INVESTIGATING THE FEASIBILITY OF VIRTUAL REALITY GAMES FOR DETECTING THE ONSET OF DEMENTIA USING A PHANTOM ARM COMPARED TO TOUCHSCREEN VERSION

by

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ABSTRACT

In this preliminary study, a virtual reality game was developed to detect the onset of dementia. The game takes place in a 3D virtual kitchen, and the player is tasked to identify displaced objects from memory and to recall the order of displacement. Two different hardware platforms were used to play the game; a touchscreen tablet and a phantom robotic arm. Cognitive abilities such as object recognition, spatial memory and memory retention were assessed. Study participants were 45 seniors, out of which four were diagnosed with Mild Cognitive Impairment (MCI) and 3 with Alzheimer's disease (AD). Their performances were evaluated against the Montreal Cognitive Assessment (MoCA) test. They performed the experiments both with a phantom arm mimicking humans' arm and with a touchscreen version. Healthy older adults performed significantly better than MCI participants, who in turn performed better than AD participants. MoCA significantly correlated with the game score on both hardware interfaces. There was also a significant difference between the performance score while using phantom robotic arm compared to that when using the touchscreen, pointing towards a deficit of visuomotor ability in ageing. The scores of performances using touchscreen version of the games was a significant predictor of MoCA, while the scores of using phantom arm was a significant predictor of age. MCI participants performed much worse on order recall tasks compared to object identification tasks, suggesting a more pronounced deficit in memory retention. More MCI and AD participants should be investigated to determine the designed experiments' sensitivity and specificity in detecting dementia.

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Dedicated to The Memory of My Grandfather

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
aMCI	amnestic Mild Cognitive Impairment
ANCOVA	Analysis of Covariance
API	Application Programming Interface
CDT	Clock drawing test
CSF	Cerebrospinal Fluid
DLL	Dynamically linked library
DMN	Default Mode Network
EC	Entorhinal Cortex
EPP	Enhanced Parallel Port
FTD	Fronto-Temporal Dementia
GPCOG	General Practitioner Assessment of Cognition
IDE	Integrated Development Environment
IPL	Inferior Parietal Lobule
MANCOVA	Multivariate Analysis of Covariance
MCI	Mild Cognitive Impairment
MIS	Memory Impairment Screen
MMSE	Mini Mental State Examination
MoCA	Montrael Cognitive Assessment
MRI	Magnetic Resonance Imaging
PC	Perirhinal Cortex
PCC	Posterior Cingulate Cortex
rTMS	repetitive Transcranial Magnetic Stimulation
SD	Standard Deviation
VR	Virtual Reality

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CHAPTER I: INTRODUCTION

1.1 Motivation

Inspired by feedback from the caregivers of Alzheimer's patients participating in other studies conducted at the University of Manitoba biomedical engineering research lab, the motivation for this work was to develop a novel virtual reality(VR) experiment (game) that could be used to screen for early signs of dementia. Since the experiments were designed to be like a game, herein we use the term experiment and game interchangeably. The game was designed to be independent of language and computer knowledge, sensitive and engaging that could also be completed under 10 minutes so that it would become a potentially useful diagnostic tool for clinical settings.

It is important to note here that the virtual reality environment created in this game supports immersive elements such as a VR headset, haptic and audio feedback. The game can be played with or without these immersive elements.

1.2 Objectives

Since senior participants may not know how to use a computer mouse, the experiments were designed to be played on two hardware interfaces: a touchscreen tablet and a phantom robotic arm with 6 degrees of freedom that mimics a human arm. To evaluate the game's efficacy for detecting dementia, the game was evaluated against the popular neurocognitive assessment tool, the Montreal Cognitive Assessment (MoCA) test. The objectives of this study were:

- Investigate whether the participants' scores of the game either in the phantom arm or touchscreen version are correlated with their MoCA scores.
- Investigate whether there is a difference of the participants' performance when the game is played on either of the two hardware interfaces (phantom arm vs touchscreen versions).
- Investigate which version of the hardware interface would be a better predictor of the MoCA score.

1.3 Organization

This report is divided into five chapters. Chapter I introduces the research as well as stating the motivation and objectives. Chapter II provides a literature review on the onset of dementia, brain changes, functional impairments and methods of detecting dementia including neuro-cognitive assessments and serious games. Chapter III details the methodology that enables this research, including the research design, protocol, data measurement and analysis. Chapter IV and chapter V presents results of the study with discussions of their significance. Finally, Chapter VI concludes the research and suggests directions for future work.

CHAPTER II: LITERATURE REVIEW

This chapter contains a literature review that gives rise to the methodology for this research. An overview of dementia is provided with a specific focus on its onset from an anatomy and physiology point of view. This leads to specific detection tools such as neuro-cognitive assessment tests and serious games. The review zooms in on the more popular and accessible tests, analyzing their advantages and disadvantages.

2.1 Dementia Onset

Dementia is one of the most significant challenges facing the social welfare systems [1]. There are an estimated 50 million people with dementia worldwide, and the estimation would double every 20 years [2]. The most common symptom of dementia is impaired memory as well as impaired ability in thinking, communication, orientation and coping with everyday tasks. Other symptoms include personality changes, anxiety, depression, suspiciousness, delusions and compulsive behaviours [3]. Alzheimer's disease (AD) is the most common form of dementia and accounts for 50%-60% of all dementia cases [4]. There's an overlap of symptoms between early stages of AD and Mild Cognitive Impairment (MCI); MCI is considered as a transitional state from healthy ageing to dementia [5]. Patients diagnosed with MCI could appear normal or return to a healthy state, but more than half advance into dementia within five years [4]. Identifying MCI individuals at high risk of AD conversion is critical to being able to enroll them in therapeutic interventions to avoid further decline.

The concept of MCI originated from memory clinics where milder cases of cognitive impairment did not meet the “two cognitive domains impaired” criteria for a diagnosis of AD developed by McKhann [6]. Although initially believed that all MCI cases were a precursor to AD, follow up studies discovered multiple types of MCI: static MCI commonly caused by vascular injury, and progressive MCI that most commonly caused by AD but potentially vascular or other neurodegenerative diseases, such as Fronto-Temporal Dementia (FTD) [8]. Memory clinics report amnestic MCI (aMCI) as the most common form of MCI; others who do not suffer from memory deficits are grouped into non-amnestic MCI (na-MCI). Those who have multiple types of cognitive deficits are categorized as multi-domain MCI (a-MCI+) and are considered at a higher risk of developing AD [9]. There is an estimated 10 to 20% of adults above the age of 65 who are afflicted with MCI [10], and 10% of MCI adults progress to AD [11].

2.2 Dementia Onset and Brain Regions

An autopsy of MCI individuals has revealed changes similar to AD patients, including the presence of beta-amyloid plaques and neurofibrillary tau tangles. These neuropathological changes occur first in the hippocampus and the entorhinal cortex within the medial temporal lobe. In MCI and preclinical AD, these changes spread from the parahippocampal gyrus to the temporal pole and inferior, middle temporal gyri. Finally, the temporal, parietal, and frontal neocortex are all affected in AD patients [12].

In early-stage MCI patients, neuroimaging studies have also shown brain atrophy in the entorhinal cortex, perirhinal cortex, hippocampus [13], precuneus, posterior cingulate [14] and inferior parietal lobule [15]. Volume loss [16] and hypometabolism [17] were also observed in these regions. The following sections describe the brain regions that are commonly affected by the onset of dementia and functional impairments caused by atrophy within these regions.

2.2.1 Entorhinal Cortex

As shown in Figure 1, the Entorhinal cortex (EC) is a small structure situated in the anterior temporal lobe [18]. It is a part of the medial temporal lobe along with the adjacent perirhinal cortex, parahippocampal cortex and the hippocampus. The medial temporal lobe is considered crucial to memory and navigation functions, and the EC is regarded as a relay station, buffering information between the hippocampus and neocortex [19]. Sensory, motor and the associational information are processed in the EC and hippocampus before permeant storage in the neocortex.

In healthy, MCI and AD individuals, the volume of the entorhinal cortex has been found to be positively correlated with the performance of verbal and visuo-spatial episodic and working memory tests [20]. Functional magnetic resonance imaging (fMRI) studies have demonstrated entorhinal cortex engagement during memory functions such as spatial encoding and retrieval [21] [22]. In addition, deep-brain stimulation of EC has shown to improve memory of spatial information [23].

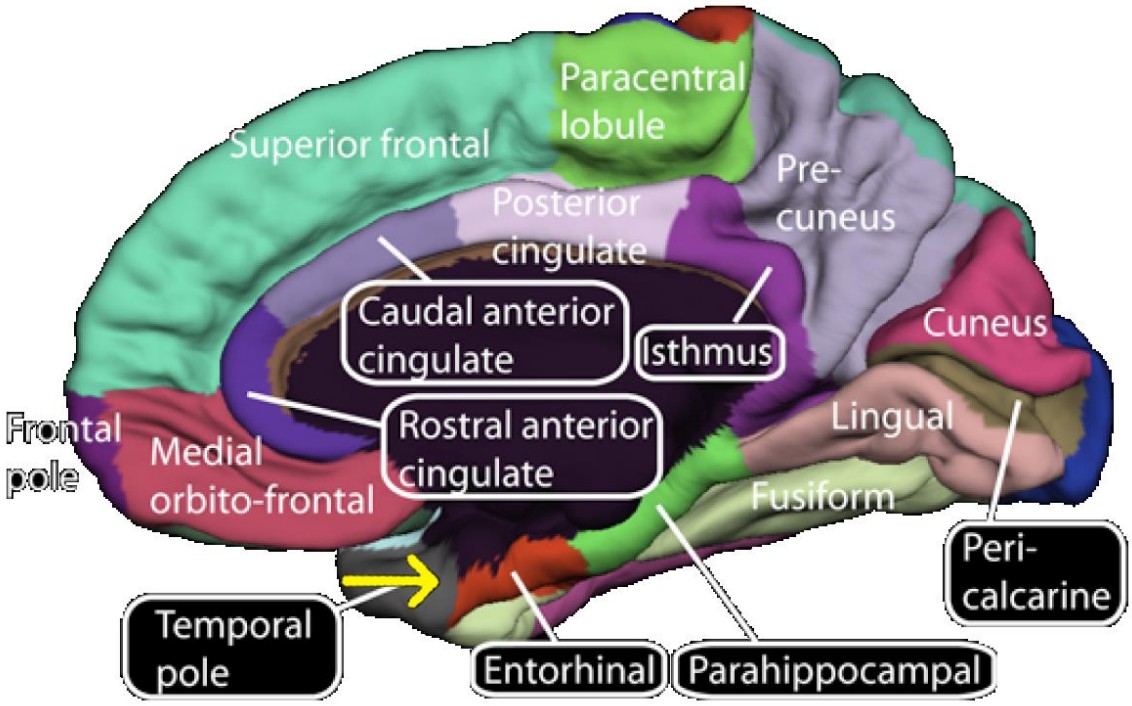

Figure 1: Brain regions [24]

2.2.2 Perirhinal Cortex

The perirhinal cortex (PC) is a small strip of tissue that resides on the undersurface of the temporal lobe, and it plays an essential role in the perception and memory [25]. It is essential for recognition and memory formation of an object's features while identifying an object as a single entity. It is also vital in establishing an association between tactile, gustatory, visual and auditory information with objects [26]. This is due to PC's interconnection with a wide range of sensory cortical areas representing virtually all modalities [27]. In monkeys, damage to the perirhinal cortex impairs performance in visual recognition memory tasks [28]. In human participants performing similar visual recognition memory tasks, mild AD participants had very low scores, while MCI participants scored between healthy controls and AD participants; this suggests memory impairment is correlated to medial temporal lobe atrophy [29].

2.2.3 Hippocampus

Hippocampus is a complex C-shaped brain structure embedded deep in the medial temporal lobe. It consists of densely packed neurons and has a significant role in learning, memory and spatial navigation. Connections between hippocampus and neocortex are important for awareness and knowledge as they enable encoding and retrieval of memory [30]. Semantic memory is enabled through the polysynaptic pathway, where the hippocampus receives input from the parietal, temporal and occipital areas via the entorhinal cortex and connects through the fornix to the anterior thalamus, posterior cingulate cortex and the retrosplenial cortex. Episodic and spatial memory is

enabled through the direct intra-hippocampal pathway, where the hippocampus receives input from the temporal association cortex through the entorhinal and perirhinal cortex and connects to the inferior temporal cortex, temporal pole, and prefrontal cortex [31].

The hippocampus is one of the earliest and most affected brain regions by dementia. The popular hypothesis 'hippocampo-cortical-dissociation' argues that atrophy in the hippocampus causes reduced connectivity from itself to the cerebral cortex [32]. MRI-based studies demonstrated tau tangles associated atrophy along the polysynaptic pathway are associated with semantic memory deficits. Volume loss in the hippocampus has been linked to reduced performance in episodic memory [33] as well as working memory [34]. These behavioural deficits are consistent with those in neurodegenerative diseases such as amnestic MCI and AD [35].

2.2.4 Precuneus

The precuneus is located within the posteromedial parietal cortex. Its location and wide-spread connections suggest that the precuneus is responsible for a broad range of higher-order cognitive functions such as visuospatial processing, episodic memory retrieval, self-processing and consciousness [36]. Modern imaging studies have shown that the precuneus is activated in spatial processing tasks such as attentive tracking of objects [37] and attention shifting between object features [38]. Fletcher et al. showed significant bilateral activation of the anterior precuneus in episodic memory recall of visual imagery [39]. The posterior precuneus was shown to be activated during a paired word association memory task [40]. Stimulation of the precuneus with repetitive

Transcranial Magnetic Stimulation (rTMS) was shown to improve working memory performance in a delayed match-to-sample task [41]. A study of amnestic MCI individual during virtual maze navigation showed significant correlation of reduced right-side precuneus and inferior parietal cortex volumes with poor performance [42].

2.2.5 Posterior Cingulate Cortex

The posterior cingulate cortex (PCC) is a highly connected and metabolically active region within the cingulate cortex [43]. Although there is no universal agreement on its function, the PPC has been shown to play a role in supporting the focus of attention [44] as well as retrieving autobiographical spatial memories [45] and plans [46].

The PCC is commonly affected by neurodegenerative diseases such as AD, where amyloid deposition, atrophy and hypometabolism were observed [47]. The default mode network (DMN) is disrupted as connectivity between the PPC, and the hippocampus is reduced [48], and performance of working memory task is positively correlated with the strength of this functional connectivity. Abnormal PCC function due to a traumatic brain injury is also correlated with cognitive impairment and attention deficit [49].

2.2.6 Inferior Parietal Lobule

The inferior parietal lobule (IPL) is a large structure below the intraparietal sulcus and behind the postcentral sulcus. Studies of primates have found connections

between the IPL and the entorhinal cortex [50] as well as the hippocampus [51]. Its function has been involved with sensory, motor association, language, math, visuospatial semantic networks [52] and working memory [53].

A post-mortem autopsy of MCI and AD individuals' revealed the presence of both amyloid plaques and neurofibrillary tangles in the IPL [12]. A decrease in metabolic rate in the IPL along with genetic factors has been linked to cognitive decline in non-demented participants [54]. Differences in activation levels IPL have also been found in AD individuals compared to healthy controls when performing verbal episodic memory tasks [55].

2.3 Dementia Onset and functional impairments

Upon examining the brain regions affected by the onset of dementia, some of the functional deficits in the early stage of the disease include object identification, working memory, spatial memory and visuospatial processing. There are two general hypotheses regarding age-related cognitive decline: the slowing hypothesis and the limited resource hypothesis. The slowing hypothesis states that there is a general slowing down of cognitive processes in ageing, especially in working memory and executive functions [56]. The limited resources hypothesis states that the overall cognitive decline is due to decreased attentional abilities and executive function [57]. Typically, the performance of MCI patients cognitive abilities are in between healthy and AD patients. It is therefore important to differentiate MCI patients from individuals with normal age-related

cognitive decline. The following sections examine these deficits from a pathological and normal ageing perspective.

2.3.1 Working Memory

Working memory is the ability to encode short-term information for later retrieval and manipulation. It requires the ability to selectively allocate attention and making complex decisions. Auditory information is controlled by the phonological loop to promote abilities such as language. Visual information is maintained by the visuospatial sketchpad to enable abilities such as visuospatial memory. Working memory can be assessed using behavioural tasks that require the encoding of a stimulus (or multiple stimuli) and the recall of such stimulus after a specific duration which results in a quantitative measurement of memory capacity as well as memory retention interval [58]. Visuospatial memory is examined in this review since it is a necessity for more complicated visuospatial tasks such as navigation.

Iachini et al. [59] compared young and older healthy adults in general cognitive functions and visuospatial memories. Older adults showed an impairment in attention capacity and visuospatial working memory as well as impaired ability to infer new information from memorized spatial information and the ability of abstract spatial reasoning. Another study found that processing speed is a leading indicator of age-related impairments in memory and spatial ability [60]. Kochan et al. [61] found poor visuospatial working memory capacity in MCI individuals with various MCI subtypes compared to age-matched nonimpaired controls when the number of stimuli increased.

Moreover, MCI participants demonstrated slower response rate compared to that of the age-matched non-impaired controls.

In a study of memory retention intervals, older adults were significantly less accurate than younger adults at a spatial information recall task only after a 30-minute retention interval. There was no significant difference of age on the same task with retention interval of 3 minutes or 15 minutes [62]. Another study assessed shorter retention interval (under a minute) during a delayed sentence recall, where MCI and AD participants had poor working memory span and retention interval when compared to healthy age-matched controls. The same study also found that MCI participants who later progressed to AD had worse retention interval than those who remained stable [63]. This suggests that age does not have a significant effect on short memory retention interval.

Although memory deficit is the hallmark of dementia, it is also associated with other clinical conditions such as depression, anxiety, learning disability and physical illness. Memory disorders with no dementia in the older adult population are found with a prevalence of 22% to 56% [64]. Therefore, assessing working memory alone would not be sensitive enough for dementia detection.

2.3.2 Visuospatial Processing

Visuospatial processing refers to the ability to process geometric properties such as distance and size, as well as dynamic properties such as speed and force. This ability allows individuals to identify and interact with objects and the environment [65].

Ungerleider and Mishkin [66] proposed a separation between spatial information and object information with two streams: the dorsal stream processes spatial information for the object's location, whereas the ventral stream processes the object features for its recognition. Together with visuospatial memory, visuospatial processing enables complex functions such as spatial navigation.

Sharps and Gollin [67] examined free recall of objects location in situations with and without distinctive contextual cues. In that study, older adults performed poorer compared to young adults when no contextual cues were absent. When contextual cues were present, no difference in performance between the age groups was observed, suggesting that contextual cues facilitate object recall in space. Troyer et al. [68] compared amnestic MCI against healthy age-matched controls on standardized tests of object–location recall. Object recall performance in the aMCI group was markedly lower than that of controls.

2.4 Dementia detection

Although physicians can generally recognize dementia in patients, there is about 40% of MCI cases undiagnosed [69]. Many clinical and biological tests have been used to identify MCI and AD, including neurocognitive tests, neuroimaging, serious games, cerebrospinal fluid (CSF) and a biomarker combination [70]. While neuroimaging and CSF analysis can be used as a complementary diagnostic tool to neurocognitive assessments, neuroimaging is expensive, and CSF analysis is invasive in addition to having limited accessibility. The following sections review the two inexpensive and

accessible options that can be used to detect dementia: neuro-cognitive assessments and serious games.

2.4.1 Neuro-Cognitive Assessments

Currently, there is no universally recognized cognitive assessment tool [71]. The preferred criteria for an assessment would be a brief test that is independent of language and education level as well as having high sensitivity and specificity. As of 2015, the Mini Mental State Examination (MMSE) remains the most popular and well-studied screening tool for measurement of cognitive impairment in clinical and research purposes [72]. Lorentz et al. [73], Brodaty et al. [74] and Milne et al. [75] recommended three promising tests according to the aforementioned criteria as well as psychometric properties: the Mini-Cog, Memory Impairment Screen (MIS) and the General Practitioner Assessment of Cognition (GPCOG). The clock drawing test (CDT) and the MoCA test are gaining popularity due to high sensitivity and engagement of executive function [76]. A brief overview of MMSE, CDT, MoCA, Mini-cog, MIS and GPCOG, as well as their advantage and limitations, are provided below.

The MMSE contains five sections: orientation, registration, attention and calculation, recall and language. [77]. However, advanced age, low education level, foreign culture, and sensory impairment can produce false positives and requires adjustment for age and education [78]. In a Sao Paulo Ageing & Health Study, the MMSE was found to have a low sensitivity (78.7%) and specificity (77.8%) for older illiterate adults at its regular cut-off point [79] . The MMSE also has limited sensitivity to frontal and executive function [80] . The accuracy of the MMSE has been studied

using meta-analytical methods with 34 dementia and 5 MCI cases, it was found that the MMSE is ineffective for diagnosing MCI against healthy controls and neither is it effective at differentiating MCI compared to AD cases [81].

The Clock Drawing Test (CDT) emerged as a popular screening tool for dementia due to its demand of a wide range of intellectual and cognitive skills [82]. The cognitive skills include comprehension, planning, visual memory, visuospatial ability, motor programming and execution, abstraction, concentration, and response inhibition. Unfortunately, the CDT's scoring and interpretation are complex and debated upon as there are multiple scoring systems available in the literature [83]. Lessig et al. [84] analyzed three scoring systems to construct an algorithm with six common errors of inaccurate time setting, no hands, missing numbers, number substitutions or repetitions, and failure to attempt clock drawing; the algorithm classified dementia with a specificity of 88% and a sensitivity of 71%. The CDT takes less than a minute conduct and provides a user-friendly visual presentation of cognitive function that is well suited for busy clinics. However, the CDT is also affected by education level and language although to a far lesser extent compared to the MMSE [82]. As a single measurement, the CDT's main limitations lies in the fact that it has low sensitivity in predicting cognitive impairment and it is often accompanied by other tests in modern screening.

The MIS is a 5-minute four-item delayed and cued recall test that uses controlled memorization and recall to optimize encoding specificity. In a study with English speaking participants, sensitivity and specificity were found to be 80% and 96%, respectively. The MIS was also not significantly affected by age, education, and gender.

As a single measurement, the MIS does not examine executive function or visuospatial functions [85].

The Mini-cog is a 3-minute screening tool that consists of the CDT and several versions of delayed 3 words recall test [86]. In a study of 249 older participants with similar cultural, language and educational background, the Mini-Cog had a sensitivity of 99%. The same study demonstrated that the Mini-Cog had comparable psychometric properties to MMSE [87]. Compared to MMSE, the Mini-Cog was also found to be less biased by language, cultural and educational background [88].

The GPCOG is a 6-minute screening tool with nine cognitive tasks including time orientation, CDT, news reporting, a word recall task and 6 informant questions assessing patient's personal change. In a study with English speaking participants of age 75 or older with memory issues, the GPCOG was found to have sensitivity and specificity of 85% and 86%, respectively; these are comparable with those of MMSE [89]. The GPCOG has the advantage of patient-specific personal input that can be used to assess the patient's progress.

Originally designed to detect MCI, the 10-minute MoCA test examines several cognitive domains: visuospatial, naming, working memory, attention, language, abstraction and orientation. The MoCA incorporates 5/6 of the most often used tools in screening for dementia including the CDT and the delayed word recall [90]. In a study of 94 MCI participants and 90 healthy elderly controls, a cut-off score of 26 out of 30 was used to detect MCI with sensitivity and specificity of 90% and 87%, respectively [90] Therefore, the MoCA is an effective screening tool for MCI and it was suggested that

MoCA should be administered first for participants with cognitive complaints without functional impairment. MoCA's psychometric properties and efficacy have been validated in multiple studies [91] [92] [93], and it has been recommended by the Canadian Consensus Guidelines for detection of MCI and AD [94]. It is important to note that MoCA test score is highly sensitive to educational level [95] [96], and it has a corresponding 1 point adjustment for participants with less than 12 years of education. Moreover, MoCA test has also been found to have poor specificity in settings, where the overall prevalence of MCI is low [97]. Lastly, MoCA's subtest scores were found to be poor predictors of impaired performance on the corresponding cognitive domain [98], which renders MoCA ineffective at assessing domain-specific information [99]. The MoCA test is illustrated in Figure 2.

Cognitive screening tests are brief, simple, inexpensive, portable and require no specialized qualification for administration. Modern tests such as MoCA examines many cognitive domains and has high sensitivity for detecting MCI. However, almost all tests suffer from suboptimal specificity, especially when it comes to participants with low literacy, different cultural background and education level. There is also a ceiling effect where tests are insensitive to changes among patients with high intelligence or previous high functional roles. Similarly, there is also a floor effect, where tests are insensitive to patients with low intelligence and low education. As a tool for monitoring a participant's condition, the score is dependent on the assessor and can be significantly skewed due to familiarity. Therefore, additional in-depth assessments are often required for proper dementia diagnosis [100].

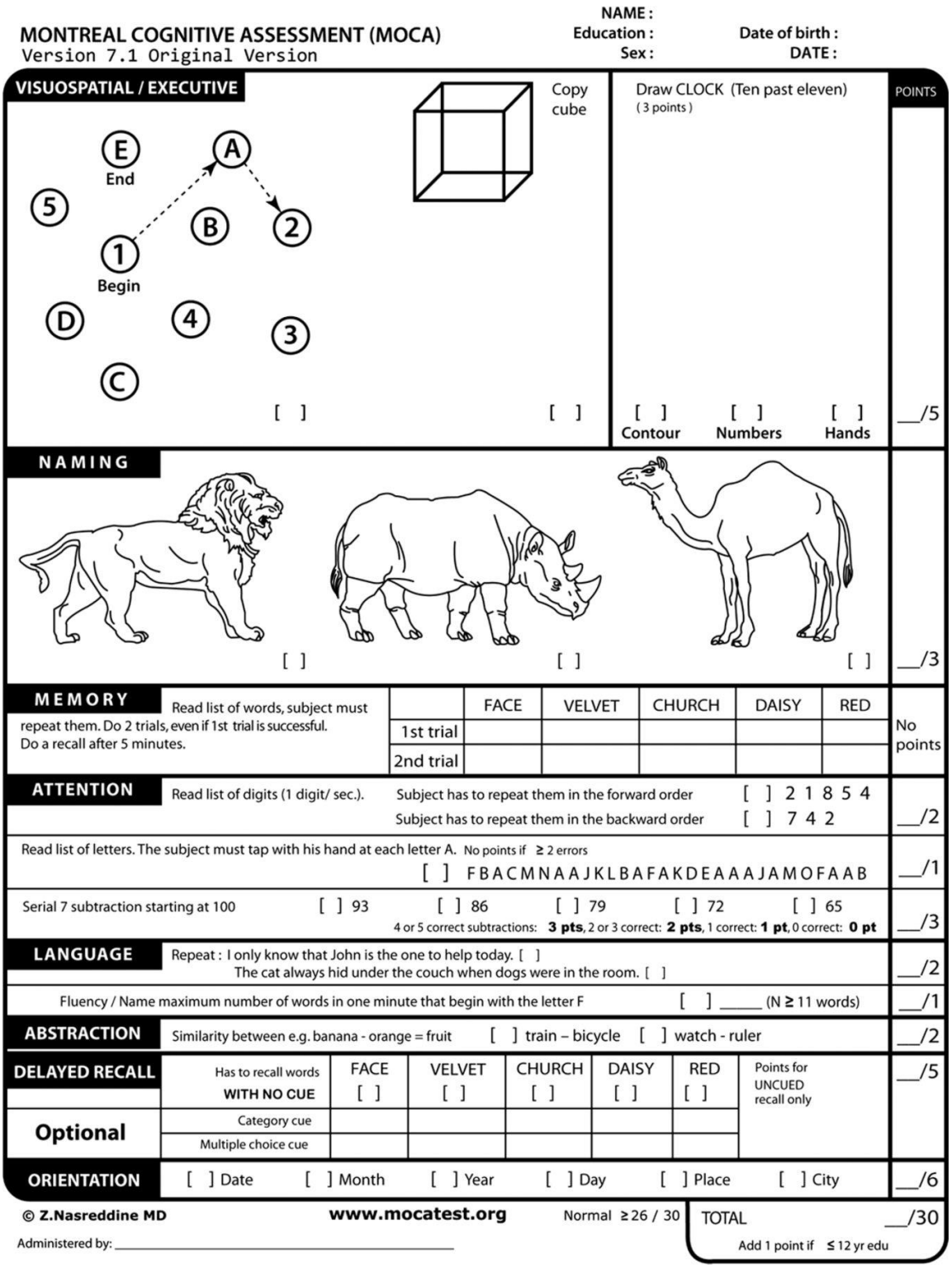

Figure 2: MoCA test full

2.4.2 Neuro-cognitive Serious Games

Serious games have been used in various laboratory and commercial settings for research and cognitive health monitoring of dementia participants. Recently, there has been a growing interest in using serious games to evaluate patient's cognitive and functional impairment for early detection of dementia [101].

A serious game, if used repeatedly, has been shown to improve the cognitive decline associated with healthy ageing [102] as well as a being a beneficial motivating tool in improving executive function and processing speed in healthy [103]. Anguera et al. [104] reported that serious games improved both trained and untrained cognitive abilities such as sustained attention and working memory. The process, in which untrained abilities are gained from training, known as transfer effect, has been supported with neurophysiological findings in MCI participants; this suggests training-induced neuroplasticity as a result of playing serious games [105]. For MCI and AD patients, a serious game can be an effective intervention tool that directly or indirectly targets cognitive functioning as opposed to interventions that target behavioural, emotional or physical functions [106]. A Nintendo Wii based bowling interactive video game has been shown to promote intellectual stimulation in MCI patients [107].

Serious games are also effective at detecting dementia at an early stage. Vallejo et al. evaluated a 3D serious game that assessed several cognitive functions in navigation, shopping and cooking tasks among AD and healthy controls; A significant performance difference between AD and healthy controls was found in terms of percentage of achievement and time needed to complete the tasks [108]. 3D virtual

reality has also been effective as a diagnostic tool as it creates a realistic experience in scenarios that would otherwise be dangerous or impossible. A VR supermarket cognitive training exercise was used to examine MCI participants compared to healthy controls. For MCI detection, in a population of 6 MCI participants and 6 healthy older adults, the game yielded a correct classification rate of 91.8% with sensitivity and specificity of 94% and 89%, respectively [109].

Serious games are user-friendly, motivating, low cost, safe, self-assessing and promotes learning process with real-time feedback. Despite the increasing interest and encouraging results and in assessing MCI and AD patients with cognitive serious games, there is no rigorous feasibility and efficacy study and no established clinical standard for serious game based dementia assessment. Furthermore, serious games often have non-naturalistic interactions with wires and non-natural displays that can cause discomfort. Virtual Reality based serious games often cause motion sickness which causes symptoms such as nausea, vomiting, disorientation and vertigo. The development of serious games is often expensive, and the engineering process lacks standard and regulation [110].

CHAPTER III: METHODOLOGY

This chapter presents details of all components that enable this research, including research design, research protocol, outcome measurement and data analysis.

3.1 Research design

After a thorough literature review on early dementia detection, the following specification was developed as a guideline to research design.

- A 3D serious game should be developed.
- The game should produce a score to represent spatial memory capacity, spatial processing ability and processing speed.
- The game should be played on two different hardware platforms, a touchscreen and a phantom arm.
- The game should be fun, engaging, and user-friendly without causing any side effects such as motion sickness.
- The game should not exceed the length of a cognitive assessment with a maximum playtime of 10 minutes.
- The outcome of the game should be evaluated against a standard neurocognitive assessment tool for early dementia such as the MoCA test.
- The outcome of the game on the different hardware interfaces shall be compared to determine a more suitable assessment tool.

3.1.1 Hardware

A touchscreen device was selected as one of the hardware interfaces since many older adults do not know how to use a computer mouse. The touchscreen device that was used in this research is a Microsoft Surface Pro tablet with 12.3 inches of coloured display. Since the game does not require a large screen nor does it require high resolution and high framerate, the Surface Pro was adequate for this study.

A phantom robotic arm was selected as the other hardware interface since it mimics the human arm and could potentially be a more intuitive way to interact with the virtual world compared to the touchscreen tablet. The Phantom premium 3.0L was selected for this research due to the need for a high precision haptic device that can realistically emulate a human hand in motion.

As shown in Figure 3, the 3DSystems Phantom Premium 3.0L high-precision haptic device has 6 degrees of freedom and can emulate a human arm in 3 joints: The shoulder, elbow and wrist. The 3 translational degrees of freedom, width, height and depth has a position resolution of 0.02mm and can produce up to 4.9lbf/22N of force. The wrist joint is an encoder stylus gimbal, which provides an additional 3 degrees of freedom, pitch, roll and yaw. The rotational degrees of freedom have a precision of 0.0023 degrees and can produce 24 oz-in/170mNm of force. The haptic force feedback is only enabled when the user's hand makes firm contact with the entire gimbal.

Figure 3: Phantom Premium 3.0L

The Phantom robotic arm's control and data interface is the enhanced parallel port (EPP), which goes through a parallel to firewire (IEEE1394) converter and connects to a desktop PC with a firewire port.

The haptic feedback is enabled when the user interacts with objects in the virtual world, requiring the player to navigate through space to the desired location while avoiding obstacles. This creates a more realistic scenario where the accuracy of the desired interaction can be compromised by obstacles along the way. Only three degrees

of freedom, height, width and depth were enabled for the Phantom arm version of the game. The three degrees of freedom are sufficient for the player to navigate and complete tasks in the virtual world, while the additional three degrees of freedom at the wrist joint creates a distraction and add an unnecessary level of complication.

3.1.2 Software

The software design of this study consists of the game flow design, the 3D environment design, the scripting that ties all pieces of the game together, interface with the Phantom robotic arm, game scoring, game inputs and outputs. The Unity 3D engine was selected to be the basis for the 3D environments due to the abundance of online learning resources, reasonable learning curve and portability to Oculus rift for potential virtual reality application. Visual Studio Community was selected to be the script editor Integrated development environment (IDE) due to the built-in Unity support and real-time debugging capabilities. The scripting language was chosen to be C# due to author's past familiarity.

3.1.2.1 Game Design

As shown in Figure 4, the welcome screen of the game consists of a set of input boxes, where the player is invited to fill out personal information before clicking a button to start the game.

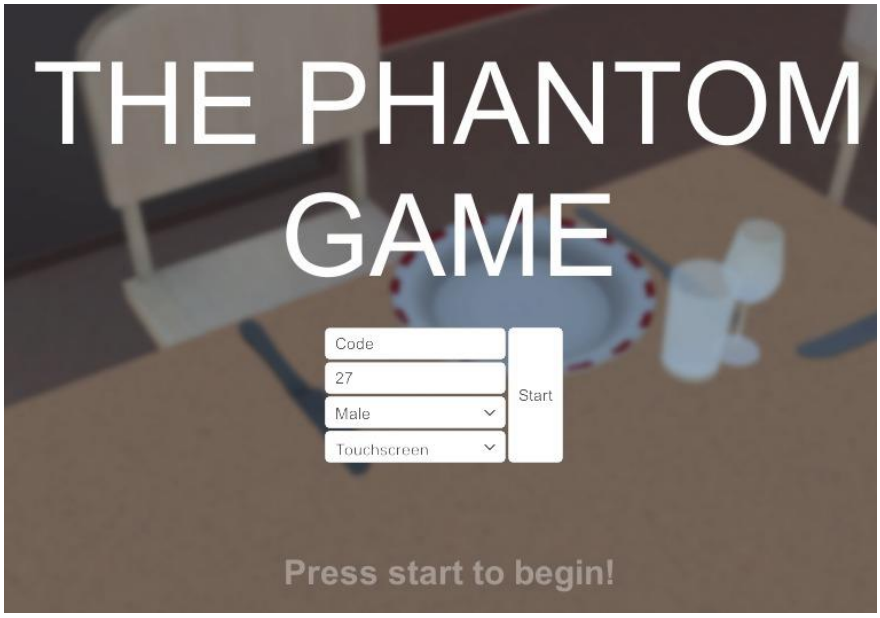

Figure 4: Welcome screen

There are two main tasks that the player must accomplish in each trial, object identification and order recall. At the start of each trial, the player is shown a kitchen setting and 10 seconds is given for the player to memorize what they see. This is shown in Figure 5.

Figure 5: Memorization

The screen dims, and one object is displaced randomly in the dark before light returns. The player is given 30 seconds to identify the displaced object. This is shown in Figure 6.

Figure 6: Displaced item

In the touchscreen mode, the user may simply tap the displaced object to identify it. In the robotic arm version, a virtual hand is created to map the position of the Phantom gimbal in real space, and the player must touch the displaced object using the virtual hand. This is shown in Figure 7.

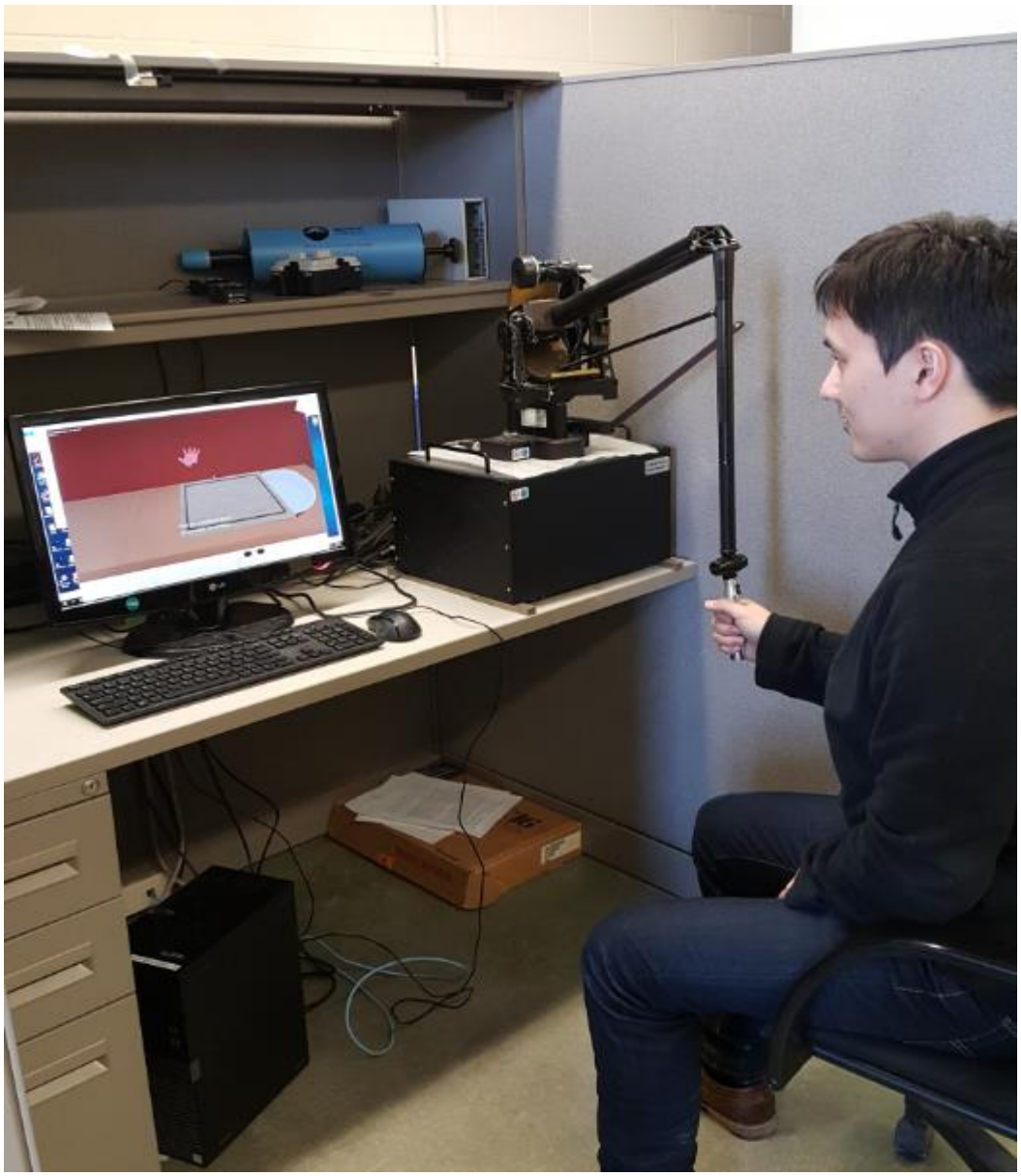

Figure 7: Player with the Phantom premium 3.0L

As shown in Figure 8, if the player touches the displaced object, it turns green and the screen dims before the next object identification task starts. The object identification task repeats three times.

Figure 8: Object identification

After the player completes all three object identification tasks, the screen dims, and the original scene is shown where no objects are displaced. The player is then given 30 seconds to recall the order of the displaced objects. Depending on the hardware interface, this can be done by either tapping the objects in order or touching the objects in order using the virtual hand. Touching any of the displaced objects turns it green. Once the correct order is found, the trial ends, and the next trial begins, as shown in Figure 9:

Figure 9: Order recall

As shown in Figure 10, the screen always dims before the player perform a task and the countdown does not start until the player hits any button. This allows the player

to get ready and provides room for instruction between the player and the game administrator.

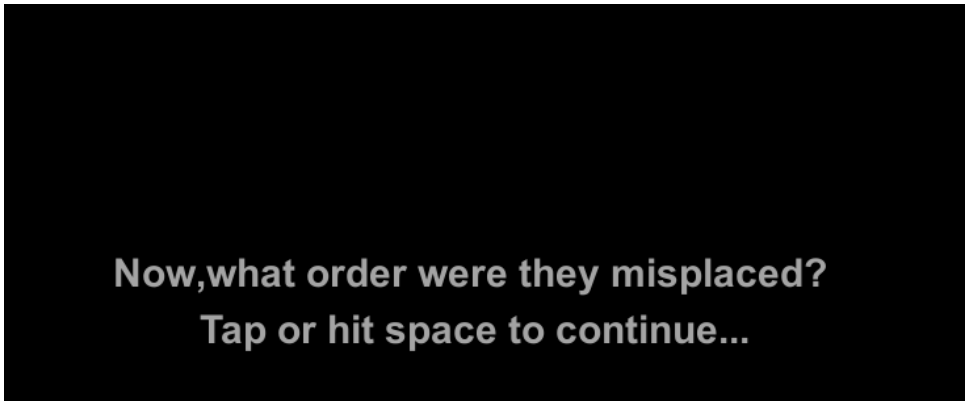

Figure 10: Dim screen

For each trial, the three displaced objects are randomly selected from a list of four displaceable objects from the original setting. The order of the displaced objects is also random. The randomness prevents the user from memorizing the displaced object between the touchscreen and the robotic arm version while choosing three objects out of four decreases the chance of the player guessing the order.

The participants are instructed to complete the task as quickly as they can. If the player is stuck at any point, a task can be skipped by pressing the enter key, and no scores will be given. The entire game can be exited at any time by pressing the escape key.

3.1.2.2 Game Setting

The four trials all take place in a 3D virtual kitchen, where the setting and objects within the setting are all familiar in everyday life. This allows the game to be more

immersive and enjoyable, providing the player with a positive experience. Moreover, the choice of a kitchen was inspired by Alzheimer's patients in similar studies, where laying out complete sets of tableware was a challenge. All Unity 3D objects, meshes, materials, textures and shades were acquired from the unity asset store with permission. The entire 3D kitchen in the Unity development environment is shown in Figure 11.

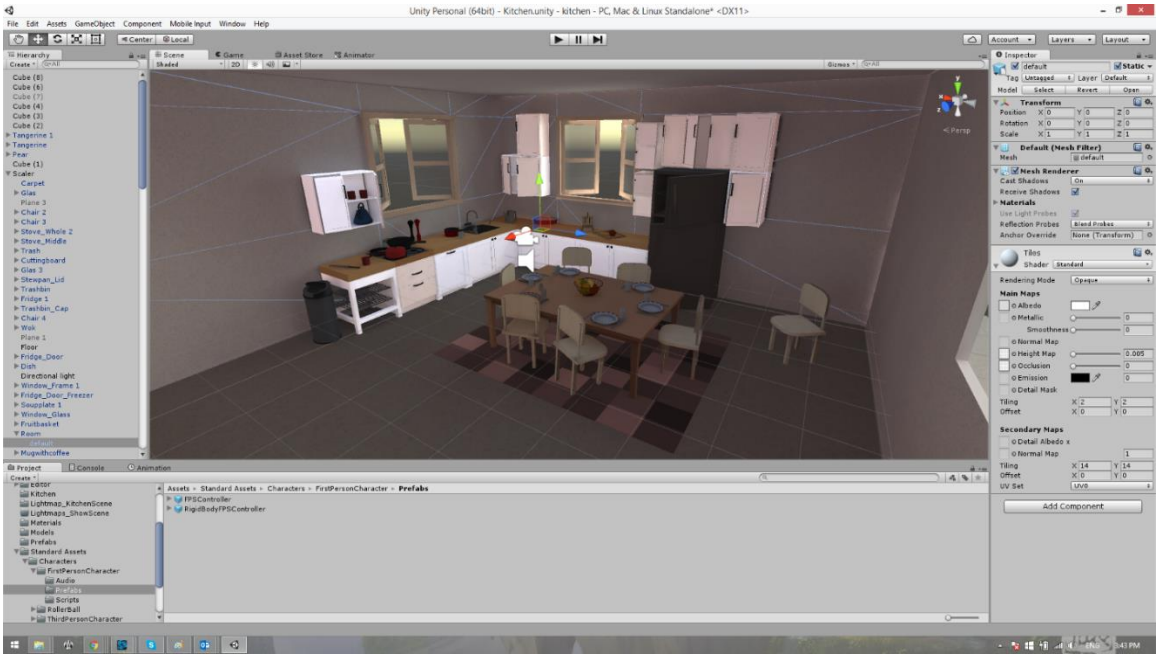

Figure 11: 3D Kitchen in Unity

A first-person controller was created to navigate and interact with objects in the Kitchen. The first-person controller was set at the equivalent of a 1.8m tall human looking down at a natural 45 degrees angle to create realism.

As shown in Figure 5, the training trial takes place in the kitchen counter, where all four objects in the setting can be selected for displacement.

The second trial happens at the sink, where there are decoy objects that prevents the user from guessing. In addition, since any kitchen objects may appear at any area

around the sink, there are no ways for the player to make an educated guess as to what object appears out of place. The four objects that can be displaced are a black pot, a white pitcher, a black spoon and a white lid. This is shown in Figure 12.

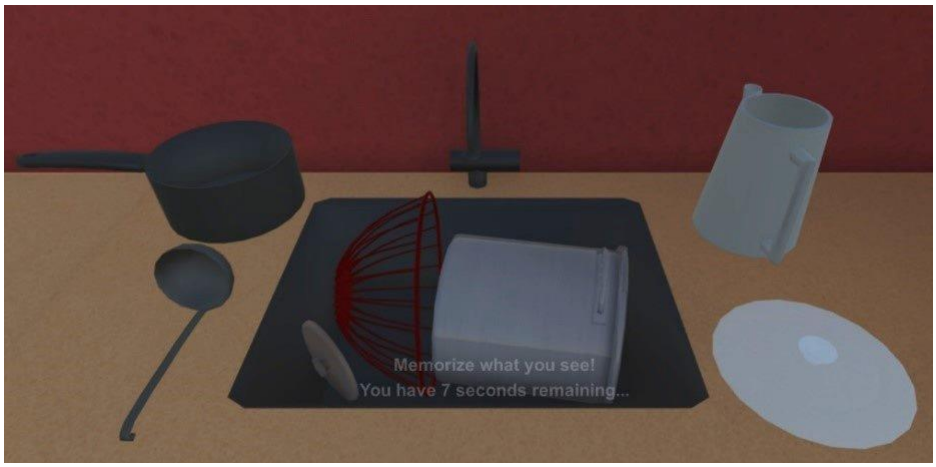

Figure 12: Sink area

As shown in Figure 13, The third trial occurs at the stove area. In addition to the decoys, the four objects of interest are a Salt and pepper shaker, a white pot and a smaller black frying pan. In the stove area, the user can make an educated guess if the pot and frying pants are away from the burners.

Figure 13: Stove area

The fourth and final trial is at the dining table. In addition to the decoys, there are duplicate copies of displaceable objects. The four displaceable objects are all closer to the camera than the decoys: water glass, plate, knife and apple. Note that every set of tableware (dishes, glasses and cutleries) are identical from the perspective of a person in front of it. Therefore an observant player can make an educated guess as to what is displaced. The last trial is shown in Figure 14.

Figure 14: Dining table

3.1.2.3 Game Scripting

The main game manager script (game.cs) controls the flow of the game, displays the instructions on the screen, communicates with submodules to delegate tasks, creates the displaced settings for each trial and logs data.

All objects to interact in every setting has been assigned either box or convex collision boxes to prevent unwanted movement and positioning of objects. To displace an object, the game places it at a random location within the setting that is higher than the table and allows it to free fall and land; invisible collision boxes are placed around the setting to prevent objects from rolling out of the setting. The displacement happens when the screen is dimmed so the player cannot track the moving objects.

Each displaceable object is also assigned a particular pick up script (pickup.cs). When interaction is made by the player, the pickup script allows the objects to report to the game manager script of correct or incorrect user action.

Finally, a user interface script (UI.cs) handles the user interface functionality and displays relevant debugging information on the screen.

3.1.2.4 Phantom Interface

Incorporation the Phantom robotic arm into the 3D kitchen was achieved through another set of scripts. The library OpenHaptics provides the lower level drivers that enables communication to the Phantom robotic arm through the firewire port. The OpenHaptics library is a dynamically linked library (DLL) that can be accessed via application programming interface (API)s to control the robotic arm.

Interfacing with the OpenHaptics API is implemented in the phantom script (Phantom_DLL.cs). The script initiates the Phantom robotic arm, catches and handles all phantom arm related error conditions, calibrates the arm for a zero location that the game can use as a reference, retrieves the location of the arm in all 6 degrees of freedom, keeps a dynamic list of all forces that should be applied to the phantom, computes the resultant force and actives the haptic feedback with the appropriate force. Since scripting in the Unity 3D engine is done in the managed programming language C#, accessing a DLL written in an unmanaged language such as C++ required some additional pointer and memory manipulation in the software domain. Direct communication with the OpenHaptics API was achieved through callback functions, and parameters are passed as C# delegates [111].

The virtual hand that is unique to the Phantom arm version of the game is controlled by the hand script (hand.cs). The script controls the location of two hand

objects in the game based on the location of the phantom arm; one of the two hands are visible hand and the other one invisible. The location of the hands is calculated using a vector transformation matrix based on the orientation of the first-person controller. The invisible hand can travel through objects when the user incorrectly navigates the phantom arm. The visible hand tracks the invisible hand's position when the invisible hand is not colliding with any objects; and stops tracking the invisible hand as soon as the invisible hand collides with another object. The two-hand implementation prevents the players from seeing the virtual hand in places that is not allowed, such as inside of a table.

In the Phantom robotic arm version of the game, additional functionalities were added to the scripts mentioned in the previous section. The touch script is applied to all interactable object in the game; when the invisible hand collides with an object, a force in the opposite direction of the hand entry is calculated and sent to the phantom script for execution. The magnitude and direction of the haptic feedback force are calculated based on the location of the invisible hand and the point of entry during the collision.

The interactable objects in the game are either static or dynamic. Static objects (table, heavy plates, desk, wall etc.) cannot be moved by any other objects in the game; while the dynamic objects (tableware, cookware etc.) are subject to game physics such as gravity and momentum, it can be moved by any other objects in the game, including the virtual hands.

When the invisible hand collides with a dynamic object, an opposite force is generated, and momentum is assigned to the dynamic object, the dynamic object moves away, and the collision ends, no more force in the robotic arm is sustained.

When the invisible hand collides with a static object and stays collided with the object, such as pressing against the table, the Phantom arm cannot prevent a player from sustaining the collision since it can only generate a limited amount of force; it can only serve as an error feedback that the player has encountered an obstacle. In addition, large, sudden changes of force by the phantom can be dangerous for the player. Therefore, the force generation follows a spring model and Hooke's law, where all opposite forces scale linearly with the extent of the collision. In the table pressing example, the more the hand goes through the table, the more force is experienced in the opposite direction up to a maximum, as shown in the equation below. On the left-hand side are forces in the x, y and z-axis respectively. The stiffness k is a constant that was assigned to the object, and X, Y, Z are the distance between the invisible hand and the point of collision, depending on the axis.

$$F_x = -kX$$

$$F_y = -kY$$

$$F_z = -kZ$$

3.2 Protocol

Figure 15 presents a diagram of the study protocol with all key components.

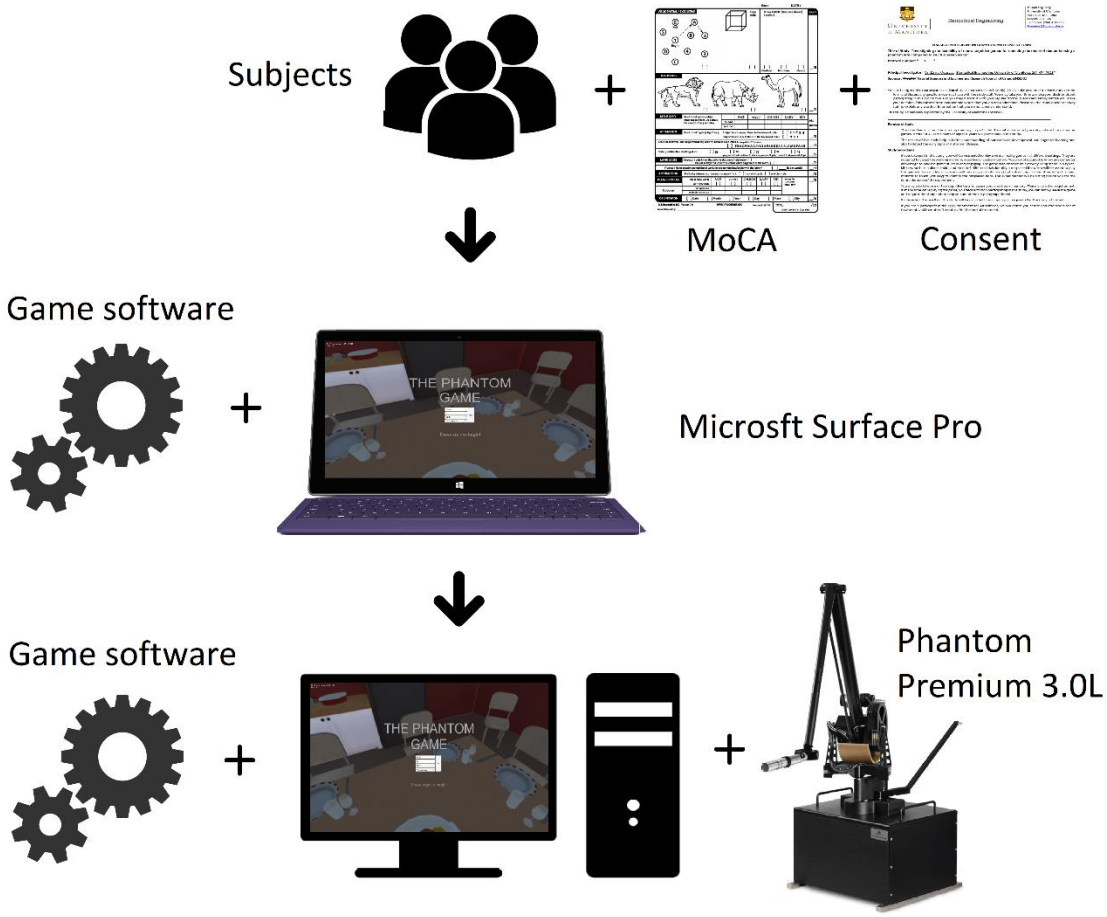

Figure 15: Study Overview

Older adult volunteers were invited to read and sign the research consent form approved by the Biomedical Ethics Research Board of the University of Manitoba (Appendix A). After they signed the consent form, we ran the MoCA test. If the participant's MoCA test score was above 18, they were enrolled in the study. We set the

MoCA score of 18 as an eligibility threshold because individuals with MoCA score lower than 18 would be unlikely able to complete the study and produce any meaningful data to be analyzed [112]. In addition to the MoCA test, the following information was collected from the participants: age, gender, date of birth, any diagnosis of dementia, handedness, hobbies, education, family history of dementia, employment background and history of depression. Other relevant information that the participant provided, such as plausible episodes of stroke were recorded. This information helps to control for confounding factors, construct hypotheses and eliminate any potential outliers. All the personal information of the participants was kept strictly confidential. All electronic data files and game output were identified only by an anonymized code and are securely stored.

After a participant was enrolled in the study, s/he played the games in its two versions, using either the phantom arm or the touchscreen. The game was played on the touchscreen device before it was played with the robotic arm. The touchscreen tablet is common in everyday life. By playing that first, the participant was familiarized with the game flow before moving on to the robotic arm. We chose this order to reduce any effect of game flow unfamiliarity on the game score. To further reduce this effect, the game consisted of one training trial and three scoring trials, where the participant could play as many times on the training trial before moving on to the scoring trials. The training trial also tests the participant for any potential motion sickness. After the participants completed the game on both hardware interfaces, the participants were asked to provide as much feedback as they had, specifically to what they found challenging.

The virtual reality headset was not utilized in the Phantom due to the potential for motion sickness.

3.2.1 Participants

All participants were selected from a database of participants in previous studies conducted by the University of Manitoba Biomedical research lab. A total of 45 participants with memory problems, mild cognitive impairment or diagnosis of early-stage dementia, confirmed by collaborating neuropsychiatrist and other studies conducted by the University of Manitoba biomedical research team, were recruited in the study. The inclusion/exclusion criteria for this study were:

Inclusion criteria:

- Participants must be 50 years old or older.
- Participants must have some memory problems due to ageing, diagnosed with mild cognitive impairment or early stage of Alzheimer's disease.
- Participants must have a Montreal Cognitive Assessment score above 18.
- Participants are capable of understanding and performing the experiment.

Exclusion criteria:

- Participants are diagnosed with any other neurological disorders such as Huntington disease, Parkinson's disease or Schizophrenia etc.
- Participants cannot adequately communicate in English and understand the experiment protocol.
- Participants are cognitively incapable of giving informed consent.

- Participants have a history of motion sickness or vertigo
- Participants cannot see or hear and this cannot be corrected with glasses, contact lenses or hearing aids.

The relatively small number of recruited participants was due to the difficulty of transportation to the University of Manitoba Engineering building. In addition, if the data in this study have a moderate or greater effect size, the number of 45 can provide a minimum statistical power of 0.8 for many of the statistical tests conducted.

Since this research was only a pilot study aimed at finding whether the game was effective as a neuro-cognitive assessment tool, there is no younger adult group against which the results can be compared, and no retest was performed.

3.3 Outcome Measurement

The game's scores were the outcome measures of this study. For each of the object identification tasks, the player scores points based on how many seconds remains from the allotted 30 seconds when the displaced item is found. Incorrectly identifying the object has no penalty and does not end the timer, if the displaced object is not found after 30 seconds, no score is given. The allotted 30 seconds is more than sufficient to identify the object if the user exhibits a guessing behaviour than the trial is skipped, and no score is given.

For each of the order recall task, the player scores points based on how many seconds remains in the allotted 30 seconds, multiplied by three to give the two different tasks equal scoring weights. Incorrectly recalling order has no penalty but does end the

timer, the player can try another time if the mistake was accidental. Otherwise, no score is given. For both tasks, the player can score up to 270 possible points for all three scoring trials. A total of 540 points for the entire game.

3.3.1 Game input and outputs

The game logs the player's code name, age, gender and their score along with the result of every task. Below is an example of the output log.

Name Test

Age 28

Sex 0

Trial#	obj#	Time	Score	Notes
1	3	28	28	Found object!
1	0	26	54	Found object!
1	2	29	83	Found object!
1	2	24	83	Order incorrect
1	2	28	83	Skipped Order

3.4 Data analysis

All data analysis was performed in the IBM SPSS Statistics software package due to its ease of use for both data entry and analysis, as well as the abundance of education materials. The data analysis was designed to investigate the objectives listed in section 1.2. A p-value of 0.05 was used for all tests for significance.

3.4.1 Variables

All variables subject to statistical analyses in this section are listed in Table 1.

Table 1: All variables, abbreviation and derivation

Description	**Abbreviation**	**Derivation**
Gender		
Age		
MoCA score		
Touchscreen object identification score	T_OI	
Touchscreen order recall score	T_OR	
Phantom arm object identification score	P_OI	
Phantom arm order recall score	P_OR	
Total touchscreen score	T_all	T_OI+T_OR
Total Phantom arm score	P_all	P_OI+P_OR
Total object identification score	OI_all	T_OI+P_OI
Total order recall score	OR_all	T_OR+P_OR

T_OI, T_OR, P_OI and P_OR are the four main game score measurements, T_all, P_all, OI_all and OR_all are the derived game score measurements.

3.4.2 Correlation Study

To investigate correlation as well as convergent validity [113], the Pearson correlation coefficient of all variables mentioned in section 3.5.1 were calculated.

3.4.3 Repeated Measures Multivariate Analysis of Covariance

To investigate whether there's a difference between the touchscreen and Phantom arm for object identification and order recall, a repeated measure multivariate analysis of covariance (MANCOVA) was used. The independent categorical variable is gender. The covariates are MoCA score and age; these two variables are treated as covariates since it is generally a waste of data to categorize a continuous variable [114]. The dependent variables are T_OI, T_OR, P_OI and P_OR scores; where T_OI and P_OI are repeated measures for object identification; T_OR and P_OR are repeated measures for order recall. A multivariate analysis controls for type 1 error probability [115] while an analysis of covariance improves statistical power [116].

The assumption testing for the repeated measures MANCOVA include the following [117]:

- Dependent variable and covariates are on a continuous scale, the independent variable consisted of two or more categorical independent groups, and there should be independence of observations between the groups of the independent variable. These research design related assumption are met for all analyses of covariance studies and not specifically tested.

- There should be a linear relationship between each pair of dependent variables within each group of the independent variable. This assumption is tested using a scatterplot matrix.
- There should be a linear relationship between the covariate and each dependent variable with each group of independent variables. This assumption is tested using a scatterplot matrix.
- There should be homogeneity of regression slopes. This assumption is tested by comparing the interaction effect of the independent variable and the covariates in the between-group analysis.
- There should be homogeneity of variance and covariances. This assumption is tested by comparing the Box'M Test of Equality of Covariance Matrices with a critical value of 0.001.
- There should be no significant univariate outliers. This assumption is tested by examining the residuals for absolute values greater than 3.
- There should be no significant multivariate outliers. This assumption is tested by looking at the Mahalanobis distance with a critical value of 15 for a small sample size.
- There should be multivariate normality for the dependent variables within the groups of independent variables. This assumption is tested by looking at the Shapiro Wilk test [118] of residuals [119] for each dependent variable.
- The sphericity assumption should be satisfied; since there are only two repeated measurements, this assumption testing is not needed.

3.4.4 Univariate Analysis of Covariance

To investigate the effect of MoCA, age, gender in the object identification, order recall tasks in either touchscreen game or phantom arm, four analyses of covariance were conducted [120]. Gender is the independent variable, age and MoCA scores are covariates and T_OI, T_OR, P_OI or P_OR were the dependent variables.

The assumption testing includes the following [117]:

- The dependent variable should not have any significant outliers. This assumption was tested by examining at the residuals for values outside of -3 and 3.
- The dependent variable should be normally distributed. This assumption was tested by looking at the Shapiro Wilk test of residuals [119].
- The dependent variable should have homogeneity of variance. This assumption was tested with Levene's test.
- The dependent variable should be linearly related to all the covariates at each level of the independent variable. This assumption was tested with scatterplot matrix.
- The dependent variable should have homogeneity of regression slopes. This assumption was tested by looking at the interaction effect of the independent variable and the covariates in the between-group analysis.

3.4.5 Regression Study

To investigate which version of the neuro-cognitive game could be a better predictor of MoCA score, two multiple regression studies were performed using the enter method [121]. Both multiple regression studies predict MoCA score with predictors T_OI and T_OR in the first study; P_OI and P_OR as predictors in the second study. The same predictors were also used to predict age in two other multiple regressions studies.

These assumptions must be met before a multiple regression study can be conducted [117]:

- There should be independence of errors. This was checked by the Durbin Watson statistics with a value between 1 and 3.
- There should be a linear relationship between the dependent variable collectively with the independent variable. This was checked with scatter plot.
- The residuals should be normally distributed. This was checked with a Shapiro-Wilk test on residuals.
- There should be no significant outliers. This assumption was tested by examining at the residuals for values outside of -3 and 3.
- There should be homoscedasticity. This is checked by plotting standardized predicted value vs standardized residual and look for an absence of distinct patterns such as fanning.
- There should not be multicollinearity of the predictors, using a critical Pearson value of 0.8.

3.4.6 Hypotheses

The research hypotheses are:

1. There is a significant correlation between the MoCA score and the object identification score in hardware both versions.
2. There is a significant correlation between the MoCA score and the order recall score in hardware both versions.
3. Performance of the game in the robotic arm version is significantly different compared to the touchscreen version.
4. There is a significant correlation between age and the Phantom score of the robotic arm version.
5. The touchscreen version of the game better predicts MoCA score compared to the robotic arm version.

CHAPTER IV: RESULT

This chapter presents results obtained from data analysis mentioned in section 3.7. Detailed assumption testing is shown in Appendix B.

4.1 Descriptive Statistics

A total of 45 participants were examined in this research; there were 19 male and 26 female participants. Among those participants with lower MoCA scores, four were diagnosed with MCI and 3 with AD. The AD participants did not participate in the Phantom robotic arm version of the game due to their inability to understand how to operate the Phantom arm. In addition, 2 of the Alzheimer's participant did not score a MoCA score higher than 18, which rendered their data unusable. Table 2 illustrates the four main game scores measurements by diagnosis.

Table 2: Game scores by diagnosis

Diagnosis	**Age Mean ±SD**	**MoCA Mean ±SD**	**Touchscreen Object Identification (T_OI) Mean ±SD**	**Touchscreen Order Recall (T_OR) Mean ±SD**	**Phantom Object Identification (P_OI) Mean ±SD**	**Phantom Order Recall (P_OR) Mean ±SD**
Healthy (n=38)	70.29 ±6.76	27.68 ±2.068	211.66 ±20.11	143.45 ±61.67	199.16 ±27.75	81.63 ±52.73
MCI (n=4)	74.25 ±4.35	25 ±1.633	149.75 ±43.83	33.75 ±23.42	168.25 ±57.94	11.25 ±13.05
AD (n=3)	71.33 ±17.01	15 ±7.211	117 ±84.64	0	N/A	N/A

Since Alzheimer's participants did not participate in the Phantom arm game, they were removed from the statistical analysis.

MoCA score was divided into three groups: Low (19≤ MoCA ≤ 26), Medium (27 ≤ MoCA ≤ 28) and High (29 ≤ MoCA ≤ 30). The cut off value of 26 for defining low MoCA value is commonly used in the literature [90]. Table 3 illustrates the four main game score measurements by MoCA group.

Table 3: Game scores by MoCA

MoCA	**Age Mean ±SD**	**Touchscreen Object Identification (T_OI) Mean ±SD**	**Touchscreen Order Recall (T_OR) Mean ±SD**	**Phantom Object Identification (P_OI) Mean ±SD**	**Phantom Order Recall (P_OR) Mean ±SD**
Low (n=13)	71.00 ±4.62	182.62 ±34.02	71.54 ±57.64	187.38 ±36.62	43.62 ±44.71
Medium (n=11)	72.27 ±5.35	213.45 ±22.62	147.55 ±56.04	197.55 ±16.20	73.91 ±37.64
High (n=18)	69.44 ±8.43	217.78 ±17.77	168.50 ±48.82	201.78 ±35.73	98.17 ±59.75

The mean, standard deviation, skewness, kurtosis is calculated for all measurements mentioned in section 3.4.1. This is shown in Table 4: Descriptive statistics for all measurements.

Table 4: Descriptive statistics for all measurements

Data	Mean ± SD	Min	Max	Skewness	Kurtosis
Age	70.67±6.639	51	81	-0.903	0.889
MoCA	27.43±2.166	23	30	-0.556	-0.762
Touchscreen Object Identification (T_OI)	205.76±29.046	86	242	-1.820	5.8
Touchscreen Order Recall (T_OR)	133.00±67.339	0	240	-0.388	0.365
Touchscreen Total score (T_all)	338.76±89.655	134	479	-0.578	-0.458
Phantom Object Identification (P_OI)	196.21±32.011	83	241	-2.160	5.886
Phantom Order Recall (P_OR)	74.93±54.399	0	210	0.301	-0.545
Phantom Total score (P_all)	271.14±75.360	83	451	-0.3	0.772
Object Identification Total score (OI_all)	401.98±55.284	169	475	-2.224	7.380
Order Recall Total score (OR_all)	207.93±111.304	0	420	-0.033	-1.142

4.2 Correlation study

The correlation coefficient among the four main game score measurements with age and MOCA are shown in Table 5. There was a significant correlation between MoCA and all touchscreen measurements. Age significantly correlated with all robotic arm measurements. There was also no significant correlation between age and MoCA score.

Table 5: Pearson correlation of main measurements

	Age	**MoCA**	**Touchscreen Object Identification (T_OI)**	**Touchscreen Order Recall (T_OR)**	**Phantom Object Identification (P_OI)**	**Phantom Order Recall (P_OR)**
Age	1					
MoCA	-.107	1				
Touchscreen Object Identification (T_OI)	-.343*	.583**	1			
Touchscreen Order Recall (T_OR)	-.255	.668**	.680**	1		
Phantom Object Identification (P_OI)	-.443**	.199	.639**	.344*	1	
Phantom Order Recall (P_OR)	-.375*	.474**	.519**	.668**	.487**	1

*. Correlation is significant at the 0.05 level.

**. Correlation is significant at the 0.01 level.

The correlation coefficient among the derived game score measurements with age and MOCA are shown in Table 6. The touchscreen game had a stronger correlation with MoCA compared to the phantom arm game. The phantom arm game had significant correlation with both age and MoCA score.

Table 6: Pearson correlation of derived measurements

	Age	**MoCA**	**Touch screen Total score (T_all)**	**Phantom Total score (P_all)**	**Object Identification Total score (OI_all)**	**Order Recall Total score (OR_all)**
Age	1					
MoCA	-.107	1				
Touchscreen Total score (T_all)	-.303	.690**	1			
Phantom Total score (P_all)	-.459**	.427**	.681**	1		
Object Identification Total score (OI_all)	-.437**	.422**	.708**	.789**	1	
Order Recall Total score (OR_all)	-.338*	.636**	.915**	.834**	.608**	1

*. Correlation is significant at the 0.05 level.

**. Correlation is significant at the 0.01 level.

4.3 Repeated measure MANCOVA study

The results of the within participants effect of the repeated measures MANCOVA is shown in Table 7. The within-participant factor for object identification

is labelled TvP_OI, the within-participant factor for order recall is labelled TvP_OR. As shown in Table 7, there was a significant difference between the touchscreen and Phantom arm version for both object identification and order recall tasks. In addition, there was a strong interaction effect of MoCA for both tasks.

Table 7: Repeated measures MANCOVA within participants result

Test	**Result**
TvP_OI	$F_{1,36}$=11.213, p < .005
TvP_OI*MoCA	$F_{1,36}$=13.553, p < .005
TvP_OI*Age	$F_{1,36}$=0.770, p > .05
TvP_OI*gender	$F_{1,36}$=0.002, p > .05
TvP_OR	$F_{1,36}$=5.736, p < .05
TvP_OR*MoCA	$F_{1,36}$=8.035, p < .05
TvP_OR*Age	$F_{1,36}$=0.481, p > .05
TvP_OR*gender	$F_{1,36}$=0.115, p > .05

It was observed that many of the high scorers of the touchscreen game performed poorer in the Phantom arm version of the game, and these participants usually have high MoCA score. In comparison, participants with lower MoCA score also performed worse in the Phantom arm version, although the difference in game score across the hardware platform was smaller compared to the higher MoCA scorers.

4.4 ANCOVA study

Applying ANCOVA on the touchscreen object identification score showed MoCA as the only significant effect *($F_{1,36}=25.93, p<.0001$)* while age was not significant *($F_{1,36}=3.457, p > .05$).* Performing ANCOVA on the touchscreen order recall score showed MoCA as the only significant effect *($F_{1,36}=28.28, p<.001$).* Again, age was shown not to influence the touchscreen score *($F_{1,36}=1.862, p > .05$).*

Age was the only significant effect *($F_{1,36}=9.852, p<.005$)* when applying ANCOVA to the phantom arm object identification score, although MoCA was nearly significant *($F_{1,36}=3.318, p > .05$).* Finally, applying ANCOVA on phantom arm order recall score showed MoCA to be the only significant factor *($F_{1,36}=8.783, p < .005$).* Age was nearly significant *($F_{1,36} = 3.526, p > .05$).*

Gender was not a significant factor in any of the ANCOVA tests.

4.5 Regression study

A multiple regression model predicting MoCA using touchscreen game result was found to be significant *($F_{2,39}=21.614$ $p<.001$ $R^2 = 0.539$).* In addition, both touchscreen object identification *($\beta = 0.374, p<.05$)* and order recall *($\beta=0.414, p<0.05$)* was significant on MoCA score. A multiple regression model predicting MoCA using phantom arm game result was also found to be significant *($F_{2,39}=23.097$ $p<.005$ $R^2 = 0.251$).* Only phantom arm order recall *($\beta=0.460, p<0.01$)* was a significant predictor of MoCA score.

The multiple regression model predicting age using touchscreen score was not found to be significant. However, the model predicting age with the phantom arm score was significant *($F_{2,39}=5.694$ $p<.01$ $R^2 = 0.235$).* Only the phantom arm object identification score had a significant effect on age *($\beta=-0.389$, $p<.05$).*

The multiple regression study agreed with correlation and ANCOVA study, where touchscreen score better predicted MoCA, and robotic arm score better predicted age.

CHAPTER V: DISCUSSION

It was expected that the MCI participant's cognitive ability lies between that of healthy older adults and AD patients [5]. The large disparity in game score between MCI and healthy participants suggest the game can be a sensitive measurement for dementia detection. It is important to note that MCI participants scored much lower in order recall task compared to object identification task. This is congruent with findings in the literature where memory retention interval is significantly impaired in MCI [63]. This also suggests that memory retention ability might be a more sensitive measurement at dementia detection compared to spatial memory. However, the small number of MCI and AD patients was a major limitation.

Since the MoCA was designed to detect MCI, it was a good benchmark for our game due to the large overlap of cognitive abilities examined, such as visuospatial, attention and memory abilities [90]. Specifically, object identification tests the user's spatial memory span, while the order recall tests the user's memory retention interval. In the touchscreen version, there was a significant correlation between the MoCA score and both types of memory tasks, while age is only correlated with object identification. This finding concurs with literature where spatial memory declines with age while short-term memory retention ability is preserved in healthy older adults [62]. Although MoCA and age do not significantly correlate with each other, age does affect many of the cognitive abilities assessed by MoCA. In addition, one cognitive impairment may mask another deficit. For example, unable to recall the object renders the ability to navigate to the object undetectable. The game was designed in a way such that the better the ability to

perform object identification, the easier it is to perform order recall. The longer a participant spends identifying the displaced object, the longer the displaced objects must be memorized. Participants who could not identify the displaced object would not be able to complete order recall at all. Good performers of object identification did even better in order recall, while bad object identification performers did worse in order recall.

Initially, it was thought that the phantom robotic arm would be a more naturalistic and intuitive way for the participants to navigate in the virtual environment. In our study, the significant difference in scores between the hardware platforms could be attributed to a deficit in visuomotor ability. To perform visuomotor tasks, information from different modalities and coordinate systems must be integrated and transformed [122]. In the touchscreen version of the game, the visual location of an object relative to the hand needs to be translated into motor commands that enables touch. The visuomotor task has increased difficulty in the phantom arm version of the game, where the coordinate system within the 3D virtual environment must be transformed to the coordinate system of the phantom robotic arm, which then allowed generation of the correct motor commands. Heuer and Hegele [123] found a decline of visuomotor adaptation at older working age, where the ability to acquire explicit knowledge and application of visuomotor transformation becomes poorer. This is consistent with our result where age correlated with game scores in both tasks played with the phantom arm.

In older adults with mild cognitive decline, Schaffert et al. [124] found less adaptability in participants with low MoCA score using a normal error feedback system;

when the error feedback is enhanced, similar visuomotor adaptability were observed regardless of MoCA score; the same study also found that spatial working memory and processing speed are correlated with visuomotor adaptability. In our game, MoCA had no significant correlation with phantom arm object identification score. This was unexpected since MoCA had significant correlation with touchscreen object identification score. Based on the study of Schaffert et al., one explanation is that the phantom arm provided error feedback in the form of haptic feedback compared to the touchscreen version. Another possibility is that any deficit of visuomotor transformation was masking the effect of spatial memory since the inability to operate the phantom arm resulted in lower score regardless of whether the participant could remember the displaced object. The interaction effect of MoCA score on the differences in game score across the hardware interfaces was perhaps due to the high scorers of the touchscreen game struggling mainly from the difficulty of visuomotor transformation in the phantom arm game; whereas lower MoCA scorers suffered from additional impairments that masked the effect of the visuomotor transformation. Therefore, the touchscreen game result better predicts the MoCA score compared to the phantom arm version of the game.

In addition to functions mentioned in section 2.2.5, the PPC is thought to have a role in visuomotor transformation, as damage to the PPC can result in difficulty in hand reaching tasks without any visual or motor deficits [125]. Hawkins and Sergio [126] suggest that visuomotor ability may be disrupted in the very early stages of AD due to disruption of communication between the hippocampal, parietal, and frontal brain

regions. Verheij et al. [127] found that AD patients need significantly more time to start and execute hand reaching task. Tippett and Sergio [128] found similar results where there were significant differences between patients and controls on reaction time and movement time; significant increased error in task completion was also found in the patient's group, even with participants suffering minimal cognitive deficits. Since the neural networks involving the PPC are affected in the early stage of the AD [15], the phantom arm game could also be a very sensitive tool for separating MCI and AD since it assesses both the accuracy and execution time of visuomotor transformation.

The limitations of MoCA was mentioned in section 2.4.1. Our game does not suffer from said limitations due to its independence of language or educational background [96] . Our game is also randomized to prevent any learned effect on the game score. Furthermore, the scoring of our game is not dependent on the assessor compared to many neuro-cognitive assessments. Finally, our game performs a more thorough examination of spatial memory ability, whereas MoCA does not adequately test its subset of cognitive abilities [98] [99]. Although the phantom arm version of the game further examines visuomotor transformation, the Phantom robotic arm is not portable, and an administrator is required. The touchscreen version of the game can be played alone with only a tablet, making it an excellent complementary tool to the MoCA test.

CHAPTER VI: CONCLUSION AND FUTURE WORK

Effective detection of dementia onset can lead to the preservation of an individual's cognitive ability as well as delay or prevent neuro-degenerative disease such as Alzheimer's. Inspired by caretakers of Alzheimer's patients and closely related research, we developed a video game as a brief assessment tool to detect the onset of dementia. The game was played on a touchscreen tablet and a phantom robotic arm; players were asked to perform memory-based object identification and order recall tasks. The game examines cognitive domains that were affected early in dementia, such as object recognition, spatial memory and memory retention. MoCA test was used to be compared against the game's score.

As expected, MCI had performance in between those of healthy older adults and AD participants. Since the game and MoCA have many overlaps in cognitive evaluation, we found a significant correlation between the MoCA and the game score. Players also had significantly better performance in the touchscreen version compared to the robotic arm version. Touchscreen game score was found to be a significant predictor of MoCA score while phantom arm score is a significant predictor of age. Examining the two types of tasks, we found that object identification and order recall skills are mostly preserved in healthy older adults, while there was a significant deficit in order recall ability in MCI participants. In conclusion, the proposed game is user-friendly, non-expensive, non-invasive can be a very sensitive and specific measurement for dementia detection.

Since this is a preliminary study, there was limited availability of MCI and AD patients. A clinical trial could follow with participation from MCI, AD and healthy age-matched control participants to determine the game's sensitivity and specificity. A longitudinal study can be performed on participants who participated in this research to determine test-retest reliability. The game itself can be tweaked to test individual cognitive abilities more distinctively to measure the extent of impairment in each cognitive domain. The game score of each task can also be weighted differently to maximize sensitivity and specificity.

References

[1] S. McCallum, "Gamification and serious games for personalized health.," *Studies in Health Technology and Informatics,* vol. 177, pp. 85-96, 2012.

[2] "Alzheimer's Disease International: Dementia statistics," [Online]. Available: http://www.alz.co.uk/. [Accessed 11th Jan 2018].

[3] S. McCallum and C. Boletsis, "Dementia Games: A Literature Review of Dementia-Related Serious Games," *International Conference on Serious Games Development and Applications,* pp. 15-27, 2013.

[4] S. Gauthier, B. Reisberg and M. Zaudig, "Mild cognitive impairment," *Lancet,* vol. 367, pp. 1262-70, 2006.

[5] J. Morris, M. Storandt, J. Miller, D. McKeel, J. Price, E. Rubin and L. Berg, "Mild cognitive impairment represents early-stage Alzheimer disease.," *Arch Neurol,* vol. 58, pp. 397-405, 2001.

[6] G. McKhann, D. Drachman and M. Folstein, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease," *Neurology,* vol. 55, pp. 815-828, 1984.

[7] R. Petersen, G. Smith and S. Waring, "Mild cognitive impairment: clinical characterization and outcome.," *Archives of Neurology,* vol. 56, pp. 303-308, 1999.

[8] R. Petersen, Conceptual Overview. Mild Cognitive Impairment: Aging to Alzheimer's Disease, New York: Oxford University Press, Inc, 2003.

[9] R. Peterson, "Mild cognitive impairment clinical trials.," *Nat Rev Drug Discov.,* vol. 2, pp. 646-653, 2003.

[10] T. Hänninen, M. Hallikainen, S. Tuomainen, M. Vanhanen and H. Soininen, "Prevalence of mild cognitive impairment: a population-based study in elderly subjects.," *Acta Neurologica Scandinavica,* vol. 106, pp. 148-154, 2002.

[11] J. Mitchell and M. Shiri-Feshki, "Rate of progression of mild cognitive impairment to dementia-meta-analysis of 41 robust inception cohort studies.," *Acta Psychiatrica Scandinavica,* vol. 119, pp. 252-265, 2009.

[12] H. Braak and E. Braak, "Neuropathological staging of Alzheimer-related changes.," *Acta Neuropathol,* vol. 82, pp. 239-59, 1991.

[13] T. Schmidt-Wilcke, S. Poljansky, S. HierlMeier, J. Hausner and B. Ibach, "Memory performance correlates with gray matter density in the ento-/perirhinal cortex and posterior hippocampus in patients with mild cognitive impairment and healthy controls--a voxel based morphometry study," *Neuroimage,* vol. 47, pp. 1914-20, 2009.

[14] G. Chetelat, B. Desgranges, V. De La Sayette, F. Viader, F. Eustache and J. Baron, "Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment," *Neuroreport,* vol. 13, pp. 1939-1943, 2002.

[15] C. Mcdonald, L. Mcevoy, L. Gharapetian, C. Fennema-Notestine, D. Hagler, D. Holland, A. Koyama, J. Brewer and A. Dale, "Regional rates of neocortical atrophy from normal ageing to early Alzheimer disease," *Neurology,* vol. 73, pp. 457-465, 2009.

[16] N. Schuff, D. Tosun, P. Insel, G. Chiang, D. Truran and P. Aisen, "Nonlinear time course of brain volume loss in cognitively normal and impaired elders," *Neurobiol ageing,* vol. 33, pp. 845-855, 2013.

[17] D. Karow, L. McEvoy, C. Fennema-Notestine, D. Hagler, R. Jennings, J. Brewer, C. Hoh and A. Dale, "Relative Capability of MR Imaging and FDG PET to depict changes associated with prodromal and early Alzheimer disease," *Radiology,* vol. 256, pp. 932-942, 2010.

[18] J. Pruessner, S. Kohler, J. Crane, M. Pruessner, C. Lord and A. Byrne, "Volumetry of temporopolar, perirhinal, entorhinal and parahippocampal cortex from high-resolution MR images: considering the variability of the collateral sulcus.," *Cereb. Cortex,* vol. 12, pp. 1342-1353, 2002.

[19] P. Lavenex and D. Amaral, "Hippocampal-neocortical interaction: a hierarchy of associativity.," *Hippocampus,* vol. 10, pp. 420-430, 2000.

[20] M. Di Paola, E. Macaluso, G. Carlesimo, F. Tomajuolo, K. Worsley, L. Fadda and C. Caltagirone, "Episodic memory impairment in patients with Alzheimer's disease is correlated with entorhinal cortex atrophy. A voxel-based morphometry study.," *J Neurol.,* vol. 254, pp. 774-81, 2007.

[21] C. Kirwan and C. Stark, "Medial temporal lobe activation during encoding and retrieval of novel face-name pairs.," *Hippocampus,* vol. 14, pp. 919-930, 2004.

[22] P. Bellgowan, E. Buffalo, J. Bodurka and A. Martin, "Lateralized spatial and object memory encoding in entorhinal and perirhinal cortices," *Learn Mem.,* vol. 24, pp. 433-9, 2009.

[23] N. Suthana, Z. Haneef, J. Stern, R. Mukamel, E. Behnke, B. Knowlton and I. Fried, "Memory enhancement and deep-brain stimulation of the entorhinal area.," *N Engl J Med.,* vol. 366, pp. 502-10, 2012.

[24] C. L. G. X. M. R. H. C. e. a. Hagmann P, "Mapping the structural core of human cerebral cortex," *PLoS Biol.,* vol. 6, 2008.

[25] E. Murray and B. Richmond, "Role of perirhinal cortex in object perception, memory, and associations.," *Curr Opin Neurobiol.,* vol. 11, pp. 188-93, 2001.

[26] A. Parker and D. Gaffan, "Lesions of the primate rhinal cortex cause deficits in flavour-visual associative memory.," *Behav Brain Res,* vol. 93, pp. 99-105, 1998.

[27] W. Suzuki, "Neuroanatomy of the monkey entorhinal, perirhinal and parahippocampal cortices: organization of cortical inputs and interconnections with amygdala and striatum.," *Semin Neurosci,* vol. 8, pp. 3-12, 1996.

[28] M. Meunier, J. Bachevalier, M. Mishkin and E. Murray, "Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys.," *J Neurosci,* vol. 13, pp. 5418-5432, 1993.

[29] E. Barbeau, M. Didic, E. Tramoni, O. Felician, S. Joubert, A. Sontheimer, M. Ceccaldi and M. Poncet, "Evaluation of visual recognition memory in MCI patients.," *Neurology,* vol. 62, pp. 1317-22, 2004.

[30] I. Morgado-Bernal, "Learning and memory consolidation: Linking molecular and behavioral data.," *Neuroscience,* vol. 176, pp. 12-9, 2011.

[31] K. Anand and V. Dhikav, "Hippocampus in health and disease: An overview," *Ann Indian Acad Neurol,* vol. 15, pp. 239-246, 2012.

[32] V. Dhikav and K. Anand, "Potential predictors of hippocampal atrophy in Alzheimer's disease.," *Drugs Aging,* vol. 28, pp. 1-11, 2011.

[33] A. Pelletier, C. Bernard, B. Dilharreguy, C. Helmer, M. Goff, S. Chanraud, J. Dartigues, M. Allard, H. Amieva and G. Catheline, "Patterns of brain atrophy associated with episodic memory and semantic fluency decline in ageing," *Aging,* vol. 9, pp. 741-752, 2017.

[34] S. Geva, J. Cooper, D. Gadian, M. Mishkin and F. Vargha-Khadem, "Impairment on a self-ordered working memory task in patients with early-acquired hippocampal atrophy.," *Dev Cogn Neurosci,* vol. 20, pp. 12-22, 2016.

[35] S. Mueller, N. Schuff, K. Yaffe, C. Madison, B. Miller and M. Weiner, "Phippocampal atrophy patterns in mild cognitive impairment and Alzheimer's disease.," *Hum Brain Mapp.,* vol. 31, pp. 1339-47, 2010.

[36] A. Cavanna and M. Trimble, "The precuneus: a review of its functional anatomy and behavioural correlates.," *Brain,* vol. 129, pp. 564-83, 2006.

[37] O. Simon, J. Mangin, L. Cohen, D. Le Bihan and S. Dehaene, "Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe.," *Neuron,* vol. 33, pp. 475-87, 2002.

[38] Y. Nagahama, T. Okada, Y. Katsumi, H. Hayashi, H. Yamauchi and N. Sawamoto, "Transient neural activity in the medial superior frontal gyrus and precuneus time locked with attention shift between object features.," *Neuroimage,* vol. 10, pp. 193-9, 1999.

[39] P. Fletcher, T. Shallice, C. Frith, R. Frackowiak and R. Dolan, "Brain activity during memory retrieval: the influence of imagery and semantic cueing.," *Brain,* vol. 119, pp. 1587-96, 1996.

[40] B. Krause, D. Schmidt, F. Mottaghy, J. Taylor, U. Halsband and H. Herzog, "Episodic retrieval activates the precuneus irrespective of the imagery content of word pair associates: a PET study.," *Brain,* vol. 122, pp. 255-63, 1999.

[41] B. Luber, L. H. Kinnunen, B. Rakitin, R. Ellaser, Y. Stern and S. Lisanby, "Facilitation of performance in a working memory task with rTMS stimulation of the precuneus: Frequency- and time-dependent effects," *Brain res,* vol. 1128, pp. 120-9, 2007.

[42] G. Weniger, M. Ruhleder, C. Lange, S. Wolf and E. Irle, "Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment.," *Neuropsychologia,* vol. 49, pp. 518-527, 2011.

[43] R. Leech and D. Sharp, "The role of the posterior cingulate cortex in cognition and disease," *Brain,* vol. 137, pp. 12-32, 2014.

[44] D. Gusnard and M. Raichle, "Searching for a baseline: functional imaging and the resting human brain.," *Nat Rev Neurosci,* vol. 2, pp. 685-94, 2001.

[45] R. Maddock, A. Garrett and M. Buonocore, "Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval," *Neuroscience,* vol. 104, pp. 667-76, 2001.

[46] D. Gusnard, E. Akbudak, G. Shulman and M. Raichle, "Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function.," *Proc Natl Acad Sci USA,* vol. 98, pp. 4259-64, 2001.

[47] R. Buckner, J. Andrews-Hanna and D. Schacter, "The brain's default network: anatomy, function, and relevance to disease.," *Ann N Y Acad Sci.,* vol. 1124, pp. 1-38, 2008.

[48] M. Greicius, G. Srivastava, A. Reiss and V. Menon, "Default-mode network activity distinguishes Alzheimer's disease from healthy ageing: evidence from functional MRI.," *Proc Natl Acad Sci USA,* vol. 101, pp. 4637-42, 2004.

[49] V. Bonnelle, R. Leech, K. Kinnuen, T. Ham, C. Beckmann and X. De Boissezon, "Default mode network connectivity predicts sustained attention deficits after traumatic brain injury.," *J Neurosci,* vol. 31, pp. 13442-51, 2011.

[50] S. Ding, G. Van Hoesen and K. Rockland, "Inferior parietal lobule projections to the presubiculum and neighboring ventromedial temporal cortical areas.," *The Journal of comparative neurology,* vol. 425, pp. 510-520, 2000.

[51] D. Clower, R. West, J. Lynch and P. Strick, "The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum.," *The Journal of neuroscience: The official journal of the Society of Neuroscience,* vol. 21, pp. 6283-6291, 2001.

[52] J. Burks, L. Boettcher, A. Conner, C. Glenn and P. Bonney, "White matter connections of the inferior parietal lobule: A study of surgical anatomy," *Brain Behav,* vol. 7, 2017.

[53] J. Baldo and N. Dronkers, "The role of inferior parietal and inferior frontal cortex in working memory.," *Neuropsychology,* vol. 20, pp. 529-38, 2006.

[54] G. Small, L. Ercoli, D. Silverman and e. al., "Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease," *Proc Natl Acad Sci U S A,* vol. 97, pp. 6037-6042, 2000.

[55] F. Re´my, F. Mirrashed, B. Campbell and W. Richter, "Verbal episodic memory impairment in Alzheimer's disease: a combined structural and functional MRI study," *NeuroImage,* vol. 25, pp. 253-266, 2005.

[56] T. A. Salthouse, "The processing-speed theory of adult age differences in cognition," *Psychol. Rev.,* vol. 103, pp. 403-428, 1996.

[57] F. Craik, "A functional account of age differences in memory," in *Hum. Memory Cogn. Capabilities: Mech. Perf.*, Elsevier Science Publishers, 1986, pp. 409-422.

[58] A. Baddeley, M. Eyesenck and C. Anderson, Memory, New York, NY, USA: Psychology Press, 2015.

[59] T. Iachini, G. Ruggiero, F. Ruotolo and R. Pizza, "Age and gender differences in some components of spatial cognition," in *Women and Aging*, New York, Nova Science Publisher, 2008.

[60] Finkel D, C. Reynolds, J. McArdle and N. Pedersen, "Age changes in processing speed as a leading indicator of cognitive ageing," *Psychol Aging.,* vol. 22, pp. 558-68, 2007.

[61] A. Kochan, M. Breakspear and J. Slavin, "Functional alterations in brain activation and deactivation in mild cognitive impairment in response to a graded working memory challenge.," *Dementia and Geriatric Cognitive Disorders.,* vol. 30, pp. 553-568, 2010.

[62] P. Rutledge, R. Hancock and L. Walker, "Effects of retention interval length on young and elderly adults' memory for spatial information," *Exp Aging Res,* vol. 23, pp. 163-77, 1997.

[63] L. Gagnon and S. Belleville, "Working memory in mild cognitive impairment and Alzheimer's disease: contribution of forgetting and predictive value of complex span tasks.," *Neuropsychology,* vol. 25, pp. 226-36, 2011.

[64] C. DeCarli, B. Miller, G. Swan, T. Reed, P. Wolf and D. Carmeli, "Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung and Blood Institute Twin study," *Arch Neurol,* vol. 58, pp. 643-647, 2001.

[65] N. Eilan, "Molyneux's question and the idea of an external world.," in *Spatial representation: Problems in philosophy and psychology,* Malden, MA, US, Blackwell publishing, 1993, pp. 236-255.

[66] L. Ungerleider and M. Mishkin, Analysis of visual behavior, Cambridge, MA: MIT Press, 1982.

[67] M. Sharps and E. Gollin, "Aging and free recall for objects located in space.," *J Gerontol,* vol. 43, pp. 8-1, 1988.

[68] A. Troyer, K. Murphy, N. Anderson, B. Hayman-Abello, F. Craik and M. Moscovitch, "Item and associative memory in amnestic mild cognitive impairment: performance on standardized memory tests.," *Neuropsychology,* vol. 22, pp. 10-6, 2008.

[69] J. Chodosh, D. Petitti, M. Eliott, R. Hays, V. Crooks, D. Reuben, B. Galen and N. Wenger, "Physician recognition of cognitive impairment: evaluating the need for improvement," *J Am Geriatr Soc.,* vol. 52, pp. 1051-9, 2004.

[70] A. Anoop, P. Singn, R. Jacob and S. Maji, "CSF Biomarkers for Alzheimer's Disease Diagnosis," *Int J Alzheimers Dis,* 2010.

[71] Anonymous, "Medicare coverage of Annual Wellness Visit providing a personalized prevention plan," Fed Regist, 2010.

[72] I. Arevalo-Rodriguez, "Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI)," Cochrane Database Syst Rev, 2015.

[73] W. Lorentz, J. Scanlan and S. Borson, "Brief screening tests for dementia," *Can J Psychiatry,* vol. 47, pp. 723-33, 2002.

[74] H. Brodaty, L. Low, L. Gibson and K. Burns, "What is the best dementia screening instrument for general practitioners to use?," *Am J Geriatr Psychiatry,* vol. 14, pp. 291-400, 2006.

[75] A. Milne, A. Culverwell, R. Guss, J. Tuppen and R. Whelton, "Screening for dementia in primary care: a review of the use, efficacy and quality of measures.," *Int Psychogeriatr,* vol. 20, pp. 911-926, 2008.

[76] Z. Ismail, T. Rajji and K. Shulman, "Brief cognitive screening instruments: an update," *International Journal of Geriatric Psychiatry,* vol. 25, pp. 111-120, 2010.

[77] M. Folstein, S. Folstein and P. McHugh, "Mini-mental state. A practical method for grading the cognitive state of patients for the clinician.," *J Psychiatr Res,* vol. 12, pp. 189-198, 1975.

[78] G. Bravo and R. Herber, "Age and education specific reference values for the Mini-Mental and modified Mini-Mental State Examinations derived from a non-demented elderly population.," *Int J Geriatr Psychiatry,* vol. 12, pp. 1008-1018, 1997.

[79] M. Scazufca, O. Almeida, H. Vallade, W. Tasse and P. Menezes, "Limitations of the Mini-Mental State Examination for screening dementia in a community with low socioeconomic status: results from the Sao Paulo Ageing & Health Study.," *Eur Arch Psychiatry Clin Neurosci,* vol. 259, pp. 8-15, 2009.

[80] M. Folstein, "Mini-mental and son.," *Int J Geriatr Psychiatry,* vol. 13, pp. 290-294, 1998.

[81] A. Michell, "A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment.," *J Psychiatr Res,* vol. 43, pp. 411-431, 2009.

[82] K. Shulman, "Clock-drawing: is it the ideal cognitive screening test?," *Int J cognitive screening instruments,* vol. 15, pp. 548-561, 2000.

[83] A. Garcia-Caballero, M. Recimil and I. Garcia-Lado, "ACE clock scoring: a comparison with eight standard correction methods in a population of low educational level.," *J Geriatr Psychiatry Neurol,* vol. 19, pp. 216-219, 2006.

[84] M. Lessig, J. Scanlan, H. Nazemi and S. Borson, "Time that tells: critical clock-drawing errors for dementia screening.," *Int Psychogeriatr,* vol. 20, pp. 459-470, 2008.

[85] H. Buschke, D. Pond and N. Kemp, "Screening for dementia with the memory impairment screen," *Neurology,* vol. 52, pp. 231-238, 1999.

[86] S. Borson, J. Scanlan, M. Brush and P. Vitaliano, "The mini-cog:acognitive 'vital signs' measure for dementia screening in multi-lingual elderly.," *Int J geriatr Psychiatry,* vol. 15, pp. 1021-1027, 2000.

[87] S. Borson and J. Scanlan, "The Mini-cog as a screen for dementia: validation in a population-based sample.," *J Am Geriatr Soc,* vol. 53, pp. 1451-1454, 2003.

[88] S. Borson and J. Scanlan, "Simplifying detection of cognitive impairment: comparison of the Mini-Cog and Mini-Mental State Examination in a multiethnic sample.," *J Am Geriatr Soc,* vol. 53, pp. 871-874, 2005.

[89] H. Brodaty, D. Pond and N. Kemp, "The GPCOG: a new screening test for dementia designed for general practice.," *J Am Geriatr,* vol. 50, pp. 530-534, 2002.

[90] Z. Nasreddine, N. Phillips, S. Charbonneau, V. Whitehead, I. Collin, J. Cummings and H. Chertkow, "The Montreal Cognitive Assessment (MoCA©): A Brief Screening Tool for Mild Cognitive Impairment," *Journal of the American Geriatrics Society,* vol. 53, pp. 695-699, 2005.

[91] T. Smith, N. Gildeh and C. Holmes, "The Montreal Cognitive Assessment: validity and utility in a memory clinic setting.," *Can J Psychiatry,* vol. 52, pp. 329-332, 2007.

[92] C. Luis, A. Keegan and M. Mullan, "Cross validation of the Montreal Cognitive Assessment in community dwelling older adults residing in the Southeastern US.," *Int J Geriatr Psychiatry,* vol. 24, pp. 197-201, 2009.

[93] J. Lee, W. Dong and S. Cho, "Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal cognitive assessment.," *J Geriatr Psychiatry Neurol,* vol. 21, pp. 104-110, 2008.

[94] H. John, "The Montreal Cognitive Assessment(MoCA)," *Occupational Medicine,* vol. 65, pp. 764-765, 2015.

[95] A. Ng, I. Chew, K. Narasimhalu and N. Kandiah, "Effectiveness of Montreal Cognitive Assessment for the diagnosis of mild cognitive impairment and mild Alzheimer's disease in Singapore," *Singapore Med J,* vol. 54, pp. 616-619, 2013.

[96] E. yancar Demir and T. Ozcan, "Evaluating the relationship between education level and cognitive impairment with the Montreal Cognitive Assessment Test," *Psychogeriatrics,* vol. 15, pp. 186-90, 2015.

[97] S. McLennan, J. Mathias and L. Brennan, "Validity of the Montreal Cognitive Assessment(MoCA) as a Screening Test for Mild Cognitive Impairment(MCI) in a Cardiovascular Population," *Journal of Geriatric Psychiatry and Neurology,* vol. 24, pp. 33-8, 2011.

[98] P. Moafmashhadi and L. Koaski, "Limitations for Interpreting Failure on Individual Subsets of the Montreal Cognitive Assessment," *J Geriatr Psychiatry Neurol,* vol. 26, pp. 19-28, 2013.

[99] R. Coen, D. Robertson, R. Kenny and B. King-Kallimanis, "Strengths and Limitations of the MoCA for Assessing Cognitive Functioning: Findings From a Large Representative Sample of Irish Older Adults.," *J Geriatr Psychiatry Neurol,* vol. 29, pp. 18-24, 2016.

[100] P. Iracleous, J. Nie, C. Tracy, R. Moineddin and Z. Ismail, "Primary care physicians' attitudes towards cognitive screening: findings from a national postal survey," *Int J Geriatr Psychiatry,* vol. 25, pp. 23-9, 2010.

[101] S. N. Wan Shamsuddin, L. Valerie and U. Hassan, "Virtual environment design guidelines for elderly people in early detection of dementia.," *World Acad. Sci. Eng. Technol.,* vol. 5, pp. 1860-1864, 2011.

[102] K. Zinke, M. Zeintl, N. S. Rose, J. Putzmann, A. Pydda and M. Kliegel, "Working memory training and transfer in older adults: effects of age, baseline performance, and training gains," *Dev. Psychol.,* vol. 50, pp. 304-315, 2014.

[103] R. Nouchi, Y. Taki, H. Takeuchi, H. Hashizume, Y. Akisuki and Y. Shigemune, "Brain training game improves executive functions and processing speed in the elderly: a randomized controlled trial," *PLoS One,* vol. 7, 2012.

[104] J. A. Anguera, J. Boccanfuso, J. L. Rintoul, O. Al-Hashimi, F. Faraji and J. Janowich, "Video game training enhances cognitive control in older adults.," *Nature,* vol. 501, pp. 97-102, 2013.

[105] I. Tarnanas, S. Dimitriadis, N. Laskaris and U. Mosimann, "Serious gaming enhances cognitive function in MCI due to Alzheimer's disease," in *Alzheimer's and Dementia,* Copenhagen, 2014.

[106] A. Bahar-Fuchs, L. Clare and B. Woods, "Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia," *Cochrane Database Syst Rev,* 2013.

[107] E. Weybright, J. P. Dattilo and F. R. Rusch, "Effects of an interactive video game(Nintendo Wii) on older woman with Mild Cognitive Impairment," *Therapeutic recreation journal*, vol. 44, 2010.

[108] V. Vallejo, P. Wyss, L. Rampa, A. Mitache, R. M. Müri, U. Mosimann and T. Nef, "Evaluation of a novel serious game based assessment tool for patients with Alzheimer's disease," *PLoS One*, vol. 12, 2017.

[109] S. Zygouris, K. Ntovas, D. Giakoumis, K. Votis, S. Doumpoulakis, S. Sequouli, C. Karagiannidis, D. Tzovaras and M. Tsolaki, "A preliminary study on the feasibility of using a virtual reality cognitive training application for remote detection of mild cognitive impairment," *J Alzheimers Dis.*, vol. 56, pp. 619-627, 2017.

[110] P. Robert, A. Konig, H. Amieva and S. Andrieu, "Recommendations for the use of Serious Games in people with Alzheimer's Disease, related disorders and frailty," *Front Aging Neurosci*, vol. 6, p. 54, 2014.

[111] A. Traks, ".NET and C++ Interoperation(master's thesis)," University of Tartu, Tartu, Estonia, 2016.

[112] P. Trzepacz, H. Hochstetler, S. Wang, B. Walker and A. Saykin, "Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults," *BMC Geriatrics*, vol. 15, pp. 107-115, 2015.

[113] D. Campell and D. Fiske, "Convergent and discriminant validation by the multitrait-multimethod matrix," *Psychological Bulletin*, vol. 56, pp. 81-105, 1959.

[114] O. Naggara, "Analysis by Categorizing or Dichotomizing Continuous Variables Is Inadvisable: An Example from the Natural History of Unruptured Aneurysms," *American Journal of Neuroradiology*, vol. 32, pp. 437-440, 2011.

[115] C. Huberty and J. Morris, "Multivariate Analysis versus Multiple Univariate Analyses," *Psychological Bulletin*, vol. 105, pp. 302-308, 1989.

[116] G. Miller and J. Chapman, "Misunderstanding Analysis of Covariance," *Journal of Abnormal Psychology*, vol. 110, pp. 40-48, 2001.

[117] A. Field, Discovering statistics using SPSS: (and sex and drugs and rock 'n' roll), 3rd ed., London: Sage, 2009.

[118] N. Razali and Y. Wah, "Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Liliefors and Anderson-Darling tests," *Journal of Statistical Modeling and Analytics*, vol. 2, pp. 21-33, 2011.

[119] M. Kery and J. Hatfield, "Normality of raw data in general linear models: The most widespread myth in statistics," *Bulletin of the Ecological Society of America*, vol. 84, pp. 92-94, 2003.

[120] A. Rutherford, Introducing Anova and Ancova, London: Sage, 2001.

[121] J. Cohen, P. Cohen, S. West and L. Aiken, Applied multiple regression/correlation analysis for the behavioural, 3rd ed., Mahwah, NJ: Erlbaum, 2003.

[122] E. Buch, S. Young and J. Contreras-Vidal, "Visuomotor Adaptation in Normal Aging," *Learn Mem.,* vol. 10, pp. 55-63, 2003.

[123] H. Heuer and M. Hegele, "Age-related variations of visuomotor adaptation beyond explicit knowledge," *Front Aging Neurosci,* vol. 6, 2014.

[124] J. Schaffert, C. Lee, R. Neill and J. Bo, "Visuomotor adaptability in older adults with mild cognitive decline," *Acta Psychol (Amst),* vol. 173, pp. 106-115, 2017.

[125] C. Buneo, M. Jarvis, A. Batista and R. Andersen, "Direct visuomotor transformations for reaching.," *Nature.,* vol. 416, pp. 632-6, 2002.

[126] K. Hawkins and L. Sergio, "Visuomotor Impairments in Older Adults at Increased Alzheimer's Disease Risk," *Journal of Alzheimer's Disease,* vol. 42, pp. 607-621, 2014.

[127] S. Verheij, D. Muilwijk, J. Pel, T. van der Cammen, F. Mattace-Raso and J. van der Steen, "Visuomotor impairment in early-stage Alzheimer's disease: changes in relative timing of eye and hand movements.," *J Alzheimers Dis.,* vol. 30, pp. 131-43, 2012.

[128] W. Tippett and L. Sergio, "Visuomotor integration is impaired in early stage Alzheimer's disease.," *Brain Res.,* vol. 1102, pp. 92-102, 2006.

[129] D. Colombo, S. Serino, C. Tuena, E. Pedroli, A. Dakanalis, P. Cipresso and G. Riva, "Egocentric and allocentric spatial reference frames in ageing: A systematic review," *Neurosci Biobehav Rev,* vol. 80, pp. 605-621, 2017.

APPENDIX A: CONSENT FORM

Biomedical Engineering

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

Title of Study: “Investigating the feasibility of neuro-cognitive games for detecting the onset of dementia using a phantom arm compared to touchscreen version”

Protocol number: “___1____”

Principal Investigator: “Dr. Zahra Moussavi, Biomedical Engineering, University of Manitoba”

Sponsor: Natural Sciences and Engineering Research Council of Canada(NSERC)

You are being asked to participate in a Clinical Trial (a human research study). Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this clinical trial and you may discuss it with your regular doctor, friends and family before you make your decision. This consent form may contain words that you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not clearly understand.

This study is financially supported by the University of Manitoba and NSERC.

Purpose of Study

The objective is to test the working memory, in particular the spatial memory type using interactive computer games. A total of 32 participants of age 50+ years will participate in this study.

The results of this study help in better understanding of human brain development and cognitive learning and also to detect the early signs of Alzheimer disease.

Study procedures

If you take part in this study, you will be instructed to play a virtual reality games in 4 different settings. They are designed to assess the working memory, in particular spatial memory. You are not required to know any computer knowledge to play the game; it is fun and engaging. The game is to observe an everyday living scene in a typical kitchen, such as a dinner table, and then in 4 different trials identify a displaced item. You will be asked to play this game in two modes: in one you will be using a robotic arm (a phantom), and in the other a touchscreen monitor to touch (virtually) to identify the displaced item. The experimenter will be sitting beside you for the entire duration of the experiment.

You may also take one or two cognitive tests to assess your short-term memory. There is no other requirement. If at any time while playing the game, you decide to stop participating in this study, you can simply leave the game and request the study staff to help you out of the on-going experiment.

If interested, the results of this study will be provided to you upon your request after the study is finished.

If you are a participant in the rTMS treatment for Alzheimer's, we will assess you before and after the block of treatment, and then after 6 months after the end of treatment.

Risks and Discomforts

While it is unlikely, there might be some people who may feel dizziness, headache or nausea as a results of our virtual reality experiment. If you feel any dizziness and discomfort (e.g. nausea, headache) during the experiment, please let the research assistant know and s/he will stop the experiment. In case of feeling any symptom of dizziness, nausea or headache, the research assistant will call a taxi and pay you $20 for your fare to home. If you come by your own car, still you should take the taxi and later come back with someone to pick up your car. Alternatively, you may call someone to come and drive back with you; in that case the research assistant will stay with you until you are being picked up.

Confidentiality

Information gathered in this research study may be published or presented in public forums; however, your name and other identifying information will not be used or revealed. Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. Despite the efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

All study documents related to you will bear only your assigned code and /or initials. Your data acquired during the games will be recorded and stored in computer

files with your code. These data will be analyzed for the main purpose of study which is to investigate the human brain development and motor learning that lead to skilled human movement in terms of temporal and spatial accuracy. Students and researchers who will analyze your data will not have access to your identification and only know the files by their codes.

The University of Manitoba Biomedical Research Ethics Board may review research-related records for quality assurance purposes. All records will be kept in a locked secure area and only those persons identified will have access to these records. If any of your medical/research records, need to be copied to any of the above, your name and all identifying information will be removed. No information revealing any personal information such as your name, address or telephone number will leave the University of Manitoba.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw from the study at any time. You will not lose any benefits or care to which you are entitled upon the refusal to participate in or withdraw from the study.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Questions

You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study, contact the study doctor and the study staff: Dr. Zahra Moussavi.

For questions about your rights as a research participant, you may contact The University of Manitoba Biomedical Research Ethics Board. Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Dr. Zahra Moussavi and or his/her study staff. I have had my questions answered by them in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statement or implied statements. Any relationship (such as employee, student or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this clinical trial is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed.

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

I agree to being contacted in relation to this study. Yes □ No □

Participant signature_____ Date (day/month/year)

Participant printed name: _____

For Alzheimer's Participants only _____

Parent/legal guardian's signature (if applicable): _____

Date _____

Parent/legal guardian's printed name (if applicable):

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent

Printed Name: _____ Date (day/month/year)

Signature: _____

Role in the study: _____

I, _____ , confirm that I have no dizziness and can go home by myself.

Signature: _____

APPENDIX B: ASSUMPTION TESTING

Before the repeated measures MANCOVA can be conducted, all assumptions must be tested. When examining for outliers with residuals, it was found that there were two outliers for the object identification scores. These two outliers were removed for the rest of the statistical analysis. The minimum and maximum residuals are listed in Table 8.

Table 8: Standardized residual testing for univariate outliers

Data	Minimum	Maximum
T_OI	-2.18	2.49
T_OR	-2.07	2.27
P_OI	-2.47	1.67
P_OR	-2.31	2.48

Normality of the dependent variables were examined with Shapiro Wilk on their respective univariate standardized residuals. All four dependent variables passed the Shapiro-Wilk normality test, as shown in Table 9.

Table 9: Repeated measures MANCOVA residual normality testing

Variable	P value
T_OI	0.967
T_OR	0.719
P_OI	0.530
P_OR	0.940

Multivariate outliers were tested by measuring the Mahalanobis distance [117] between all dependent variables and the independent variable. The maximum Mahalanobis distance was found to be 9.162, which is lower than the critical value of 15. Linearity between dependent variables and covariates were tested with scatterplot matrix, as shown in Figure 16.

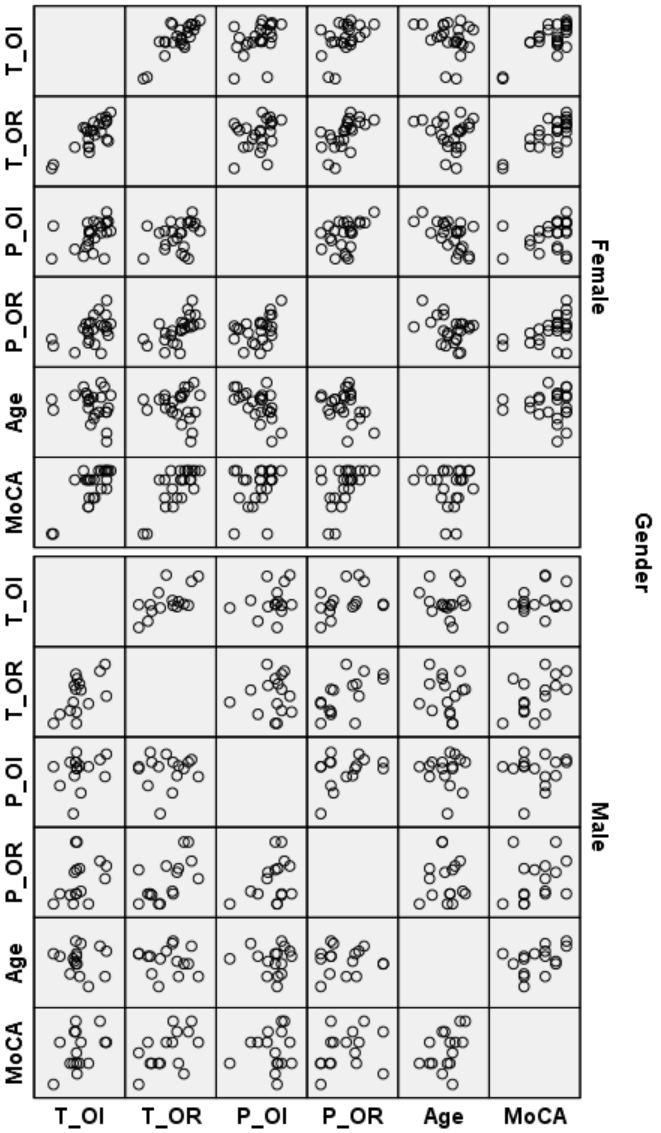

Figure 16: Scatterplot matrix for repeated measure MANCOVA study

The scatter plot matrix demonstrated that there was a linear relationship between all dependent variables as well as covariates in the female group. In the male group, the linear relationship is weak between some dependent variables and some covariates. The homogeneity of variance and covariances were tested with the Box'M test of equality of covariance matrices [117]; the resultant p-value is 0.756 which is greater than the critical value of 0.001.

The homogeneity of regression slopes was tested by running a custom model of the MANCOVA and looking at the significance of interaction effects between covariates and independent variables in the between participants analysis. The p-value for interaction sex and MoCA was found to be 0.828, and the p-value for interaction sex*age was found to be 0.588. Since there exists a potential violation of the linearity assumption; Pillai's Trace [117] statistic was used for interpretation due to its power and robustness.

Before the analysis of covariance study can be conducted, all assumptions must be tested. All four dependent variables, T_OI, T_OR, P_OI and P_OR have undergone normality, outlier and linearity checks in section 4.3.

The homogeneity of variance assumption was tested with Levene's test of equality of error variances; the significant value for the variable T_OI is 0.084. The homogeneity of regression slopes assumption was tested by looking at the interaction effect of the dependent variable and the covariates; the interaction effect of sex*age on T_OI is 0.342, and the interaction effect of sex*MoCA is 0.976.

The homogeneity of variance assumption was tested with Levene's test of equality of error variances; the significant value for the variable T_OR is 0.063. The homogeneity of regression slopes assumption was tested by looking at the interaction effect of the dependent variable and the covariates; the interaction effect of sex*age on variable T_OR is 0.119, and the interaction effect of sex*MoCA is 0.435.

The homogeneity of variance assumption was tested with Levene's test of equality of error variances; the significant value for the variable P_OI is 0.918. The homogeneity of regression slopes assumption was tested by looking at the interaction effect of the dependent variable and the covariates; the interaction effect of sex*age on the variable P_OI is 0.207, and the interaction effect of sex*MoCA is 0.638.

The homogeneity of variance assumption was tested with Levene's test of equality of error variances; the significant value for the variable P_OR is 0.54. The homogeneity of regression slopes assumption was tested by looking at the interaction effect of the dependent variable and the covariates; the interaction effect of sex*age on P_OR is 0.674, and the interaction effect of sex*MoCA is 0.83.

Four multiple regression studies were conducted to investigate the predictive power of touchscreen game score or Phantom arm game score on MoCA score or age. Assumption testing was performed prior to the multiple regression study. As shown in Figure 17: Scatterplot matrix for multiple regression. The linearity assumption was met for all four multiple regression studies.

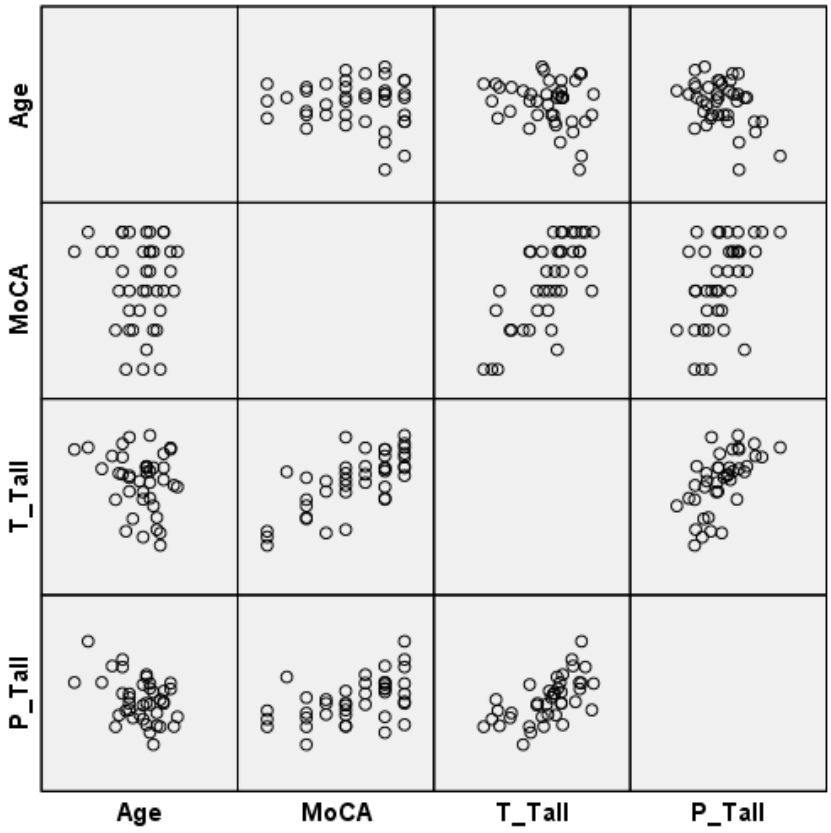

Figure 17: Scatterplot matrix for multiple regression

The standard residuals for all four multiple regression studies passed the outlier test, as shown in Table 10.

Table 10: Multiple regression residuals

Test	Minimum	Maximum
MoCA prediction with touchscreen game scores	-2.305	1.714
MoCA prediction with Phantom arm game scores	-2.447	2.061
Age prediction with touchscreen game scores	-2.635	1.623
Age prediction with Phantom arm game scores	-2.623	1.919

The standard residuals for all four multiple regression studies passed the Shapiro-Wilk normality test, as shown in Table 11.

Table 11: Multiple regression residuals normality test

Test	**P value**
MoCA prediction with touchscreen game scores	0.665
MoCA prediction with Phantom arm game scores	0.445
Age prediction with touchscreen game scores	0.299
Age prediction with Phantom arm game scores	0.904

All four regression studies passed the multicollinearity test, the correlation between the two predictors for all studies are shown in Table 12.

Table 12: Multiple regression predictor correlation

Test	**Correlation**
MoCA prediction with touchscreen game scores	0.731
MoCA prediction with Phantom arm game scores	0.415
Age prediction with touchscreen game scores	0.731
Age prediction with Phantom arm game scores	0.415

All four regression studies passed the independence of errors test; the Durbin Watson values are shown in Table 13.

Table 13: Multiple regression Durbin Watson value

Test	Durbin Watson value
MoCA prediction with touchscreen game scores	1.779
MoCA prediction with Phantom arm game scores	1.796
Age prediction with touchscreen game scores	2.071
Age prediction with Phantom arm game scores	2.231

For MoCA prediction with touchscreen game score, homoscedasticity assumption was met since the residuals plots exhibit no pattern, as shown in Figure 18.

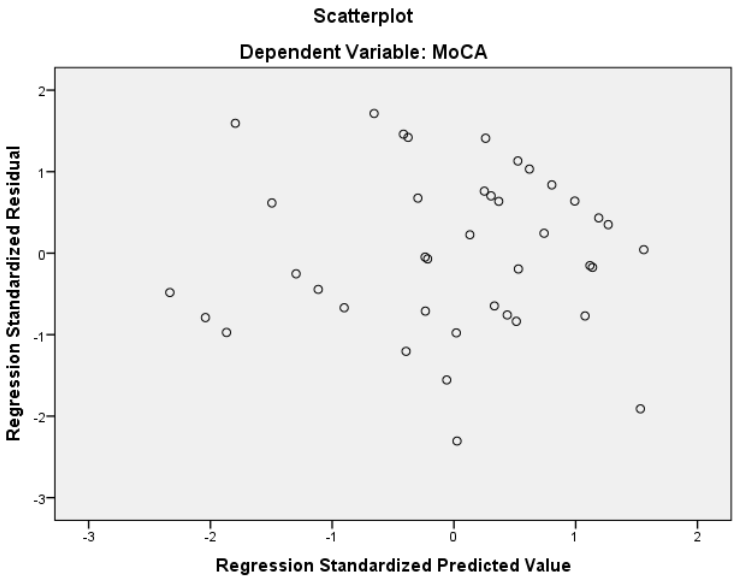

Figure 18: MoCA prediction with touchscreen residual scatterplot

For MoCA prediction with phantom arm score, homoscedasticity assumption may not be met since the residuals plots exhibit a fan out pattern, as shown in Figure 19.

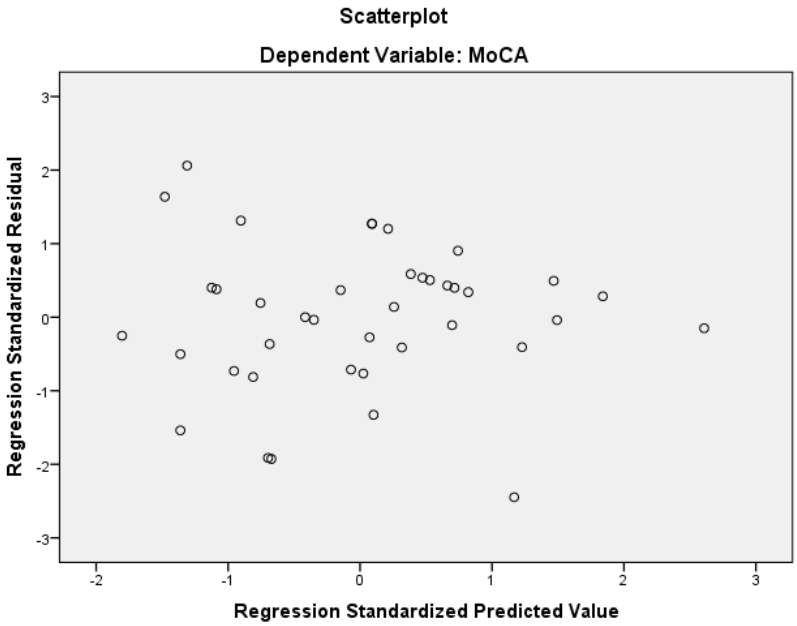

Figure 19: MoCA prediction with Phantom residual scatterplot

For age prediction with touchscreen score, homoscedasticity assumption is met since the residuals plots exhibit no pattern, as shown in Figure 20.

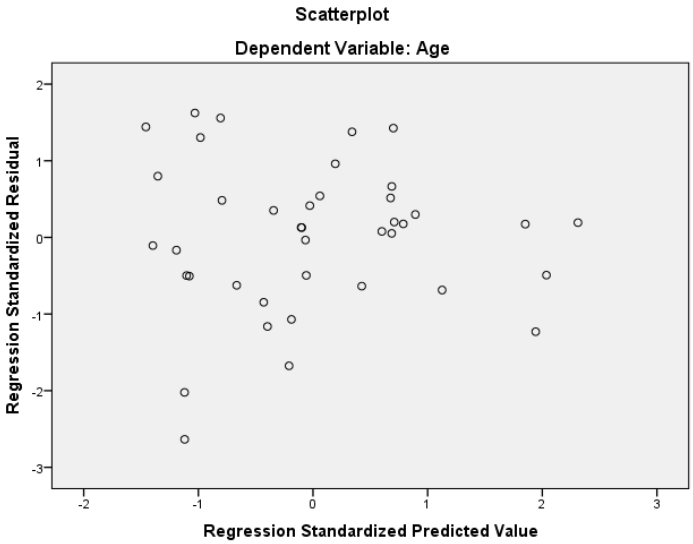

Figure 20: Age prediction with touchscreen residual scatterplot

For age prediction with phantom arm score, homoscedasticity assumption is met since the residuals plots exhibit no pattern, as shown in Figure 21.

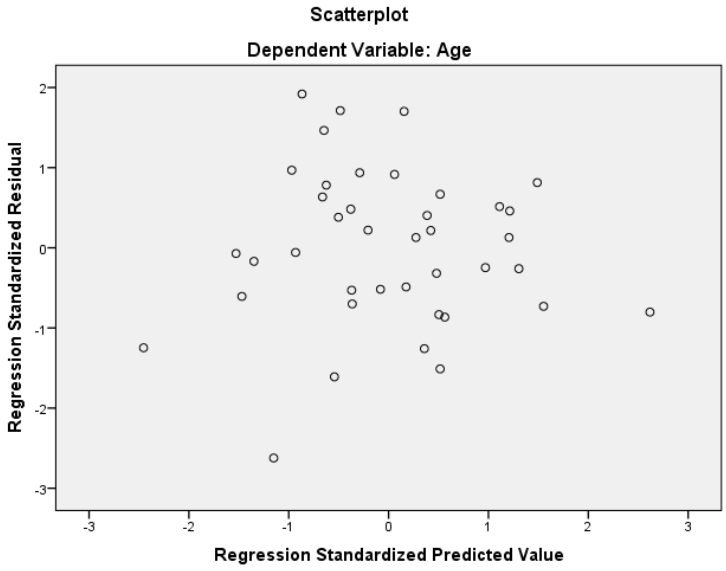

Figure 21: Age prediction with phantom residual scatterplot