COGNITIVE ASSESSMENT USING THE KINARM
EXOSKELETON ROBOT IN PATIENTS WITH TRANSIENT
ISCHEMIC ATTACK

by

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A research project submitted to the Department of Biomedical and Molecular Sciences
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Abstract

**Background:** Transient ischemic attack (TIA) is a condition causing focal neurological deficits lasting less than 24hrs. TIA patients present similarly to other conditions with rapid onset of neurological symptoms such as migraine. The accurate diagnosis of TIA is critical because it serves as a warning for subsequent stroke. Furthermore, cognitive deficit associated with TIA may predict the development of dementia. Therefore, characterizing the cognitive symptoms of TIA patients and discriminating these patients from those with similar symptoms is important for proper diagnosis and treatment. Currently the diagnosis of TIA is made on clinical and radiographic evidence. Robotic assessment, with instruments such as the KINARM, may improve the identification of cognitive impairment in TIA patients.

**Methods:** In this prospective cohort study, two KINARM tests, trail making task (TMT) and spatial span task (SST), were used to detect cognitive deficits. Two study groups were made. The TIA group was tested at 5 time points over the span of a year. The migraine active control group had one initial visit and another a year later. Both of these groups were compared to a normative database of approximately 400 healthy volunteers. From this database age and sex matched normative data was used to calculate Z-scores for the TMT. The Montreal Cognitive Assessment (MoCA) was also administered to both groups.

**Results:** 31 participants were recruited, 20 TIA group and 11 active controls (mean ± SD age= 66 ± 11.3 and 62 ± 14.5). There was no significant difference in TIA and active control group MoCA scores. The TMT was able to detect cognitive impairment in TIA and migraine group. Also, both KINARM tasks could detect significant differences in performance between TIA and migraine patients while the MoCA could not. Changes in TIA and migraine performance on the MoCA, TMT, and SST were observed.

**Conclusions:** The robotic KINARM exoskeleton can be used to assess cognitive deficits in TIA patients.
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List of Abbreviations

The following table is a list of abbreviations used throughout this thesis. The page number of the abbreviations first appearance is also provided.

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<th>Meaning</th>
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<td>Age, Blood pressure, Clinical features, Duration, Diabetes</td>
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<td>CAD</td>
<td>Coronary artery disease</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>DWI</td>
<td>Diffusion weighted imaging</td>
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<td>FAST</td>
<td>Face, arm, speech test</td>
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<td>KINARM</td>
<td>Kinesiological Instrument for Normal and Altered Reaching</td>
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<td>Myocardial infarction</td>
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<td>Montreal cognitive assessment</td>
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<td>National Institute of Health Stroke Scale</td>
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Chapter 1

Introduction

1.1 Transient Ischemic Attack (TIA)

The World Health Organization (WHO) defines stroke as a condition consisting of rapid development of disturbances to cerebral functioning lasting longer than 24 hours or potentially leading to death with vascular etiology\(^1\). Transient ischemic attack (TIA) on the other hand, is defined as a condition with the symptoms of stroke resolving within 24 hours and is commonly known as a mini-stroke. The colloquial term downplays the severity of these attacks. Clinically TIAs are seen as a “warning stroke” because they are often followed by a subsequent more severe stroke. The following sections will discuss the epidemiology, diagnosis, risk factors, and treatment of TIA. Current knowledge of TIA patients is growing and evolution of new techniques to assess these patients is necessary to expand our knowledge on providing proper diagnosis and treatment for this condition.

1.1.1 Epidemiology of TIA

Incidence of TIA each year in the United States reaches 200,000 to 500,000 cases\(^2\). Men are more likely than women to experience a TIA\(^2\). The first 24hrs after an attack have been reported to be the most crucial period where 50% of recurrent TIA or stroke occur during this time\(^3\). As time progresses the risk of recurrence decreases. Although risk of recurrence may decrease, cognitive impairment may progress beyond the 24 hour time period\(^4,6\). Fifteen percent of strokes are preceded by TIA and TIA patients carry an 11-15% risk of stroke within 90 days\(^2\). The mortality rates for TIA patients within 1 year are also high at 13%. The problem with detection of these mini-strokes is that approximately 60% of TIA’s last less than an hour and of
these 67% last less than 10 minutes. Due to the transient nature of a TIA, it has been estimated that nearly 50% go unreported. Because of the severe consequences of a TIA diagnosis it is imperative to develop more accurate diagnostic and monitoring tools for this patient population.

1.1.2 Diagnosis of TIA

Accurate diagnosis and timely treatment is imperative for the management of TIA patients. There have been 80% reductions in the risk of developing a stroke after a TIA in cases of prompt diagnosis and treatment of the initial TIA. Clinicians will judge whether the symptoms of the patient match the accepted WHO definition of clinical stroke symptom recovery within 24 hours of TIA. Recently there has been debate over the so-called transient symptoms TIA patients experience. Many studies have found prolonged (>24hr) symptom presentation in patients diagnosed with TIA. Thus, there may be a need for alterations to the definition of TIA. Recently, a tissue based definition of TIA has been gaining momentum. This definition is determined using brain imaging where neurological dysfunction caused by focal ischemia without visible infarction is defined as a TIA regardless of the length of time the symptoms persist. Neurological dysfunction including visible infarction would then be defined as an ischemic stroke not a TIA. This definition relies on accurate and sensitive imaging, such as diffusion weighted imaging (DWI), which is not always readily available and thus, difficult to employ in all situations. In order to obtain an accurate diagnosis a consensus on the definition of TIA is necessary.

Assessing patients for TIA and ruling out stroke mimics can be difficult. Initially the potential TIA patient should be assessed using the face, arm, speech test (FAST). This crude test is for determining stroke based on facial nerve palsies, limb weakness or numbness, and language or speech production deficits. Initial blood tests and echocardiography are routinely used in determining the cause of stroke and ruling out other conditions that may mimic stroke.
Subsequent neurological examination is common practice. During the process of the neurological examination of potential TIA patients neurologists will often use a stroke scale to objectively assess neurological deficits perceived by the patient. The National Institute of Health Stroke Scale (NIHSS) is a commonly used stroke assessment scale validated in 1989\textsuperscript{14}. Since symptoms can vary based on the location of the infarction assessment of patients with suspected TIA usually involves brain imaging such as computed tomography (CT) and magnetic resonance imaging (MRI). Non-invasive cerebrovascular imaging is also done (CT or MR angiography)\textsuperscript{13}. Diffusion weighted imaging can be used to detect brain lesions. It has been reported that nearly one third of TIA cases are seen as infarctions using DWI \textsuperscript{2}. Comparing the symptoms with imaging can localize the infarcted brain area and confirm TIA. Unfortunately misdiagnosis can occur when imaging diagnostic techniques fail to detect any lesions. Many non-ischemic conditions mimic the symptomology of TIA and need to be excluded as potential causes of the symptoms before diagnosis.

Seizures, hyperglycemia, migraines and many other conditions present similarly to TIA based on signs of rapid onset of neurological symptoms\textsuperscript{12}. In a single study 100 emergency room diagnosed TIAs were reviewed and 60 were later determined to be non-TIA patients, illustrating that accurate TIA diagnostic tools are required\textsuperscript{15}. The, ABCD\textsuperscript{2} (Age, Blood pressure, Clinical features, Duration, and Diabetes) is a tool used to predict the risk of subsequent cerebral ischemia after a confirmed TIA. Studies have evaluated the possibility of using the ABCD\textsuperscript{2} as a diagnostic tool to differentiate TIA from non-ischemic neurological conditions\textsuperscript{16}. Currently, clinicians rely on neurological examination, imaging, and obtaining an accurate history of symptoms from the patient to determine TIA diagnosis and differentiate TIA from similar conditions.
1.1.3 Risk Factors for TIA

Risk factors for TIA are similar to that of ischemic stroke. The National Institute of Health (USA) considers TIA as a medical emergency due to the increased risk of subsequent stroke. Below are the common conditions and activities that increase the risk of TIA. Potential TIA patients are asked for history of these conditions during assessment to help determine the diagnosis:

- Atrial Fibrillation
- Coronary Artery Disease (CAD) and Peripheral Vascular Disease (PVD)
- Diabetes
- Dyslipidemia
- Hypertension
- Mitral valve disease
- Myocardial Infarction (MI)
- Obesity
- Smoking

1.1.4 Treatment of TIA

According to the Canadian best practice recommendations for stroke care there are three classes of TIA patients based on urgency. These three classes will have slightly different requirements for acute care. High risk, emergent, patients who present to a physician within 48 hours of TIA and have persistent speech and motor symptoms should have an immediate examination with imaging. Ruling out conditions that mimic stroke is recommended. Upon diagnosis, a stroke management plan should be developed. The second urgent class of patients present to a physician within 48hrs to 2 weeks without persistent symptoms. These moderate risk patients are still at high risk for subsequent stroke and should be fully examined and followed
up within 24hrs of their initial contact with a health care provider. The final non-urgent class of patient presents to a physician more than two weeks after a suspected TIA and may be experiencing isolated sensory symptoms such as tingling\(^{13}\). Once diagnosis and imaging is complete, TIA patients start antiplatelet therapy regardless of which of the three classifications they belong to\(^{13}\). After acute care is completed, all TIA patients are scheduled for a follow-up assessment within one week of the initial visit. Patients are also referred to a rehabilitation or stroke prevention program for up to one year where symptom resolution takes place and monitoring for any signs of subsequent stroke.

1.2 Migraine

Migraine is a common disorder with two distinct subtypes. Migraine without aura is characterized mostly by repeated headaches while migraine with aura is characterized by neurological symptoms that may accompany a headache\(^{18}\). It is the second subtype, migraine with aura, which can often be confused with TIA. The condition was initially thought to be vascular in nature but neurological origins have also been speculated\(^{18}\). Although disabling, these symptoms are transient and the individual may return to normal activities afterwards. However, the length of the migraine attack and the interval of time between migraines is highly variable. The following sections will discuss the epidemiology, diagnosis, and treatment of migraine as well as, the relationship between migraine and TIA.

1.2.1 Epidemiology of Migraine

Approximately 28 million Americans suffer from migraines\(^{19}\). Migraines are much more prevalent in women than in men. A study by Lipton et al. (2001) found the prevalence of migraine in women to be 18.2\%, more than double that in men (6.5\%). The sex difference has been associated with the hormone estrogen\(^{20}\). Prepubescent migraine rates are similar between the
sexes (2.5%). At puberty female rates increase (6.5%), and after menopause the rate of migraine in women tapers off (5%)\textsuperscript{21}. Men experience an increase in prevalence with age (4% at puberty and down to 1.6 over the age of 60) but is less drastic than females. Prevalence of migraine is highest in middle aged individuals (30-50 years old)\textsuperscript{19}. Increased reporting of migraine symptoms is correlated with increased age for both sexes\textsuperscript{22}. The rate of migraine attacks is also large. Nearly two thirds (62%) of migraine patients experience at least one migraine a month\textsuperscript{19}. With such a high prevalence of migraines it is important to have effective treatment and diagnosis.

\textbf{1.2.2 Diagnosis of Migraine}

The diagnostic criteria for the two major classifications of migraine are quite different. A diagnosis of migraine without aura requires a history of at least 5 migraines which last between 4-72hrs, is accompanied by nausea and/or vomiting, and during the episode an avoidance of light and sound is evident\textsuperscript{18}. Migraine with aura requires at least two attacks with one of the following aura symptoms: visual, sensory, speech and/or language, motor, brainstem, or retinal. Also, two of the following conditions must be met: aura symptoms that spread gradually over a five minute period or symptoms in quick succession, or symptoms that last between 5-60minutes, or at least one aura symptom must be unilateral, or the symptoms must be followed by a headache within 60 minutes\textsuperscript{18}. Migraine with aura can be diagnosed without headache and thus will present similar symptoms to TIA patients. The most common migraine headache symptoms are pain, sensitivity to light and sound, nausea/vomiting, blurred vision, and aura\textsuperscript{19}. The most common of the aura symptoms is visual aura often associated with colourful flashes of light across the visual field\textsuperscript{18,23}. Sensory symptoms, such as a tingling feeling, are less common and speech deficits are even less frequent\textsuperscript{18}. Migraines patients tend to experience a lot of comorbidities including cardiovascular and cerebrovascular disease\textsuperscript{21}. These comorbidities can overshadow migraine symptoms and prevent an accurate migraine diagnosis. Thus, diagnosing migraine can be difficult at times.
1.2.3 Treatment of Migraine

Migraine treatment is centered around improving patient symptomology and for chronic cases preventative measures. Much like TIA patients, migraine patients are often referred to a neurologist for preventative treatment and monitoring. Determining the type and frequency of migraine is important for accurate, directed treatment decisions. Ruling out other potential causes of symptoms is also necessary. Patients who experience migraines at least 3 days a month are recommended to be prescribed symptom relieving drugs such as Triptans (serotonin receptor agonists) and non-steroidal anti-inflammatory drugs (NSAIDs)\(^2^4\). Patients with more frequent migraines (4-10 days a month) require preventative treatment coupled with pain and symptomatic medication. Recently, an algorithm for treating migraine patients has been developed\(^2^4\). The issue of differentiating migraine patients from other neurological conditions still remains and affects the efficacy of treatment.

1.2.4 The Complicated Relationship between Migraines and TIA

Currently receiving a migraine diagnosis is solely based on clinical criteria. Among the steps to determining a migraine diagnosis is the ruling out of potential TIA. This is because the two conditions are very similar in their presentation of symptoms\(^1^2\). However, there is a stronger relationship between the two conditions. Migraines have been linked as both a cause and risk factor for individuals suffering a TIA \(^2^3\). Due to the high prevalence of migraines it is estimated that 1/3 of TIA patients might have suffered a migraine in their past without factoring in a causal link\(^2^3\).

Both migraine and TIA patients suffer neurological symptoms. There are a range of symptoms depending on the brain area affected. Those TIAs associated with posterior circulation are often accompanied with headaches \(^2^3\). Although, headaches are a common occurrence for migraine patients, these patients may also experience an aura, which can occur independent of the
headache. Neurological symptoms of migraine aura tend to be positive such as, colourful flashes of light or tingling sensations. In contrast, TIA patients suffer neurological deficits during an episode, including blindness, numbness, and weakness. Both aura and TIA can progress gradually affecting sensation. This type of progression is said to be the clinical manifestation of the phenomenon known as the spreading depression of Leao. The wave of cortical depolarization of neurons leads to multiple symptoms affecting the individual’s sensation. Thus differentiating between migraine and TIA is complicated by the similarity in symptoms.

Migraines have been linked as a potential causal factor for TIA which further complicates the relationship. Complicated migraines which evolve to migrainous infarctions are attacks of migraine accompanied by stroke. This occurs more commonly during migraine with aura but has been reported without aura as well. The causal relationship is speculated by the close succession of migraine and stroke in these cases. It is estimated that the incidence of migrainous infarctions is 1.7/100,000 Americans. The issue with linking migraine to TIA is that there are a number of potential causes for ischemia that may confound the relationship.

1.3 Neuropsychological Testing of Cognition

Cognition involves perception, processing sensory information, storing that information and retrieving it later on. Memory, attention, reasoning, decision making and problem solving are among the many functions of cognition. Decline in different aspects of cognitive function is expected with age but certain conditions, including stroke, can negatively affect cognition. The declines in cognition beyond what is normally expected with age is known as mild cognitive impairment (MCI). Thus, cognition is on a continuum from the normal range, to MCI, then dementia.

Clinically neuropsychological testing is one of the main ways to detect cognitive decline. There are many neuropsychological tests developed and implemented for detecting cognitive
impairment. The more commonly used clinical tests are those that are short and require less subjective interpretations. For these reasons, two clinical tests for cognition have gained popularity in the clinical and research world, the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). The MMSE was the initial short tool for assessing mild cognitive impairment. This test of cognition was developed in 1975 for differentiating different types of psychiatric patients and it was later applied to detection of MCI\(^3\). The test is marked out of 30 possible points where differing scores correspond to degrees of impairment. Different cut-off scores have been used in the past but scoring above 25 or 26 tends to indicate normal cognition, whereas scores below 25 indicate MCI\(^3\). The MoCA was later developed as a short screening tool for MCI\(^2\). This screening tool was validated in 2005 and like the MMSE has 8 sections each measuring a different domain of cognition\(^2\). Again the test consists of 30 potential marks however, unlike the MMSE a clear cut-off is defined. Scores 26 and above are considers within the normal range, below 26 is considered to be cognitively impaired. The validation study for the MoCA determined the tool has a better discriminative ability and is more sensitive than the MMSE in detecting MCI\(^3\). Although there is no gold standard the MoCA is commonly used to test for cognitive impairment in clinical and research settings.

There are definite drawbacks to using traditional neuropsychological tests clinically and for research purposes. Subjectivity of these assessments can be an issue. Although the grading of the MoCA and MMSE is fairly standard, the inter-rater reliability has not been tested in the stroke population. Another problem is the potential ceiling effect that can occur with clinical tests of cognition. This is when cognitive impairment is no longer accurately reflected in the test score beyond a certain point. Studies comparing the MoCA and MMSE have determined the MMSE to exhibit a ceiling effect while the MoCA does not in the stroke population\(^3\). Finally the limited measures that can be taken from the paper or verbal cognitive tests can render them crude and
less sensitive to subtle deficits. Limiting these problems with neuropsychological testing will lead to more accurate measures of MCI.

### 1.3.1 Measuring Cognitive Impairment in the Stroke Population

For proper monitoring and care of TIA patients, lasting cognitive deficits must be identified. Although other neurological faculties may recover, cognitive impairment may still be evident. The definition of a TIA has previously been called into question partially due to cognitive symptoms persisting beyond 24hrs\(^5\),\(^10\),\(^34\). A study conducted on TIA patients between 1 and 8 months after the incident found 49% of the patient population had continued cognitive deficits\(^34\). Of the many neuropsychological tests available for assessing TIA patients, the MoCA is most commonly used. Studies comparing the two assessment tools found the MoCA to be more sensitive than the MMSE in detecting MCI in the stroke population\(^35\)–\(^38\). One study by Pendlebury et al. (2010) determined the MoCA and MMSE scores to be highly correlative; however, the MoCA had normal distribution within the TIA and stroke population while the MMSE was skewed towards higher values\(^39\). The MMSE is more likely to miss those TIA patients with slight cognitive impairments. Evidence has also shown improvement of TIA patient cognition based on repeated testing using the MoCA\(^3\). Therefore, some patients may actually improve cognitively over time; however there is a very evident risk of further cognitive decline post stroke.

Detection of cognitive deficits can play an important role in prediction of events post stroke or TIA. TIA and stroke patients with cognitive deficits are more likely to develop moderate to severe cognitive impairments such as dementia\(^27\). Patients suffering a previous TIA before stroke have an even higher incidence of dementia post stroke. It was reported that 33% of patients with a TIA less than 4 weeks before a subsequent stroke later developed dementia\(^9\). This is due to the effect that decreased blood supply to the brain has on cognition. The term for this effect is vascular cognitive impairment and it is the second most common cause of dementia\(^27\),\(^40\). Other
studies have found cognitive impairment to be a predictive factor of patient outcome. Cognitive impairment post stroke or TIA can be predictive of depression and reduced quality of life in TIA patients. On a more severe scale, deficits in cognition before first ever stroke has been linked to increased rates of mortality post stroke or TIA. The importance of better detecting cognitive impairment is more necessary knowing the role it can play in predicting patient outcome.

Some studies have moved beyond the standard pen and paper psychological testing to less subjective assessment of the cognition. Conducting testing over the phone has become a more convenient method for neuropsychological testing with the telephone interview of cognitive status (TICS) leading the way. A study of TIA and stroke patients testing the TICS and telephone delivered MoCA found they both had similar detection rates of MCI. The issue however, is the telephone delivered MoCA had a 12% lower MCI detection rate than face-to-face MoCA administration. It is becoming increasingly more important to find accurate and objective measures of cognition and introducing technology may be the answer. A recent study by Shopin et al. (2013) used a new computerized battery of neuropsychological tests, called MindStreams, on patients post TIA or stroke. MindStreams had a significant correlation with the MoCA scores, suggesting it can detect cognitive impairment in the stroke patient population. However, the MoCA detected more cognitively impaired patients than the computerized battery of tests. This may suggest MindStreams lacks sensitivity. Currently there have been no attempts to measure cognition of TIA patients using a robotic instrument.

Using robotics in the detection of cognitive deficits for TIA and migraine patients may be the answer to some current issues. Robotic instruments are able to objectively measure minor differences and potentially stratify and detect patients with cognitive deficits much better than the current pen and paper neuropsychological tests. Testing patients with clinically similar presentation to TIA such as migraine patients with robotic instruments will determine the ability to discriminate between the patient populations. Since these two populations have very different
treatment and post event risk factors differentiating between the two patient groups is very important. Using robotics could mean better detection and monitoring of TIA patients, lower rates of misdiagnosis, and a better understanding of TIA patient cognition over time. With a better understanding of TIA patient cognition, everyday life decisions like returning to work and ability to drive can be made with greater certainty. It is due to these reasons that the current studies may be turning to robotics to assess TIA patients.

1.4 The Kinesiological Instrument for Normal and Altered Reaching Movements (KINARM)

The KINARM is a unique robotic system designed by Dr. Stephen Scott to assess the neurological basis of movement in the upper limb\(^45\). There are two versions of the KINARM, the exoskeleton and the endpoint robot (Figure 1.1). The exoskeleton robot developed in 1999, has the subject in a sitting position with arms secured to arm-plates\(^46\). This set up allows for measurements to be taken at each joint of the upper limb and loads can be applied to these joints individually or simultaneously\(^45\). The subject must grab bars attached to the endpoint robot thus loads are only applied to the distal upper limb at the hand. Each of the robots has a screen situated in the horizontal plane just above the arms. The screen allows for a virtual system to display different tasks the subject must perform\(^46\). While the tasks are carried out different parameters are monitored and recorded by an attached operating system. The exoskeleton robot measures a greater number of tasks and parameters; therefore, it is employed more frequently in research.
Figure 1.1. KINARM Robots. The exoskeleton robot (above) resembles a modified wheel chair with arm plates for gravitational support of the upper limb. The endpoint robot (below) requires the participant to grasp handles in order to perform tasks. Both robots use a virtual black screen in the horizontal plane above the hands to display the tasks.
1.4.1 KINARM Exoskeleton Tasks

Ten tasks have been developed for the KINARM exoskeleton robot. These tasks can be divided into 2 major categories: sensorimotor and cognitive tasks.

**Sensorimotor Tasks**

1. *Visual guided reaching:* The subject must move their finger towards a red target seen in the virtual reality environment\(^{47}\).
2. *Perturbation:* The subject reaches for a target but during the reaching movement the KINARM exerts a force which the subject must resist\(^{48}\).
3. *Visual reverse:* Similar to the visually guided reaching task; however, the subject’s movement is inverted so that in order to reach a target on the left subject must move their hand to the right\(^{49}\).
4. *Object hit:* Both of the subject’s hands are represented by green paddles in the virtual system as red balls fall down the screen the subject must use the paddles to hit the balls away\(^{49}\).
5. *Ball and bar task:* This a new motor task that has not been previously described. A horizontal bar represents the subject’s hands in the virtual system. A ball is placed on the bar and the subject must tilt the bar to balance the ball.
6. *Arm position matching:* The robot moves one arm to a certain position and the patient must match that same position in the other arm with occluded vision of both arms\(^{49}\).
7. *Kinesthesia:* The robot moves the subject’s arm at a slow steady speed and the patient matches the movement with other arm on root to a target\(^{50}\).

**Cognitive Tasks**

8. *Object hit and avoid:* Similar to the object hit task, the subject’s hands are represented by paddles in the virtual system. This time 5 different shapes will fall down the screen 2 of which the subject must hit and 3 are to be avoided\(^{49}\).
9. *Trail making:* This task has two types, trail A has the subject connect 25 sequentially numbered targets. Trail B requires the subject to alternate between connecting numbered and lettered targets (1-A-2-B…)^49.

10. *Spatial span:* the subject will be required to remember a sequence of lit segments of a grid with 12 segments. Sequences start at 4 then increase^49.

### 1.4.2 Use of the KINARM Exoskeleton in Research

The original exoskeleton task was done to test perturbation in a reaching task using monkeys. A monkey was trained to reach for a target while in the exoskeleton robot. During the reaching motion loads were applied at different regions along the upper limb at varying time intervals^46. This same perturbation task has been modified and used in human studies today.

The KINARM robot has been used in assessing neurological function in different patient populations. The robot has even been used to detect age related deficits in proprioception^51. Patients with traumatic brain injury (TBI) have been assessed using the visually guided reaching task. TBI patients with clinically normal motor assessments were found to have sensorimotor deficits using the KINARM^52. The benefits of using robotic assessment come from its high repeatability, objective and fast measurements, and potential for high sensitivity. Recent studies in the stroke population has shown promising results in the robot’s ability to objectively detect sensorimotor deficits in stroke patients^47,50,53,54. The kinesthesia task was used to detect that 61% of acute stroke patients had kinesthetic deficits compared to normative data^50. Studies using the KINARM cognitive tasks have not been described in the literature. Also, to date none of the tasks have been used to specifically assess the TIA or migraine patient population.

Using the KINARM cognitive tasks to assess TIA and migraine patients may be beneficial in determining the ability of the robot to detect cognitive deficits. This is a very novel idea as no previous studies have used robotics to test TIA or migraine patient cognition. Previous,
studies have determined the trail making task to be a great identifier of executive function deficits\textsuperscript{32,55,56}. Executive functions control cognitive processing by determining what to focus on and when to switch tasks. The planning, problem solving and managing of information in working memory are all under executive control as well. Thus, deficits in executive functions can affect all aspects of day to day life. Another important feature of cognition is visuospatial perception and the ability to process this information in working memory. This applies to everyday activities from remembering where the keys are to whether a car is in your blind spot. Thus, deficits in this aspect of working memory is important to detect and spatial span task is designed to detect these deficits\textsuperscript{57,58}. Therefore, the KINARM robotic trail making and spatial span tasks are ideal for the use of detecting cognitive deficits in the TIA population. The increased parameter that can be measured through robotics can lead to more sensitive detection and discrimination between TIA and migraine patients.
Chapter 2

Hypotheses, Objectives, and Study Design

The current definition of TIA has been brought into question based on prolonged symptoms seen beyond the defined 24hrs. Cognitive deficits have been reported as persistent symptoms in the TIA population. Traditional assessment of cognitive impairment rely on neuropsychological testing which can be subjective and limited in ability to discriminate between clinically similar presenting conditions such as migraine. The use of robotics as an assessment tool could potentially decrease subjectivity and increase discriminative ability in measuring cognition. Also, robotic tools can measure different parameters during cognitive tasks beyond that of manual neuropsychological testing and thus, potentially increasing the sensitivity of detecting cognitive deficits. Robotic assessment of TIA patients has not previously been studied. The KINARM exoskeleton robot has newly created cognitive tasks that have not previously been tested on any patient population. Based on this information three main objectives and hypothesis have been developed for this study.

*Hypothesis 1*: Robotic assessment using the KINARM will be more sensitive to impairments in cognition than current psychological testing.

*Objective 1*: To determine if the KINARM exoskeleton robot can detect cognitive impairment in patients that may potentially elude current neuropsychological testing.
**Hypothesis 2:** Some patients will experience improvements in cognition over the year timespan while others may experience declines characteristic of the increased risk of dementia post TIA.

**Objective 2:** To characterize the temporal changes in TIA patient cognition over the span of one year.

**Hypothesis 3:** Robotic assessment will be better than current testing at discriminating between conditions with similar symptoms such as migraine and TIA.

**Objective 3:** To determine if the KINARM cognitive tasks parameters can discriminate between TIA patients and the similarly presenting migraine patients.

**Study Design**

A prospective cohort study with active controls was conducted to meet the aforementioned objectives. Comparisons of the trail making and spatial span KINARM cognitive tasks to the MoCA was done on the basis of detection of cognitive impairment. As cognitive impairment in TIA patients has been linked to development of dementia, detecting these deficits early may lead to better prevention of cognitive decline. The KINARM tasks are administered at different time points to determine temporal changes in cognition. Characterizing these temporal changes are important in understanding the progressing of cognitive decline in TIA patients. Finally, migraine patients were selected as active controls to test the MoCA and KINARM tasks discriminative ability. Since, migraine patients experience similar symptomology to TIA patients, tests that can detect differences between the two clinically similar patient groups are needed. Consistent with the definition of active controls the migraine patients will continue to receive regular health care and monitoring as will the TIA patients. Both patient groups will receive the same tested with the same KINARM tasks as well. Each of these aspects of the study design bring something important to the understanding of TIA patient cognition and the ability of the robotic KINARM to assess these cognitive deficits.
Chapter 3

Materials and Methods

3.1 Patient Recruitment

This prospective cohort study recruited from a single institute, the Stroke Prevention Clinic at Kingston General Hospital (KGH). The study was assessed by the KGH research ethics board and was approved for meeting all hospital research guidelines. Participants were informed of the study and asked, at their regular stroke prevention clinic appointment, to participate by their neurologist and principal investigator of the study Dr. Albert Jin. Informed written consent was acquired from all participants at their first official visit to the study facilities also located in KGH. Recruitment was categorized into two main study groups. The TIA group (n=20) comprised of patients diagnosed with their first-ever TIA/mini-stroke with complete resolution of clinical symptoms within 24 hours. The active control group (n=11), consisted of participants with a diagnosis of migraine. Both patient groups were examined within 14 days of their symptom onset. Exclusion criteria for both study groups included: history of stroke/TIA, limitation to upper limb movement, inability to understand KINARM instructions, and non-corrective visual impairment.

A number of steps were taken to ensure patient confidentiality. Upon the first visit patients were given a 4 digit subject key which became their only form of subsequent identification. A password protected file with patient name and subject key was the only link to the patient’s identity. All clinical and KINARM assessments at each visit as well as all databases used to store performance information strictly used the 4 digit subject key to represent study participants.
3.2 Clinical Data Collection

An extensive clinical assessment was done on all potential TIA recruits to determine if the patient was suitable for the study. The “Kingston TIA-KINARM Clinical Data collection form” displays the scores and notes for each of the pre-recruitment assessments performed on the TIA patients (Appendix B). In the first section risk factors such as hypertension, diabetes, and smoking were noted. The next section was the results of the medical research council (MRC) scale for muscle strength. The MRC scale assesses muscle strength using a scale of five. Full strength received the maximum five score and no movement received a score of zero. Next, a TIA specific assessment score, the ABCD² scale (age, blood pressure, clinical features, duration of TIA, and presence of diabetes) was recorded. This recently developed eight point scale helps predict the risk of stroke. The NIHSS score was also recorded on the clinical assessment form. The NIHSS is an objective clinical neurological assessment. The location of the TIA was also recorded either based on imaging or if not apparent based on symptoms displayed by the patient.

There were four major syndromes reported: total anterior circulation syndrome (TACS), lacunar syndrome (LACS), partial anterior circulation syndrome (PACS), or posterior circulation syndrome. Imaging results were documented as were the results of visual field analysis.

All clinical data collected for each patient was transferred to a password protected spreadsheet document. Only the 4 digit subject key was used to identify the participants on both the hard and soft copies of the documents. Missing information was represented by the “999” value on the spreadsheet file. The hardcopy of the clinical assessments were kept in a locked cabinet in a secure location.
3.3 The Montreal Cognitive Assessment (MoCA)

The MoCA is a widely used short assessment of cognition with a total of 8 sections. The original version of the MoCA was used in this study (see Appendix A). The first section tested visuospatial and executive functioning with a small trail making task, redrawing a cube, and the clock drawing task. The second section tested naming ability through identifying 3 animals. Next attention span was tested through repetition of a series of numbers, letters, and counting down from 100. Language was tested by repetition of sentences and stating as many words as possible beginning with the letter “F”. Abstraction was the next section which tested the subject’s ability to make connections between words such as train and bicycle. A section on delayed recall tested the participant’s ability to recall a list of words stated to them earlier. The final section was orientation which tested the participant’s awareness of the current date, time, and location. In this study both study groups were administered the MoCA. The control group had only 2 visits and was assessed with the MoCA at both time points (see study protocol). The TIA group had 5 visits total however, the MoCA was only given on the first and last visit. The same version was administered at each session for both study groups. After each session all MoCA scores were uploaded onto a database with the assigned subject key. Any MoCA values that were not recorded or missing were represented by “-2” value in the database. The test paper was then filled away in a secure location.
3.4 The KINARM

The KINARM is manufactured by BKin Technologies. There are two styles of this robotic assessment tool available for research purposes. The exoskeleton robot employed for this study, placed the participant in a seated position with arms secured to arm plates which provided gravitational support and free range of motion in the horizontal plane (Figure 3.1). The machine was calibrated for each participant’s differing dimensions. This includes the individual’s arm and forearm length as well as elbow angle. Tasks were carried out on a black screen in-front of the participant in the horizontal plane just above the level of the arms. This screen serves as a virtual system where the participant’s arms are blocked from their vision. Instead, a white dot represented the position of the index finger in the virtual system. This dot allowed the participant to perform tasks where their own arm movement was mimicked by the movement of the dot on the screen.
Figure 3.1: KINARM Exoskeleton Apparatus. **Left** (Anterior View): The individual is seated, fitted comfortably in the machine, and wheeled towards the virtual system. **Right** (Posterior View): The black screen in-front of the participant serves as the virtual system where all of the tasks are carried out.
3.4.1 Task 1: Trail Making Task

The first of the cognitive tasks carried out by the participants was the trail making task (TMT). There are two types of the TMT that have been proven to assess different aspects of cognition, trail-A and trail-B. The KINARM versions of these tests are virtually identical to the pen and paper versions with the exception of how the tasks are carried out. Within the KINARM, trail-A involved connecting a series of 25 numbered targets in sequential order (Figure 3.2). Trail-B involved alternating between numbered and lettered targets (1-A-2-B) (Figure 3.2). Both trail-A and trail-B each had 25 targets and participants were asked to complete them as quickly as possible. Using the white dot representing the index finger, the participants scrolled towards and landed on the correct target. Once there, the target turned green and the participants continued to the next target. If a mistake was made, the last correct target appeared red and the participants had to return to that target to continue. There were 200 variations of the arrangement of targets for each of the KINARM TMT. This allowed for a different arrangement to be used for each participants visit.

The KINARM TMT measured five parameters for both trails. Total time measured time from initiation of the task until the last target was touched. Dwell time was the total amount of time spent on a target before moving to the next target in the sequence. $2^{nd}$ half/$1^{st}$ half time was the time it took to complete targets 13-25 divided by the time to complete targets 1-12. Total time B/total time A measured the total time of trail-B divided by total time of trail-A. Finally, error count was the total number of errors made.
Figure 3.2 Trail-A vs Trail-B. This is a scaled down representation of the information received on a participant’s performance with in the KINARM TMT. The top panel shows the numeric test of trail-A with its 25 targets. The bottom panel shows trail-B with its alternating alpha numeric targets. Trail-B also has 25 targets starting at 1 and ending at 13.
3.4.2 Task 2: Spatial Span

This task measured visuospatial working memory through the presentation of a sequence of targets in a 3x4 grid. The grid of 12 boxes was displayed to the participant on the black screen. Boxes were lit up in a random order for a total of 18 trails. For each trial, the participant was asked to memorize the order of lit boxes and duplicated the sequence by scrolling over and pausing on the correct boxes in order. The length of the first sequence was only 4 targets. However, if the participant got a trial right the length of the sequence increased by 1. This continued to a maximum sequence length of 12. If the participant got the sequence wrong the length of the sequence was reduced by 1 to a minimum length of 1.

There were seven parameters measured for the spatial span task (SST). Total score was the sum of the scores from trials 3-18. The score is defined as the length of the sequence for all correct trials and as the length of the sequence minus one for all incorrect trials. Means Score was the mean score for trials 3-18. Total time was the amount of time taken to complete the task. Time per target was calculated by dividing the total time by the total number of targets presented during the task. Longest correct sequence was the number of targets in the longest trial that the participant got correct. Shortest failed sequence was the least number of targets in a trail in which the participant completed incorrectly. Unfinished sequences were the number of trials in which the participant failed to repeat the sequence in the allotted time. The participant was allotted 
\((n+1)*3\) seconds to repeat the sequence. The value “n” was the number of targets in that sequence. Therefore, for a 5 target sequence 18 seconds was allotted to repeat the sequence.
3.5 Study Protocol

After recruitment the participants were scheduled to attend their first study visit. It was at the first visit that informed written consent was obtained from the participant. Two copies of the consent form were signed one was given to the participant and the other was filed away. The participant was also informed that they were free to discontinue their participation in the study at any time. The testing for the first visit entailed administration of the MoCA, a written cognitive screening tool graded out of 30 total points (see Appendix A). The participants were also run through both the KINARM TMT and SST. After the first visit there were differences in protocol for the TIA and active control group. The TIA group was subjected to 5 total visits: visit 1 occurred within 2 weeks of the TIA, visit 2 occurred six weeks post-TIA, visit 3 at 12 weeks post-TIA, visit 4 at six months post-TIA, and finally visit 5 at one year post-TIA. Visits 2-4 only included administration of KINARM tasks without MoCA testing. The final test date, visit 5, had both KINARM tasks and MoCA administered mimicking the protocol of the first visit. The active control group was only subjected to two identical visits: visit 1 just after recruitment and visit 2 one year after visit 1. Both visits for the control group involved KINARM TMT and SST as well as MoCA testing.

**NOTE:** Due to differences in the initiation of the TMT (March 2013) and SST (August 2013) the protocols for participants were identical however the cohort of participants differ. Those participants recruited to the study after the SST was added to the protocol will have completed both TMT and SST. The cohort recruited before SST was added to the protocol will have only TMT data collected. Thus, more participants completed the TMT as compared to the SST.
3.6 Statistical Analysis

Those participants scoring <26 on the MoCA were classified as impaired. Each TMT parameters (except error count) had associated Z-scores derived from a cohort of age matched healthy individuals. That is to say, healthy people from the general public were recruited previous to this study to generate normative data. Thus, a participant is considered impaired if the absolute value of their Z-score is greater than 1.96. The following sub-groups were created based on the aforementioned cut-offs: TIA impaired, TIA non-impaired, control impaired, and control non-impaired. Due to the novelty of the SST not enough normative data has been collected. Therefore, there are no Z-scores for the SST parameters.

A one-way ANOVA was used to determine significant changes in TIA group performance over time. Student’s t-test was used to determine differences between TIA and control group performance on the MoCA, TMT, and SST. Chi-squared analysis was used to determine the discriminative ability of the MoCA and TMT parameters based on the sub-groups derived from impaired and non-impaired cut-offs. Correlational analysis was also completed for MoCA vs KINARM TMT as well and TMT vs SST and SST vs MoCA. An α value ≤ 0.05 was used to determine significance in all instances.

Note: the healthy population derived Z-scores for all the TMT parameters (except error count) allow for an addition layer of analysis and comparison. Not only are the participants, active controls and TIA patients, compared to each other but also to the healthy/normal population through their Z-scores.
Chapter 4

Results

4.1 Participants

A total of 31 participants were recruited for the TMT between March 2013 and August 2014. Of those recruited, 20 belonged to the TIA group and 11 were a part of the active controls. The mean age ± standard deviation (SD) for the TIA group was 66 ± 11.3. The control group had a mean age of 62 ± 14.5 SD. The percentage of males was 45% for both TIA (n=9) and control (n=5) group. No significant difference was noted for age or sex between the TIA and control groups.

For the SST a total of six controls and 10 TIA patients were recruited between August 2013 and August 2014. These subjects were a subset of the 31 participants recruited for the TMT. The mean age ± standard deviation is 68 ± 10.5 for the TIA group and 65 ± 14.6 for the control group. The control group is comprised of 50% males (n=3) while the TIA group is comprised of 30% males (n=3). There is no significant difference in age between the two study groups.

Since the TIA group must complete five visits for this study there are varying degrees of completion at this point. For the TMT 14 (70%) TIA group members have progressed to visit two while five (50%) participants have progressed for the SST. Twelve (60%) TMT participants completed the third visit while four (40%) have completed the SST. Five (25%) subjects have completed visit four for the TMT. No participants have completed visit four for the SST. A total of eight (40%) participants have completed the final year visit for the TMT and one (10%) has for the SST. Visit four has the lowest compliance with four TMT participants and one SST participant missing/not completing the visit.
4.2 MoCA Performance

On the first visit the TIA group MoCA scores ranged from 16 to 30 while the control group scores ranged from 23 to 30. A cutoff of 25 and below is used to determine cognitive impairment. Based on the cutoff, at visit 1, seven (35%) participants from the TIA group were classified as impaired and only two (18%) of the control group participants. Chi squared analysis of the subgroups determined no significant difference (p=0.32) between the TIA and control group MoCA scores. For the final visit (year visit) only five TIA and two control group participants have reached this point. Chi squared analysis determined no significant (p=0.15) difference between the TIA and control group at the one year visit. Three participants in the TIA group were impaired at the final visit. Only one of those participants was impaired at the first visit. At the final visit none of the control participants were impaired based on MoCA cut-offs.

There was also no significant difference in the mean MoCA scores for the TIA and active control group (mean = 26.3 and 27, respectively). From Figure 4.1, a significant correlation between TIA group MoCA score and age can be seen at visit 1 (r1=-0.53, p=0.02). However, no significant correlation between active control MoCA score and age was noted.
Figure 4.1 MoCA scores vs age for TIA and active control study group. Student’s t-test determined no significant improvement in MoCA performance over time for both study groups. Pearson’s correlation analysis was performed for correlations with MoCA scores and age. **Top:** is a scatterplot showing the relationship between MoCA score and age for the TIA study group. A significant correlation between TIA MoCA score and age (r_{visit1}=-0.53, p<0.02). **Bottom:** shows the active control MoCA scores at their first visit and one year later. No significant correlation with age is seen for the control group.
4.3 KINARM Trail Making Task Performance

Comparison of TIA and control study groups using each of the KINARM TMT parameters was done. Table 1 displays the mean values for each TMT parameter. Trail B total time and error count had significantly different mean values between the two study groups; while Trail A total time was also found to be significantly different between the groups.

Table 4.1. KINARM Trail Making Parameter Mean Values.

Mean values for both TIA and control study group performance is displayed below. Student’s t-test was performed to determine any significant differences in the means of the two study groups.

<table>
<thead>
<tr>
<th>Mean Values</th>
<th>TIA (n=20)</th>
<th>Controls (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Time (s):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>55.4*</td>
<td>39.1*</td>
</tr>
<tr>
<td>Trail-B</td>
<td>96.9*</td>
<td>58.6*</td>
</tr>
<tr>
<td><strong>Dwell Time (s):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>19.8</td>
<td>15.4</td>
</tr>
<tr>
<td>Trail-B</td>
<td>43.6</td>
<td>34.3</td>
</tr>
<tr>
<td><strong>2\textsuperscript{nd} Half/1\textsuperscript{st} Half Time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>0.79</td>
<td>0.81</td>
</tr>
<tr>
<td>Trail-B</td>
<td>1.14</td>
<td>1.13</td>
</tr>
<tr>
<td><strong>Error Count</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>1.74</td>
<td>1.55</td>
</tr>
<tr>
<td>Trail-B</td>
<td>3.90*</td>
<td>1.27*</td>
</tr>
<tr>
<td><strong>Total Time B/Total Time A</strong></td>
<td>1.84</td>
<td>1.67</td>
</tr>
</tbody>
</table>

*Significant difference between the TIA and the control group where \( \alpha \leq 0.05 \).
Impaired and non-impaired subgroups were derived from Z-scores for each parameter with the exception of error count. Table 4.2 displays the subgroups derived from the performances at the first visit. Despite the small sample size chi squared analysis showed a trend in difference between the control and TIA subgroups for total time trail-B (p=0.07).

At the first visit, a total of eight (40%) TIA group members were categorized as impaired for at least one TMT parameter. Three (15%) TIA individuals were impaired in at least one parameter for both trail-A and trail-B. Trail-B captured the most impairment with eight TIA and two (18%) controls having impaired performance in at least one parameter. Only two controls had impaired performance on trail-A parameters.

At the year visit only three (37.5%) TIA group members had impairment in at least one TMT parameter. One of the TIA participants had impairment in at least parameter for both trail-A and trail-B. Trail-B total time and dwell time identified the most impairment with three TIA participants. None of the controls were classified as impaired in for trail-A parameters at the year visit. Only one control (50%) was classified as impaired for trail-B time ratio at the year visit.
Both TIA and control study groups were subdivided into impaired and non-impaired subgroups based on performance at their first visit. Subgroups were determined using Z-scores derived from normative data where an absolute value greater than 1.96 was considered impaired. Chi squared analysis was performed to determine differences between TIA and control subgroups.

<table>
<thead>
<tr>
<th></th>
<th>TIA Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Impaired</td>
<td>Non-Impaired</td>
</tr>
<tr>
<td><strong>Total Time (s)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Trail-B</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td><strong>Dwell Time (s)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Trail-B</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td><strong>2nd Half/1st Half Time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Trail-B</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total Time B/Total Time A</strong></td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>

$ missing one control value.
Pearson correlational analysis was used to test significance for each parameter and the age of the participants. Critical values were determined based on a two tailed test with $\leq 0.05$ as the level of significance. The TIA group was analyzed at five different time points for both trail A and B (Figures 4.2-4.8). Time ratio was also tested for correlation with age although it was not graphed since it is not well interpreted graphically. Significant correlations with age were noted for trail-A total time and time ratio ($p<0.01$ and $p<0.05$). TIA group trail-B total time ($p<0.01$) and dwell time ($p<0.05$) were also strongly correlated with age (Figures 4.2 and 4.3). Significant correlations were found for the control group trail-A total time ($p<0.02$) and dwell time ($p<0.02$) at the first visit (Figures 4.9-4.12). No significant correlations were found for the control group Trail B parameters and age.

Correlational analysis for trail-A and trial-B parameters were also done. For the TIA group trail-A and trial-B test time had a significant correlation. All other TMT parameters were not strongly correlated for the TIA group. The control group had a strong, but non-significant correlation between trail-A and trail-B dwell time. None of the control group parameters were found to be significantly correlated between trails A and B.

Performance improvements in TMT were noted overtime (Figure 4.2-4.12). ANOVA F values determined no significant change in mean values for all parameters over all visits. Paired t-tests for the TIA groups first and second visits (n=14) revealed significant improvements in trail-A test time ($p<0.01$) as well as trail-B test time ($p<0.05$) and error count ($p<0.05$) (Figures 4.2, 4.5, and 4.7). Analysis of control group performance for both trail-A and B between their first and last visit yielded no significant improvement in any of the parameters (Figures 4.9-4.12).
Figure 4.2. TIA Group KINARM TMT Trail-A Total Time Results Per Visit. Pearson correlational analysis was done to determine r values and their significance (critical r=0.444). A significant correlation between trail-A test time and age is noted ($r_{visit}=0.53$). Top: shows the participant performance on trail-A TMT for visits 1 and 2. Student’s t-test determined significant improvements in time between the two visits ($p<0.05$). Bottom: shows visits 3 to the final year visit.
Figure 4.3. TIA Group KINARM TMT Trail-A Dwell Time Results Per Visit. Pearson correlational analysis was done to determine r values and their significance (critical r=0.444). Both graphs show a lack of correlation between trail-A dwell time and age. **Top**: displays improvements in trail-A dwell time from the first and second visit although not significant. **Bottom**: shows performance in dwell time from visits 3 to the final year visit.
Figure 4.4. TIA Group KINARM TMT Trail-A Error Count Results Per Visit. Pearson correlational analysis was done to determine r values and their significance (critical r=0.444). Both graphs show a poor correlation between trail-A error count and age. **Top:** shows error count performance at visits 1 and 2 for trail-A. Some improvement is seen although not significant. **Bottom:** shows error count performance at visits 1 to the final year visit.
Figure 4.5. TIA Group KINARM TMT Trail-B Total Time Per Visit. Pearson correlational analysis was done to determine r values and their significance (critical r=0.444). Correlation between trail-B total time and age is significant (r_{visit}=0.598). Significant improvement in trail-B total time from visit 1 to 2 is noted. Top: A major outlier is seen with total times double that of others at each visit. Bottom: trail-B total time for visits 3 to 5. No significant improvements.
Pearson correlational analysis was done to determine r values and their significance (critical \( r = 0.444 \)). A significant correlation is seen between trail-B dwell time and age (\( r_{\text{visit}} = 0.48 \)). **Top:** Trail-B dwell time for visits 1 and 2 with no significant improvement. **Bottom:** Dwell time for visits 3-5.
Figure 4.79. TIA Group KINARM TMT Trail-B Error Count Per Visit. Pearson correlational analysis was done to determine r values and their significance (critical r=0.444). A strong but non-significant correlation between error count and age can be seen ($r_{\text{visit1}} = 0.33$). **Top:** Number of errors for trail-B at visits 1 and 2 are seen to significantly improve. **Bottom:** Error count for visits 3-5.
Figure 4.8. TIA Group KINARM TMT Total Time-B/Total Time-A Per Visit. Pearson correlational analysis was done to determine r values and their significance (critical r=0.444). A correlation between TT-B/TT-A and age can be seen although non-significant. **Top:** No significant improvements are seen between visits 1 and 2. **Bottom:** Performance at visits 3-5 are less easily distinguishable.
Figure 4.9. Control Group KINARM TMT Trail-A and Trail-B Total time Per Visit. Pearson correlational analysis was done to determine r values and their significance (critical $r=0.602$). No significant improvement was seen in either trail-A or B between the first and the second visit based on student t-test analysis. **Top:** A significant positive correlation with trail-A total time and age at the first visit is seen ($r=0.69$). **Bottom:** There is no strong correlation with age ($r=0.28$).
Figure 4.10. Control Group KINARM TMT Trail-A and Trail-B Dwell time Per Visit. In both trails A and B improvements in dwell time performance can be seen. Student’s t-test analysis showed no significance. Pearson correlational analysis was done to determine r values and their significance (critical r=0.602). **Top:** A significant positive correlation with age and dwell time is seen (r=0.73). **Bottom:** No strong correlation with age and dwell time is noted.
Pearson correlational analysis was done to determine r values and their significance (critical $r=0.602$). **Top**: A positive trend can be seen although not significant ($r=0.58$). **Bottom**: The first and the last visit show opposing non-significant trends.

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**Figure 4.11. Control Group KINARM TMT Trail-A and Trail-B Error Count Per Visit.**
Figure 4.12. Control Group KINARM TMT Total Time-B/Total Time-A Per Visit. Pearson correlational analysis was done to determine r values and their significance (critical r=0.602). No significant correlation with age was determined. Student’s t-test determined no significant improvements over time were seen although individual improvement is evident.
4.4 Trail Making Task Vs MoCA

Correlative comparison of KINARM parameters and MoCA scores were done for both TIA and control group (Table 4.3). The TIA group had a strong correlation between trail-A error count and MoCA score. All other trail-A parameters were not significantly correlated with MoCA scores. Trail-B test time and error count were also strongly correlated with MoCA scores of the TIA group. The control group had no significant correlations between KINARM parameters and MoCA scores.

Table 4.3: KINARM Trail Making Parameter vs MoCA scores Correlative (r) Values

Pearson’s correlational analysis was run to determine correlations between MoCA performance and TMT parameters as per first visit. Critical r values for each of the groups were determined using a two tailed 0.05 level of significance. For the TIA group (n=20) the critical r value was 0.444 and for the control group (n=11) the critical value was 0.602.

<table>
<thead>
<tr>
<th></th>
<th>TIA (n=20)</th>
<th>Controls (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Time vs MoCA:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>-0.33</td>
<td>-0.08</td>
</tr>
<tr>
<td>Trail-B</td>
<td>-0.47*</td>
<td>-0.47</td>
</tr>
<tr>
<td><strong>Dwell Time vs MoCA:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>0.03</td>
<td>-0.47</td>
</tr>
<tr>
<td>Trail-B</td>
<td>-0.25</td>
<td>-0.19</td>
</tr>
<tr>
<td><strong>2nd Half/1st Half Time vs MoCA:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>0.19</td>
<td>-0.41</td>
</tr>
<tr>
<td>Trail-B</td>
<td>0.05</td>
<td>-0.30</td>
</tr>
<tr>
<td><strong>Error Count vs MoCA:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail-A</td>
<td>-0.48*</td>
<td>0.11</td>
</tr>
<tr>
<td>Trail-B</td>
<td>-0.50*</td>
<td>-0.32</td>
</tr>
<tr>
<td><strong>Total Time B/Total Time A vs MoCA:</strong></td>
<td>-0.45</td>
<td>-0.19</td>
</tr>
</tbody>
</table>

*Significant correlation between trail making task parameter and MoCA score where α ≤0.05.
4.5 KINARM Spatial Span Task Performance

Comparison of TIA and control study groups using each of the KINARM SST parameters was done. Table 5 displays the mean values for each SST parameter. Time per target is the only parameter to show a significant difference between the TIA and control group.

Table 4.4: KINARM Spatial Span Parameters Mean Values
Mean values are stated in the table below where a Student’s t-test was performed to determine significant differences in TIA and control group performance.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>TIA (n=10)</th>
<th>Controls (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td>58.1</td>
<td>68.7</td>
</tr>
<tr>
<td>Mean Score</td>
<td>3.65</td>
<td>4.33</td>
</tr>
<tr>
<td>Test Time (s)</td>
<td>243</td>
<td>233</td>
</tr>
<tr>
<td>Time Per Target (s)</td>
<td>2.33*</td>
<td>1.58*</td>
</tr>
<tr>
<td>Longest Correct Path</td>
<td>5.00</td>
<td>5.50</td>
</tr>
<tr>
<td>Shortest Failed Path</td>
<td>3.50</td>
<td>3.67</td>
</tr>
<tr>
<td>Timeout Count</td>
<td>2.40</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*Significant difference between spatial span parameter of TIA group vs control group where $\alpha \leq 0.05$. 
Unlike the TMT, the spatial span task has no Z-scores derived from normative data as of yet. Therefore, no impaired and non-impaired subgroups were made. Thus, no chi squared analysis was done for the SST set of data.

Pearson correlational analysis was run for each parameter and the age of the participants. Critical values were determined based on a two tailed test with ≤0.05 as the level of significance. The TIA and control group performance in each parameter is seen in Figures 4.13 to 4.19 at each time point. Only one participant has completed the final visit and that participant has missed the fourth visit. Thus, there is no data collected for the six month (4th visit) time point. None of the controls performance on the SST parameters were significantly correlated with age. In the TIA group five of the seven parameters had strong correlations with age at the first visit. Significant inverse correlations are seen between age and total score (p<0.02), mean score (p<0.02), and longest correct path (p<0.05). For the TIA group significant positive correlations are found between time per target (p<0.01) and timeout count (p<0.05).

Performance improvements in SST were noted overtime (Figure 4.13-4.19). ANOVA F values showed no significant change in mean values for all parameters over all visits. Paired t-tests for the TIA groups first and second visits (n=5) revealed significant improvements in shortest failed path and timeout count (p<0.05) (Figures 4.18 and 4.19). Since none of the SST control group participants have completed their second and final visit analysis for improvement overtime was not done.
Figure 4.13. Control and TIA Group KINARM SST Total Score. Pearson correlational analysis was done to determine r values and their significance (critical $r=0.811$ and $0.632$ for control and TIA group respectively). **Top:** Weak negative correlation with age and total score can be noted with the control group. **Bottom:** A strong significant negative correlation is seen between TIA group total score and age ($r=-0.73$). Performance improvements over time are not significant.
Figure 4.14. Control and TIA Group KINARM SST Mean Score. Pearson correlational analysis was done to determine $r$ values and their significance (critical $r=0.811$ and 0.632 for control and TIA group respectively). **Top:** No strong correlation with age and control mean score is seen. **Bottom:** A significant negative correlation with mean score and age can be noted for the TIA group ($r=-0.73$).
Figure 4.15. Control and TIA Group KINARM SST Test Time. Pearson correlational analysis was done to determine r values and their significance (critical r=0.811 and 0.632 for control and TIA group respectively). Top: Control group correlation with test time and age is weekly negative and insignificant. Bottom: A strong but non-significant correlation between TIA group test time and age is seen at visit 1 (r=0.54). No significant improvement in TIA test time is noted over time.
Figure 4.16. Control and TIA Group KINARM SST Time Per Target. Pearson correlational analysis was done to determine r values and their significance (critical r=0.811 and 0.632 for control and TIA group respectively). **Top:** A slight positive correlation with the control group time per target and age can be seen (r=0.21). **Bottom:** A strong positive correlation between TIA group time per target and age is noted at visit 1 (r=0.78).
Figure 4.17. Control and TIA Group KINARM SST Longest Correct Path. Pearson correlational analysis was done to determine r values and their significance (critical r=0.811 and 0.632 for control and TIA group respectively). **Top:** Virtually no correlation with age and longest correct path is seen for the control group. **Bottom:** The TIA group has a significant inverse correlation between age and longest correct path (r=-0.64). No significant improvements over time is noted.
Figure 4.18. Control and TIA Group KINARM SST Shortest Failed Path. Pearson correlational analysis was done to determine r values and their significance (critical r=0.811 and 0.632 for control and TIA group respectively). **Top**: There is no evident correlation between control group age and shortest failed path. **Bottom**: The TIA group has a weak correlation with shortest failed path and age (r=-0.59) but not significant. Between the first and second visit a significant improvement in shortest failed path is seen.
Figure 4.19. Control and TIA Group KINARM SST Total Score. Pearson correlational analysis was done to determine r values and their significance (critical r=0.811 and 0.632 for control and TIA group respectively). **Top**: A strong but non-significant invers correlation with age and timeout count can be seen for the control group (r=- 0.75). **Bottom**: The TIA group has a significant positive correlation with age and timeout count (r=0.69). Student’s t-test determined a significant improvement in performance between the first and second visits (p<0.05).
4.6 Spatial Span Task vs MoCA

Correlative comparison of KINARM SST parameters and MoCA scores were done for both TIA and control group using Pearson’s correlation r values (Table 6). The TIA group had significant positive correlations between total score vs MoCA and test time vs MoCA. All parameters were not significantly correlated with MoCA scores for the TIA group. The control group had no significant correlations in performance on the spatial span task parameters and the MoCA.

Table 4.5: KINARM Spatial Span Parameters vs MoCA Scores Correlative (r) Values

Pearson’s r values are stated below with the critical value of 0.632 for the TIA group and 0.811 for a two tailed 0.05 defined level of significance. Correlations were determined for the study groups MoCA and SST parameter performance on their first visit.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>TIA (n=10)</th>
<th>Controls (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score vs MoCA</td>
<td>0.64*</td>
<td>0.34</td>
</tr>
<tr>
<td>Mean Score vs MoCA:</td>
<td>0.62</td>
<td>0.35</td>
</tr>
<tr>
<td>Test Time vs MoCA</td>
<td>0.70*</td>
<td>0.52</td>
</tr>
<tr>
<td>Time Per Target vs MoCA</td>
<td>-0.63</td>
<td>0.30</td>
</tr>
<tr>
<td>Longest Correct Path vs MoCA</td>
<td>0.50</td>
<td>0.57</td>
</tr>
<tr>
<td>Shortest Failed Path vs MoCA</td>
<td>0.57</td>
<td>0.06</td>
</tr>
<tr>
<td>Timeout Count vs MoCA</td>
<td>-0.51</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Significant difference between spatial span parameter and MoCA score where α=0.05.
4.7 Trail Making Task vs Spatial Span Task

Correlational analysis was performed between the two KINARM tasks. Spatial span and trail making tasks A and B parameters were compared for the TIA group performance (Tables 7 and 8) as well as the control group performance (Tables 9 and 10). Only those participants that completed both TMT and SST (n=10; TIA group and n=6; control group) were included in this correlational analysis. The TIA group had significant correlations in trail-A error count vs SST total score, mean score, test time, and time per target (Table 7). For trail-B performance the TIA group had significant correlations with SST total score, mean score, shortest correct failed path, and timeout count. Among all the correlations between control group TMT and SST parameter performance, only trail-A dwell time and SST time out count had a significantly negative correlation (Table 10).
Table 4.6. TIA Spatial Span Task vs Trail Making Task Trail-A Correlation
Pearson’s $r$ values are stated below with the critical value of 0.632 for the TIA group and 0.811 for a two tailed 0.05 defined level of significance.

<table>
<thead>
<tr>
<th></th>
<th>Total score</th>
<th>Mean score</th>
<th>Test time</th>
<th>Time per target</th>
<th>Longest correct path</th>
<th>Shortest failed path</th>
<th>Timeout count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Time</td>
<td>0.04</td>
<td>0.07</td>
<td>0.06</td>
<td>0.10</td>
<td>0.07</td>
<td>0.19</td>
<td>0.46</td>
</tr>
<tr>
<td>Dwell Time</td>
<td>-0.10</td>
<td>-0.05</td>
<td>0.28</td>
<td>-0.16</td>
<td>-0.26</td>
<td>-0.23</td>
<td>0.58</td>
</tr>
<tr>
<td>Time Ratio</td>
<td>-0.02</td>
<td>-0.02</td>
<td>0.0001</td>
<td>-0.14</td>
<td>-0.01</td>
<td>-0.22</td>
<td>-0.33</td>
</tr>
<tr>
<td>Error Count</td>
<td>-0.66*</td>
<td>-0.66*</td>
<td>-0.72*</td>
<td>0.73*</td>
<td>-0.46</td>
<td>-0.52</td>
<td>0.53</td>
</tr>
</tbody>
</table>

*Significant difference between spatial span parameter and TMT trail-A parameters where $\alpha=0.05$.

Table 4.7. TIA Spatial Span Task vs Trail Making Task Trail-B Correlation
Pearson’s $r$ values are stated below with the critical value of 0.632 for the TIA group and 0.811 for a two tailed 0.05 defined level of significance.

<table>
<thead>
<tr>
<th></th>
<th>Total score</th>
<th>Mean score</th>
<th>Test time</th>
<th>Time per target</th>
<th>Longest correct path</th>
<th>Shortest failed path</th>
<th>Timeout count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Time</td>
<td>-0.73*</td>
<td>-0.70*</td>
<td>-0.57</td>
<td>0.58</td>
<td>-0.62</td>
<td>-0.78*</td>
<td>0.64*</td>
</tr>
<tr>
<td>Dwell Time</td>
<td>-0.15</td>
<td>-0.10</td>
<td>0.24</td>
<td>-0.17</td>
<td>-0.33</td>
<td>-0.37</td>
<td>0.52</td>
</tr>
<tr>
<td>Time Ratio</td>
<td>-0.06</td>
<td>-0.08</td>
<td>-0.06</td>
<td>0.01</td>
<td>0.15</td>
<td>-0.26</td>
<td>-0.24</td>
</tr>
<tr>
<td>Error Count</td>
<td>-0.37</td>
<td>-0.35</td>
<td>-0.31</td>
<td>0.21</td>
<td>-0.27</td>
<td>-0.51</td>
<td>0.29</td>
</tr>
<tr>
<td>TMB/TMA</td>
<td>-0.47</td>
<td>-0.47</td>
<td>-0.38</td>
<td>0.32</td>
<td>-0.34</td>
<td>-0.63</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Significant difference between spatial span parameter and TMT trail-B parameters where $\alpha=0.05$. 
### Table 4.8. Control Spatial Span Task vs Trail Making Task Trail-A Correlation

Pearson’s $r$ values are stated below with the critical value of 0.632 for the TIA group and 0.811 for a two tailed 0.05 defined level of significance.

<table>
<thead>
<tr>
<th></th>
<th>Total score</th>
<th>Mean score</th>
<th>Test time</th>
<th>Time per target</th>
<th>Longest correct path</th>
<th>Shortest failed path</th>
<th>Timeout count</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Time</strong></td>
<td>-0.28</td>
<td>-0.31</td>
<td>0.16</td>
<td>0.56</td>
<td>0.30</td>
<td>0.18</td>
<td>-0.32</td>
</tr>
<tr>
<td><strong>Dwell Time</strong></td>
<td>-0.21</td>
<td>-0.27</td>
<td>0.03</td>
<td>-0.001</td>
<td>-0.06</td>
<td>0.33</td>
<td>-0.84*</td>
</tr>
<tr>
<td><strong>Time Ratio</strong></td>
<td>0.06</td>
<td>0.07</td>
<td>-0.32</td>
<td>-0.53</td>
<td>-0.26</td>
<td>-0.31</td>
<td>-0.15</td>
</tr>
<tr>
<td><strong>Error Count</strong></td>
<td>-0.35</td>
<td>-0.35</td>
<td>0.001</td>
<td>0.72</td>
<td>0.09</td>
<td>-0.33</td>
<td>-0.25</td>
</tr>
</tbody>
</table>

*Significant difference between spatial span parameter and TMT trail-A parameters where $\alpha=0.05$.

### Table 4.9. Control Spatial Span Task vs Trail Making Task Trail-B Correlation

Pearson’s $r$ values are stated below with the critical value of 0.632 for the TIA group and 0.811 for a two tailed 0.05 defined level of significance.

<table>
<thead>
<tr>
<th></th>
<th>Total score</th>
<th>Mean score</th>
<th>Test time</th>
<th>Time per target</th>
<th>Longest correct path</th>
<th>Shortest failed path</th>
<th>Timeout count</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Time</strong></td>
<td>-0.58</td>
<td>-0.58</td>
<td>-0.37</td>
<td>0.39</td>
<td>-0.70</td>
<td>-0.10</td>
<td>-0.46</td>
</tr>
<tr>
<td><strong>Dwell Time</strong></td>
<td>-0.32</td>
<td>-0.34</td>
<td>0.18</td>
<td>0.18</td>
<td>-0.29</td>
<td>0.23</td>
<td>-0.52</td>
</tr>
<tr>
<td><strong>Time Ratio</strong></td>
<td>0.27</td>
<td>0.29</td>
<td>0.51</td>
<td>0.15</td>
<td>-0.13</td>
<td>0.41</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Error Count</strong></td>
<td>-0.11</td>
<td>-0.08</td>
<td>-0.43</td>
<td>-0.20</td>
<td>-0.36</td>
<td>-0.26</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>TMB/TMA</strong></td>
<td>0.01</td>
<td>0.04</td>
<td>-0.23</td>
<td>-0.26</td>
<td>-0.58</td>
<td>-0.11</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Significant difference between spatial span parameter and TMT trail-B parameters where $\alpha=0.05$. 

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Chapter 5

Discussion

This study's objective is to determine the KINARM cognitive tasks' ability to assess and characterize TIA cognitive impairment. Recruited participants were assessed using the KINARM and the widely used MoCA. Studies using the MoCA have shown some individuals suffering a TIA with clinically resolved symptoms still experience prolonged cognitive deficits\textsuperscript{34,10}. Therefore, characterizing the temporal changes in cognition can be helpful in understanding the TIA patient population. Patients suffering from migraines experience similar symptoms to TIA\textsuperscript{23}. Thus there is a need to differentiate between these two patient groups for appropriate monitoring and treatment. Finally, understanding how the MoCA, TMT, and SST tasks relate and correlate can shed light on the KINARM cognitive tasks' ability to detect MCI in comparison to current screening tools like the MoCA. All of this is discussed in detail below to reach the ultimate goal of the study.

5.1 Study Group Demographics and Participation

Although the two study groups were not specifically age matched there was no significant difference in age between TIA and migraine participants. The increased mean age of the study groups (>60 years) is consistent with previous studies in the TIA and stroke population\textsuperscript{35}. The male-female ratio was identical for the two study groups with slightly more females than males. This statistic is to be expected in the migraine population as the prevalence of migraine is much higher in females\textsuperscript{19}. The equal ratio of sexes and similar ages in the two study groups helped eliminate some potential confounding factors in the study. Overall the demographics of the study groups were consistent with previous literature.
5.2 Detecting Cognitive Impairment in TIA Patient Population

Detecting cognitive impairment is often done through screening tools such as the MoCA. Previous studies with TIA patients have determined the MoCA to be sensitive and specific for detecting MCI\textsuperscript{33,35,37,39}. Therefore, the MoCA was an ideal assessment tool for the purposes of this study.

The MoCA was able to detect a substantial amount of cognitive deficits in the TIA study group although, the mean MoCA score at the first visit was 26.3 which is within the normal range. A study by Blackburn et al. (2013) detected a mean score of 21.8 within the first 14 days of a TIA\textsuperscript{35}. However, a study by Sivakumar et al. (2014) measured MoCA at 7 days post TIA and found 27 to be the average score\textsuperscript{5}. These discrepancies could be due in part to sampling and thus, more extensive research on MoCA detection of MCI in the acute phase post TIA (7-14 days) should be done. The TIA group had 35% of participants score in the impaired range at 14 days post TIA, which is consistent with the current literature. Rates as high as 46.2% of TIA patients with impaired MoCA scores at 14 days post TIA have previously been reported\textsuperscript{15}. Due to the low number of TIA participants that completed the final visit (n=5) there is a relatively high rate of cognitive impairment (60%) at that time point. Interestingly, the final MoCA visit was able to detect cognitive impairment in two patients who had initially scored in the normal range. These results suggest some cognitive decline in the TIA group (Figure 4.1). Correlations with the TIA group performance and age was also determined. This correlation may reflect the natural decline in cognitive function with age or it could suggest older TIA patients are more susceptible to cognitive impairment. To determine the cause of this correlation further research in the area of MoCA detection of cognitive impairment in the normal adult population must be done. The MoCA performance by the TIA group seems to show persistent cognitive deficits in the acute (7-14 days) phase and chronic (1 year) phase post TIA.
Within the migraine control study group the MoCA detected very little cognitive deficits. Only 18% of the control group was said to be cognitively impaired at their first visit based on the MoCA cutoff. Studies have shown migraine patients experience cognitive deficits during migraine attacks; however, there are mixed results as to whether these deficits are present between attacks\(^{59-61}\). There was no correlation with age and MoCA scores for the migraine control group with the majority of these participants showing no signs of MCI based on MoCA scores. This is consistent with previous studies that determined migraine patients lack cognitive impairment in the time period between attacks\(^{59-61}\). Therefore, based on the MoCA results migraine controls cognitive impairment is not seen post attack.

The trail making task is a validated test of cognitive faculties. Previous studies have determined the trail-A accurately detects visuoperceptual abilities, while trail-B detects working memory and task switching ability\(^{56}\). Thus, these tasks are tests of executive functions and can be used to recognize cognitive deficits\(^{55}\). Although the MoCA has a short trail-B test, it has been shown to have greatest detection of MCI in the stroke population based on memory deficits\(^{62}\). Previous investigation determined vascular cognitive impairment may in fact be linked to greater cognitive deficits in executive functions rather than memory\(^{62}\). Thus, the TMT may be better able to detect cognitive deficits that the MoCA may not. In addition, the use of robotic assessment tools increases the number of parameters that can be measured in a single task. For these reasons the KINARM TMT was used to assess MCI in the TIA population.

In this study the KINARM TMT was able to detect cognitive impairment based on a number of parameters. Identification of MCI at visit 1 was much greater with trail-B (n= 8 impaired TIA participants) than trail-A (n=3 impaired TIA participants). This may be due to the increased cognitive demand of task switching in trail-B\(^{55}\). The KINARM trail-B (n=8 impaired TIA participants) was able to detect slightly more impairment than the MoCA (n=7 impaired TIA participants) at the first visit indicating the trail-B robotic task may be more sensitive to detection.
of cognitive impairment in the TIA population. Both the TMT and the MoCA detected two control patients as impaired. This consistency in detecting cognitive deficits in the migraine group may mean the two tests are equally capable of detecting MCI in the migraine population. In this study, some correlations with TMT parameters and age were detected. Previous studies have found declines in TMT performance correlated with increased age. A study by Wecker et al. found reduced task switching ability to be strongly correlated with increased age. This is also seen in the present study as trail-B total time and dwell time were significantly correlated with age for both study groups. Further investigation is needed to determine whether the TMT has a greater sensitivity than the MoCA for detecting cognitive impairment in the TIA population.

The spatial span task is a test of working memory. Specifically the SST is used to assess immediate visuospatial memory. The working memory system is under executive control and therefore, the SST can be a secondary test of executive functioning as well. Spatial span deficits have also been linked to dementia in previous studies. The MoCA assess visuospatial abilities through clock and cube drawing task but does not specifically test the visuospatial aspects of working memory. Thus, there may be potential to capture more MCI patients with the SST KINARM task. There are several variations of the SST however the forward SST was used. This forward SST requires less mental manipulation than the reverse SST and has a reliability coefficient of 0.71 with a test retest reliability correlation of 0.71. It was due to these reasons that the SST was chosen as a KINARM cognitive task to use in this study of TIA patients.

The lack of normative data limits the ability of the KINARM SST to detect cognitive impairment. With future recruitment of normal individuals generation of normative data will allow for a better understanding of the task to assess cognitive deficits in the TIA population. Discriminative ability and study group performance overtime can still be assessed however. Previous studies using the SST have determined spatial span declines with age most evident in an individual’s sixties. In this study five of the seven SST parameters measured for the TIA group
were significantly correlated with age. The control group lacked any correlation with age for the SST parameters. This may be due to the low number of controls recruited for this task. Thus, the study findings for the TIA group are consistent with the current literature. Unfortunately, the ability to detect MCI was not able to be assessed at this time.

While the MoCA has been validated as a screening tool for MCI, there are many drawbacks to this neuropsychological test. Pen and paper tasks have a limited amount of measurements and their grading has the potential to be subjective. Also, previous studies have found the test to detect memory deficits best; however within the TIA and stroke population executive function loss is more prominent. Using the KINARM to detect cognitive impairment in the TIA population may be a valid alternative to these drawbacks. The results of this study have shown the ability of the TMT to detect a greater number of cognitively impaired TIA patients through its measurements of different parameters on a single trail. In the future, generation of normative data for the KINARM SST will allow for testing of its ability to detect cognitive impairment.

5.3 Discriminating between TIA and Migraine Patients

TIA and migraine patients have similar clinical presentation. Due to this fact, it is important to accurately detect differences between these two populations. Tests that can accurately discriminate between similar patient presentations are beneficial in the clinical and research world.

The MoCA’s ability to discriminate between TIA and migraine patients was poor. The mean MoCA score for the TIA (26.3) and migraine (27) groups were very similar; however, the range in scores was much larger for the TIA group. The result was no significant difference between the TIA and migraine study groups. This may reflect a limitation in the MoCA’s ability to discriminate between clinically similar patient populations.
In contrast, the KINARM TMT was capable of discriminating between the TIA and migraine groups based on 3 parameters. Trail-A total time, trail-B total time and error count were able to detect significant differences between the two study groups (Table 4.1). Thus, the TIA group took significantly longer than the migraine controls to perform each of the trails. Figure 5.1 shows the trail-A performance of a TIA patient. Deviation from a straight line when connecting targets could be the cause of increased total time. Future investigation into TIA patient movement between targets on the trail making task could be an added parameter that may differentiate between TIA and migraine patients. Also, the migraine study group had significantly less errors in selecting targets in the trail-B task. In general, trail-B has a slight advantage in discriminating between the two study groups and may be a better indicator of cognitive impairment. Since the MoCA was unable to detect differences in cognition between TIA and migraine participants the TMT may have greater sensitivity for detecting cognitive deficits in the TIA population; although, further research is necessary.

The KINARM SST like the TMT was able to discriminate between the two study groups. Overall the TIA group performed worse at the task than the migraine control group. Of the seven parameters measured during the SST, the time per target parameter was the only one capable of detecting significant differences in the performance of TIA and migraine patients. Therefore, TIA patients spent significantly more time dwelling on targets or deciding which target to select next. This shows a lapse in cognitive speed when compared to the migraine patients. Like the KINARM TMT the SST had superior discriminative ability in comparison with the MoCA.

The KINARM cognitive tasks outperform the MoCA in the ability to discriminate between TIA and migraine patients. This important finding can be applied to clinical assessment of these two patient populations. Better discrimination can lead to less misdiagnosis. Also, proper early diagnosing of TIA patients may decrease the proportion of subsequent stroke victims. More
research is necessary to validate the KINARM cognitive tasks for the assessment of cognitive impairment in the TIA population; however the current results seem promising.

Figure 5.1. TIA Performance on the Trail-A TMT. The movement of a TIA patient is represented by the red line. Deviations from the straight path between targets can be seen. The green line represents the line drawn between targets as the participant completes the task.

5.4 Characterizing Change in TIA Patients Cognition Overtime

The MoCA was administered to the TIA study group at two time points one year apart to determine temporal changes in cognition. Of the five TIA participants that completed the final one year visit, only two were not impaired. One of those participants had improved cognitive status as they were initially classified as impaired at the first visit. Previous studies have noted improvements in cognition based on serial MoCA administration over a 6 month period\(^5\). The general trend however, was cognitive decline between the first and last visit for the TIA group (Figure 4.1). This is not uncommon, studies have shown post TIA cognitive deficits can lead to
more severe MCI and dementia\textsuperscript{4,6}. Therefore trends in the MoCA performance point to progressive MCI in the TIA study group.

The KINARM TMT was administered to the TIA group at five different visits to assess changes in cognition over a year time period. To assess changes in cognition between the first and second visit (14 days and 42 days) paired t-test revealed a significant improvement in TIA group performance on a number of parameters (trail-A total time, trail-B total time, and trail-B error count). For those individuals lacking improvement in trail-B total time previous, studies have shown this poor performance to be predictive of subsequent stroke\textsuperscript{62}. This could warrant future monitoring of those TIA participants who performed poorly in parameters linked to significant improvement in the acute phase (6 weeks post TIA). Performance improvement, although not always significant, was the general trend in the six weeks post TIA for each of the parameters (Figures 4.2-4.8). Studies have shown similar trends in cognitive improvement for TIA patients\textsuperscript{5}. This is not the case for all TIA participants. Three (15\%) of the TIA participants were classified as impaired in both trails-A and B at the first visit. Those individuals continued to show cognitive impairment at subsequent visits. This suggests that impairment in both trail-A and B in the acute phase post TIA may be predictive of prolonged and progressive cognitive impairment. This link between TIA/stroke and risk of progressive cognitive impairment or dementia has been previously described\textsuperscript{4,10}. Overall, cognitive improvement was evident between the first and second visits.

Over the full year time period, TIA patients improved in all trail-A parameters; however, trail-B parameters had varied trends in performance. The number of participants completing each visit declines overtime limiting the analysis. Thus, the one-way ANOVA found no significant changes over the year time period in both the study groups. Generally, TIA group performance across all visits improved for all trail-A parameters. TIA performance in trail-B test time and dwell time declined over the course of the year. While all of the trail-B parameters remained
fairly stable. These trends may indicate the trail-B task is more sensitive to detecting deficits in TIA cognition.

TIA group performance in the KINARM SST was also determined. Significant improvements in the first six weeks (visit 1-2) are noted in shortest failed path and timeout count. This means the participants are remembering longer sequences and completing more trials than their initial visit. General trends over the year time period, show improvement in performance for each of the parameters (Figure 4.13-4.19). This would suggest that TIA patient’s visuospatial working memory generally improves in the year post attack.

The control group KINARM task measurements were taken twice one year apart. For the TMT the control groups showed improvement in performance between their first and last visit in all parameters for each trail. This trend is limited since only two control patients have been assessed at the final visit. For the SST none of the recruited controls have been assessed at the year time point. Therefore, trends in their performance cannot be determined at this point.

Determining trends in cognitive assessment in this study was limited by the decreased number of participants at later visits. Generally, the MoCA and some of the TMT trail-B parameters detected an overall cognitive decline in the TIA group and improvement in the control group. Therefore, progressive cognitive impairment was evident, specifically in executive functioning, for TIA participants in this study. The trail-A parameters showed improvement for both study groups in each parameter. Since trail-A is sensitive for visuoperceptual abilities, TIA and migraine increased performance would suggest these cognitive abilities remain unaffected in the two populations. Therefore, the MoCA and trail-B may be more sensitive to trend in detection of cognitive impairment in the TIA population overtime. Future investigation with more participants is needed to accurately determine TIA cognitive status changes overtime.
5.5 Correlations between Cognitive Impairment Assessment Tools

Within the KINARM cognitive tasks few correlations were found. The TMT trails had significant correlations between trails-A and B total time for the TIA group. Therefore, those participants with lengthy trail-A total times similarly took longer to complete trail-B. For the control group, dwell time performance was significantly correlated for both trails. Previous studies have determined correlations between performance on the trails-A and B of the TMT\textsuperscript{56}. The SST task was also correlated with both trails A and B (Tables 4.6-4.9). TIA trail-A error count and trail-B test time were each significantly correlated with four of the SST parameters (Tables 4.6 and 4.7). This correlation may show overlap in the TMT and SST parameters for detection of performance in similar cognitive domains. For instance those participants who perform poorly in SST have lapses in working memory; therefore, lapses in working memory may also cause increased errors and longer test times in the TMT. To accurately make conclusion based on these correlations further investigation is needed. Controls had no significant correlations for trail-B and SST parameters and only one significant correlation for trail-A dwell time and SST time out count. Therefore, controls who took long to select the next target in the trail-A task also took too long to complete the SST. This correlations shows decreased cognitive speed consistent with some studies on migraine patients\textsuperscript{59-61}. Connections between the KINARM cognitive tasks are to be expected as visuospatial working memory (SST) is under the control of executive functioning (trail-B) and linked to other visuospatial abilities (trail-A).

Comparing the MoCA and KINARM cognitive tasks revealed some correlations. The TMT revealed significant correlations between trail-B total time and trail-A and B error count with MoCA scores (Table 4.3). Since the MoCA had previously been validated as a screening tool for MCI these correlations may indicate the KINARM TMT is a valid test for assessing cognitive impairment. It may also suggest trail-B total time and trail-A and B error count are closely related to declines in memory as the MoCA has been previously linked to strong detection
of memory deficits in the stroke population. The other TMT parameters that are not significantly correlated with the MoCA may be better detectors of visuoperceptual (for trail-A parameters) and executive functioning (for trail-B parameters) deficits and not memory. The SST had significant correlations with the MoCA based on total score and test time parameters. Spatial span is a more direct measure of working memory much like the MoCA. Thus, correlations between the two tests are to be expected. Overall, future investigation focused on validating the KINARM cognitive tasks for assessing cognitive impairment is needed. The correlations between the previously validated MoCA and the KINARM cognitive tasks show promise for the KINARMS ability to detect cognitive deficits.

5.5 Study Limitations

There are a few limitations to this study worth noting. The sample size is low as would be expected for a pilot study. With the low sample size there is an increased chance of making a type I and type II error in statistical analysis. When it comes to participant completion of visits over the year time period, completion of the later visits are quite low. This lack of completion of later visits also complicates characterizing cognitive changes over time. Continued recruitment and follow-up with current participants will improve this issue. The use of the SST to detect cognitive deficits is limited by the lack of normative data. Future recruitment of normal control participants can remedy this problem. Another limitation, is despite resolution of symptoms some of the TIA patients could have had infarction. It would be beneficial to divide the TIA group into infarcted and non-infarcted participants using DWI to determine this effect on symptoms. Finally, conclusive evidence of the KINARM cognitive tasks ability to detect cognitive deficits based on sensitivity and specificity cannot be determined at this point. Instead, future validation studies need to be carried out within the TIA/stroke population.
Chapter 6

Conclusions and Future Directions

The use of the robotic KINARM in the assessment of cognition in the TIA population was the overall purpose of this study. Three general objectives were determined based on this goal. Detecting cognitive deficits in patients, discriminating between TIA and migraine patients, as well as characterizing changes in TIA cognition overtime was attempted. The use of the MoCA, a validated screening tool for MCI, was an integral part of the study design. Through comparison of the MoCA and KINARM cognitive tasks the general ability of the KINARM tasks to assess cognition was determined. Future investigation based on the results of this study could elicit new information on how cognition is affected in the TIA population.

Some basic conclusions can be made from the results of this study. Detection of cognitive deficits was apparent through the KINARM TMT task and MoCA. In fact, the TMT was able to detect slightly more impaired individuals than the MoCA. The most crucial finding is the ability of both the TMT and SST to discriminate between TIA and migraine patients while the MoCA could not. Quantitative data from the KINARM robot may be analyzed in the future to characterize and refine this discriminative ability. Persistent cognitive deficits are seen in the TIA population overtime in this study. The general trend based on the KINARM tasks is improvement in performance in the year time period. With further investigation the KINARM assessment of cognition in the TIA population may prove to be a valuable tool.

There are many future directions research in this field can take. The biggest goal would be to validate the tasks using a cognitive battery of tests with the same study groups. This would allow for conclusive results on the KINARM tasks ability to detect cognitive deficits in the TIA population. Future investigation on the relationship between KINARM performance and DWI detection of lesions is another direction of research. Finally, comparison of KINARM cognitive
task performance and KINARM motor task performance may also add to the understanding of TIA patient deficits post attack. This study shows the potential of the KINARM robotic exoskeleton as an assessment tool for TIA patient cognitive deficits. Future investigation may provide more insight.
Chapter 7

References


## Appendix A

### MoCA Original Version

**Montreal Cognitive Assessment (MoCA)**

**Version 7.1 Original Version**

### Visuospatial / Executive

- **Copy Cube:** Draw a clock (ten past eleven) (3 points)

### Naming

- **Camel:** Camel (3 points)
- **Rhino:** Rhino (3 points)

### Memory

- **Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes:**
  - 1st trial: 2184
  - 2nd trial: 742

### Attention

- **Read list of digits:** (1 digit/sec.), subject has to repeat them in the backward order:
  - 4 or 5 correct subtractions: 3 pts. 2 or 3 correct: 2 pts. 1 correct: 1 pt. 0 correct: 0 pt

### Language

- **Fluency:** Name as many words as possible that begin with the letter F: [ ] (N ≥ 11 words)

### Abstraction

- **Similarity between e.g., banana - orange = fruit:** [ ] train - bicycle [ ] watch - ruler

### Delayed Recall

- **Has to recall words with no cue:**
  - Face: [ ]
  - Velvet: [ ]
  - Church: [ ]
  - Daisy: [ ]
  - Red: [ ]

### Orientation

- **Date:** [ ]
- **Month:** [ ]
- **Year:** [ ]
- **Day:** [ ]
- **Place:** [ ]
- **City:** [ ]

**Total:** [ ]

---

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Normal ≥ 26 / 30

Add 1 point if ≤ 12 yr educ
# Appendix B

## Clinical Data Collection Form

**Kingston TIA-KINARM Clinical Data collection form**

<table>
<thead>
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<th>Risk Factors</th>
<th>KGH Sticker</th>
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<td>Hypertension</td>
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<tr>
<td>Dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>MI/CAD</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
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</tr>
<tr>
<td>Obesity (BMI &gt; 30 kg/m²)</td>
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## Examination

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<tr>
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<td>Triceps</td>
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<th>Weight (kg):</th>
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<th>Waist Circumference (cm):</th>
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### Scales

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<td>SBP &gt; 140</td>
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<tr>
<td>Or</td>
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<td>DBP &gt; 90</td>
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<td>Speech</td>
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<td>Unilateral weakness</td>
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</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Pending</td>
</tr>
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### Notes

- **DX:**
  - TIA
  - Stroke
  - Migraine
  - Sleep Apnea
  - Seizure
  - Other

- Symptoms of event:

- Duration of Symptoms:
- Affected Side: R L B N
- Neurological Exam Normal: Yes No
- Visual Fields Normal: Yes No (if No, see reverse)

### Stroke/TIA Classification

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<td><strong>Centre</strong></td>
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<tr>
<td><strong>Lower</strong></td>
<td><strong>Lower</strong></td>
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<tr>
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<td><strong>Centre</strong></td>
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<tr>
<td><strong>Lower</strong></td>
<td><strong>Lower</strong></td>
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Appendix C

TIA TMT Z-Score Graphs

TIA Patient Total Time Z-Scores Over Time. The dotted horizontal black lines represent the cutoff Z score (±1.96). Patients outside of the cutoffs are considered to be impaired. Trail B test time (right) captured more impairment than Trail A.
TIA Patient Dwell Time Z-Scores Over Time. The dotted horizontal black lines represent the cutoff Z score (±1.96). Patients outside of the cutoffs are considered to be impaired. Trail B test time (right) captured more impairment than Trail A.
TIA Patient Time Ratio Z-Scores Over Time. The dotted horizontal black lines represent the cutoff Z score (±1.96). Patients outside of the cutoffs are considered to be impaired. Trail B test time (right) captured more impairment than Trail A.
TIA Patient Total Time Z-Scores Over Time. The dotted horizontal black lines represent the cutoff Z score (±1.96). Patients outside of the cutoffs are considered to be impaired. Trail B test time (right) captured more impairment than Trail A.
Control (Migraine) Patient Total Time Z-Scores Over Time. The dotted horizontal black lines represent the cutoff Z score (±1.96). Trail A (top) detected one control with impairment at the first visit. All other controls performed within the normal range for the total time parameter.
Control (Migraine) Patient Dwell Time Z-Scores Over Time. The dotted horizontal black lines represent the cutoff Z score (±1.96). All of the controls performed within the normal range for the dwell time parameter.
Control (Migraine) Patient Time Ratio Z-Scores Over Time. The dotted horizontal black lines represent the cutoff Z score (±1.96). Trail B (bottom) detected one control with impairment at the first visit. All other controls performed within the normal range for the total time parameter.
Control (Migraine) Patient Time Ratio Z-Scores Over Time. The dotted horizontal black lines represent the cutoff Z score (±1.96). Only one control participant had impairment at the first visit. All other controls performed within the normal range for the total time parameter.