.654	0.616	1						
Visuospatial Construction	*r*	-0.328	**-0.842**	-0.649	**-0.774**	**-0.729**	-0.311	-0.407	-0.490	**-0.664**	-0.049	-0.150	-0.400	-0.366	1					
	p-value	0.426	0.005	0.0722	0.010	0.024	0.412	0.311	0.192	0.039	0.981	0.737	0.330	0.348	1					
Language	*r*	0.441	-0.343	-0.267	-0.444	-0.492	-0.015	-0.154	0.049	0.162	-0.155	-0.345	-0.109	0.389	-0.004	1				
	p-value	0.311	0.410	0.535	0.272	0.211	1	0.731	0.981	0.724	0.731	0.374	0.850	0.329	1	1				
Attention	*r*	-0.682	-0.556	-0.542	-0.375	-0.353	-0.468	-0.401	-0.356	0.160	-0.483	-0.564	-0.659	0.127	0.344	0.078	1			
	p-value	0.051	0.164	0.175	0.348	0.380	0.216	0.317	0.356	0.724	0.200	0.110	0.051	0.794	0.374	0.919	1			
Delayed Memory	*r*	0.052	-0.466	-0.618	-0.526	-0.489	-0.320	-0.314	-0.194	-0.292	-0.317	-0.387	**-0.722**	0.393	0.348	0.279	0.262	1		
	p-value	0.981	0.272	0.096	0.172	0.213	0.410	0.410	0.659	0.436	0.410	0.329	0.026	0.329	0.373	0.459	0.499	1		
Total Scale Score	*r*	-0.056	-0.632	**-0.703**	**-0.665**	-0.622	-0.514	-0.621	-0.378	-0.181	-0.382	-0.521	**-0.707**	0.528	0.466	0.545	0.594	**0.800**	1	
	p-value	0.981	0.085	0.039	0.048	0.076	0.167	0.063	0.341	0.680	0.335	0.160	0.029	0.155	0.217	0.136	0.083	0.005	1	
BFI	*r*	-0.209	0.574	0.379	0.485	0.367	0.308	0.404	0.443	0.251	0.337	0.261	0.358	-0.173	-0.331	-0.420	0.131	-0.471	-0.401	1
	p-value	0.680	0.167	0.387	0.272	0.410	0.450	0.348	0.311	0.565	0.412	0.548	0.410	0.724	0.422	0.329	0.810	0.269	0.348	1

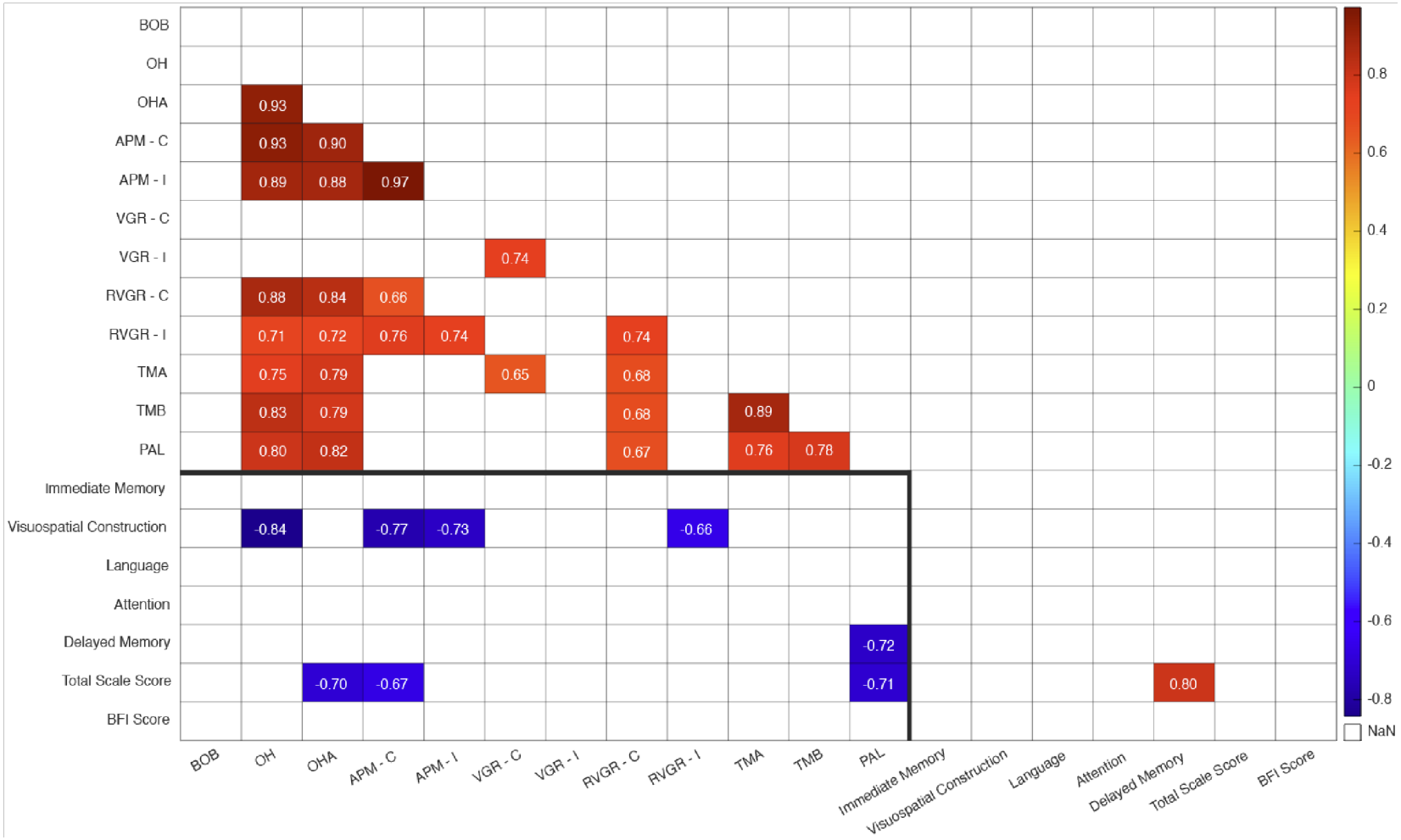

Figure 3.8: Significant correlations between the Kinarm, RBANS, and BFI

Statistically significant Pearson correlation coefficients are displayed between the Kinarm tasks, RBANS domains, and BFI score. Non-significant values have been removed. Positive correlations are depicted in red and negative correlations in blue. Area outlined in black compares Kinarm tasks to RBANS domains.

Chapter 4 Discussion

The objective of this thesis was to investigate the feasibility and application of Kinarm-based assessment in primary brain tumours. To assess neurological functioning, patients completed a suite of Kinarm standard tasks and underwent traditional neuropsychological evaluation via RBANS, a brief cognitive screening tool that has been previously validated in this population. We compared the ability of these two assessments to detect neurological impairment across cognitive, motor, and sensory functioning. We discovered that both the Kinarm and the RBANS identified varying levels of impairment among patients across cognitive domains. Significant correlations were observed between the two assessment methods in visuospatial, perceptual-motor, and memory related tasks, establishing concurrent validity. In addition, we found that participants showed impairments across multiple Kinarm tasks, pointing to a pattern of global neurological impairment. Regarding feasibility, while the Kinarm proved successful in detecting neurological impairment, the study encountered a low recruitment rate. This highlighted the challenges of working with this clinical population and identified potential barriers that should be considered in future studies.

4.1 Detection of Impairment by the Kinarm and the RBANS

In our study, Kinarm-based assessment was capable of assessing neurological functioning in brain tumour participants. The robot identified impairment in at least one neurological domain in the majority of brain tumour participants (81.5%). These findings align with studies conducted by Talachhi et al. and Tucha et al., which reported that 79% and 91% of brain tumour participants, respectively, exhibited impairment in at least one cognitive domain (Talacchi et al., 2011; Tucha et al., 2000). In our study, traditional

neuropsychological assessment using the RBANS also successfully detected impairment in brain tumor participants. We observed that 66.6% of the participants displayed impairment in at least one cognitive domain related to the DSM-V. This finding used a more stringent threshold for impairment, similar to the Kinarm assessment and previous research. By employing this threshold, we increased the certainty that those classified as impaired truly exhibited cognitive deficits, allowing for a direct comparison between the RBANS and the Kinarm in terms of impairment detection.

Multiple domains of neurological functioning demonstrated notably high rates of impairment in our study. Specifically, on the Kinarm assessment, tasks such as OH, OHA, RVGR, and TMA detected the greatest number of impairments. Similarly, on the RBANS, domains including delayed memory, immediate memory, and visuospatial construction exhibited the highest number of impairments. These findings align with previous studies that found memory and visuospatial construction to be frequently affected functions in brain tumour patients (Talacchi et al., 2011; Abete Fornara et al., 2018). This correspondence translated into significant Pearson correlation coefficients between the Kinarm and the RBANS, establishing concurrent validity between the tools across several tasks and domains. We found significant correlations between visuospatial construction on the RBANS and OH, RVGR, and APM on the Kinarm. These tasks correspond to several DSM-V related domains that include complex attention, executive function, and perceptual-motor.

Importantly, as displayed in Table 2.2, visuospatial construction is an aspect of perceptual-motor function and thus if impaired, could affect overall perceptual-motor functioning. This relationship may explain the correlation observed between visuospatial

construction on the RBANS and OH, RVGR, and APM on the Kinarm. If a participant is impaired in this domain, it is predicted that they will also exhibit impaired perceptualmotor functioning. We also discovered notable associations between PAL and delayed memory. Since both tasks assess learning and memory, it is expected that these distinct tasks would demonstrate a correlation in performance. Surprisingly, we did not find a significant relationship between PAL and immediately memory.

4.2 The Kinarm Detects a Pattern of Global Impairment

The Kinarm has previously been applied to many clinical populations and has revealed disparities in the level and nature of impairment of different neurological conditions. Some of these populations exhibit patterns of specific impairment, where participants consistently exhibit deficits on the same tasks and neurological domains while performing within the normative range on other tasks. Populations that exemplify this specific pattern of impairment include epilepsy and traumatic brain injury (Simmatis et al., 2020b; Debert et al., 2012). Epilepsy patients most commonly exhibit impairment in executive function and processing speed while traumatic brain injury patients often exhibit impairments in sensorimotor functioning. The specificity of impairment in both populations may be attributed to the focal nature of their associated lesions within the brain. A different pattern of impairment in seen in populations such as ALS and MS (Simmatis et al., 2019; Simmatis et al., 2020a). Within these patients, a broader range of impairments is observed where patients often exhibit impairment on multiple different tasks concurrently across several neurological domains. This general pattern of impairment may be explained by the widespread effect these conditions have on the brain.

Using Kinarm assessment we found that our cohort of brain tumour participants demonstrated a global pattern of impairment rather than specific, an idea that is supported by several of our findings. 1) We found a large proportion of our cohort was impaired on multiple Kinarm tasks rather than individual ones. Of the 13 participants that demonstrated impairment, 9 showed impairments on 3 or more tasks and 4 showed impairments on 7 or more tasks. 2) We found that in cumulative distributions of performance across all Kinarm tasks, there are clear divergences between participants with brain tumours and control distributions as well as systematic shifts in all task performances. 3) The impairments exhibited by our cohort spanned many domains as reflected by each Kinarm task detecting impaired performance in at least one participant. 4) We found that complex Kinarm tasks such as OH, OHA, and RVGR most commonly detected impairment in participants. Importantly these tasks are all multidimensional and assess numerous DSM-V related domains. In a cohort that demonstrates a pattern of global impairment, it is predictable that participants would perform poorly on tasks that assess several different cognitive domains. 5) Calculation of Pearson correlation coefficients revealed 28 strong positive relationships between Kinarm tasks that assess similar domains as well as those that assess different domains. The latter can be exemplified by the strong relationship between OH, a task that assesses perceptual-motor, complex attention, and executive function, and PAL, a task that assesses learning and memory. This finding corroborates the pattern of global impairment, as participants exhibiting impairment across many domains should show impairment across multiple Kinarm tasks regardless of domain assessed. Interestingly, inter-task correlations are not observed in healthy controls and inter-task correlations are much weaker in other clinical populations such as MS. Therefore, the strength and prevalence of

inter-task correlations exhibited in our cohort is particularly interesting and supports a pattern of global impairment.

In regard to existing literature, we find that previous studies support the global pattern of impairment detected by the Kinarm. Using unique neuropsychological batteries, Tucha et al. found that 71% of brain tumour patients exhibited impairment in 3 cognitive domains and 33% exhibited impairment in 8 or more domains while Talacchi et al. found that 52 % of brain tumour patients were impaired in 3 or more cognitive domains (Tucha et al., 2000; Talacchi et al., 2011). Although the assessment batteries employed in these studies focus primarily on cognitive aspects of impairment rather than a combination of cognition with sensorimotor function, their findings are consistent with ours discovered by the Kinarm. Participants showed impairment across many tasks (of different domains) concurrently, demonstrating a pattern of broad neurological impairment.

The observed pattern of global impairment in our cohort may be explained by several factors. Firstly, it is well established that brain tumours cause secondary phenomena such as mass effect and edema which can lead to significant compression of brain tissue. This is turn, may indirectly disrupt functioning of brain areas more distant from the tumour location causing impairments across several domains of neurological functioning. Secondly, although brain tumour may disrupt function in their corresponding anatomical region, they may also disrupt greater neural networks and functional connections. This may lead to impairment in areas not traditionally associated with their location in the brain. A potential example of this phenomenon in our population could be related to commonly reported impairment in visuospatial and perceptual-motor functioning. This impairment may be attributed to damage caused by the tumour to the superior longitudinal fascicles,

white matter pathways in the brain that facilitate visuospatial cognition and attention. A disruption of these pathways has been previously reported in brain tumour patients to lead to deficits in visuospatial functioning (Nakajima et al., 2017). Lastly, adjuvant therapies such as corticosteroids (dexamethasone), antiepileptic drugs, chemotherapy, and radiation therapy are known to exacerbate neurological impairment in brain tumour patients and may therefore play a role in the pattern of global impairment observed (Morshed et al., 2021).

4.3 Evaluating Feasibility

We considered several factors in determining the feasibility of Kinarm based assessment of neurological impairment in primary brain tumour patients. We demonstrated that Kinarm-based assessment was able detect neurological impairments in brain tumour participants and showed concurrent validity with the RBANS. The robotics assessment was also well tolerated, with an average data capture rate of 94.8%. Only 3 participants were unable to complete the entire suite of tasks, 1 was forced to stop assessment due to timing with hospital transport services, 1 completed the assessment before a task (BoB) was added to the assessment, and the other was unwilling to finish assessment after completing several tasks. In addition, brain tumour participants showed limited levels of fatigue as assessed by the BFI. The majority were classified as mildly impaired with only 1 participant classified as severely fatigued. Calculation of Pearson correlation coefficients showed no correlations between BFI and performance on Kinarm tasks or RBANS domains. These findings suggest that fatigue does not impact assessment and thus is not a barrier for a feasibility.

Patient enrollment however may be a barrier to feasibility of Kinarm assessment in brain tumour populations. Our recruitment rate was 0.7 participants/month with a total of 16 patients recruited over 23 months, falling short of our benchmark of 2 participants/month. This low recruitment rate could have occurred for several reasons: 1) there was an insufficient number of eligible participants, 2) an insufficient number of patients were approached for participation, or 3) an insufficient number of patients consented to the study. The majority of patients approached for our study were deemed eligible and consented for participation. Therefore, strategies to increase the number of patients approached are needed to increase the recruitment rate and overcome this barrier to feasibility.

One potential strategy is to include research dedicated associates or nurses as key players in the recruitment strategy. Involved with both patient care and research, these individuals would be responsible for identifying potential research participants by reviewing clinic bookings and hospital admissions. As part of the circle of care these individuals would have the ability to speak with clinicians and approach patients for consent to participate in research. They would then work closely with researchers and trainees to schedule participants for assessment. As members of the circle of care, research dedicated nurses would be able to track patients longitudinally for studies where follow up assessment is of interest. Overall, introducing research dedicated nurses or associates may allow for a more effective recruitment strategy to ensure future studies in brain tumours and other clinical populations obtain a sufficient number of participants.

4.4 Limitations

Our study has several limitations. One of the major limitations was our sample size. Having a small number of participants limits the certainty of our findings regarding the occurrence of impairment in brain tumour patients and the patterns of neurological impairment that emerge. Moreover, the small sample size may have limited the number of significant correlations that were identified between Kinarm tasks and RBANS domains, as well between Kinarm tasks. Since our small population was derived from one center, our results may not be generalizable to the general brain tumour patient population. There is also inherent heterogeneity in diagnoses of brain tumours within our cohort regarding type, size, location, and grade. Our small sample size prevented us from controlling for this heterogeneity. A larger population would have allowed us to stratify participants by tumour characteristics and perform statistical tests to explore which factors contribute to the neurological impairment observed in the population.

Another limitation in our study was the lack of information gathered regarding participants' treatment plans. We did not control for the impact that any therapeutic interventions such as chemotherapy, radiation therapy, corticosteroids, and anti-epileptic drugs may have had on neurological functioning. Previous literature suggests that these therapies may exacerbate or lead to neurological deficits and so should be considered when assessing brain tumour patients (Morshed et al., 2021).

4.5 Future Directions

Our study provides several future directions for subsequent research. In Kinarmbased assessment we reported task score which represents a single normalized measure of performance on a given task. A detailed analysis of the multiple individual

parameters that underly task score may provide insight into their individual contribution and reveal patterns of neurological impairment not recognizable by task score. Future studies may also look to correlate Kinarm performance with imaging data that is routinely collected in brain tumour patients. The addition of anatomical data from techniques such as MRI and functional MRI would allow for more exact relationships to be drawn between brain structure and function and Kinarm performance. Longitudinal assessment may also be a topic of interest in future studies. Evaluating brain tumour patients throughout the disease course and at salient time points such as before and after a resection surgery may provide insight into neurological functioning with disease progression. This type of assessment may also be used in future studies or trials investigating the neurological impact of novel therapeutic interventions. The Kinarm would provide quantifiable measures to evaluate the cognitive footprint and effects on the brain and thus offer an objective comparison.

4.6 Conclusion

In this thesis we investigate the feasibility of using the Kinarm to assess neurological functioning in primary brain tumour patients. By using robotic technology, we were able to assess the nature and degree of neurological impairment in this population and compare this to an established assessment tool (RBANS). The Kinarm successfully detected impairments among brain tumor participants and revealed a pattern of global neurological impairment. Although challenged by low sample size, we provide evidence that the Kinarm may be a feasible neurological assessment tool in brain tumour patients.

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