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Dementia, a devastating, progressive disease, is typically assessed using a combination of cognitive testing, physical examination and physical tasks that test the patient's ability to engage in instrumental activities of daily living (IADL). These tests are designed to evaluate skills such as memory, general motor skills, gaze etc. that enable us to function. Clinical settings have limited access to space and tools that can be used to design said tests. Virtual reality is a cost-effective alternative that can be utilized in such settings to diagnose MCI and dementia. Unfortunately, the research in this area thus far is scarce. This paper aims to assess the feasibility of and strengths and weaknesses associated with using virtual reality simulations as a diagnostic tool to assess neurodegenerative conditions like MCI and dementia. It will involve a systematic look at preexisting literature and offer suggestions for future research based on its findings.

Headings:

Mild Cognitive Impairment

Dementia

Instrumental Activities of Daily Living (IADL)

Virtual Reality

Immersion Levels

Head Mounted Display

VIRTUAL REALITY AS A DIAGNOSTIC TOOL: A SYSTEMATIC REVIEW OF STUDIES USING VIRTUAL REALITY TECHNOLOGY FOR THE ASSESMENT OF MILD COGNITIVE IMPAIRMENT AND DEMENTIA

by
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Approved by

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2 INTRODUCTION

Neurological conditions like mild cognitive impairment (MCI) and dementia do not have a single method by which they are diagnosed. Oftentimes, doctors analyze a patient's medical history, laboratory test results, characteristic changes in thinking, day-to-day function and behavior. Computed tomography (CT) or magnetic resonance imaging (MRI) are also used to evaluate potential loss in brain mass which can point to cognitive changes or degeneration.

In recent years, many clinicians have adopted virtual reality to treat and diagnose some health conditions; while this technology is more popular among mental health practitioners who use it to employ exposure therapy, sure enough, it is also slowly being adopted by neurologists and other specialists who specialize in cognitive functions. Neurodegenerative disorders like dementia and MCI affect a person's ability to engage in daily activities, as a result, a careful analysis of how well patients engage in instrumental activities of daily living (IADL) can be used to assess cognitive condition (García-Betances et al. 2015). These tests can be conducted through a physical test mockup in a hospital, but instead are often conducted via subjective surveys and tests given the constraint of space. Assessing IADL is easier to conduct using VR because it is more inexpensive than a physical mockup, it does not require the presence of a testing site, it is not invasive and it gives more precise data regarding the patient's eye movements, which can be used to assess their 'attention.' Typically, these VR scenarios involve the patient to undertake a task they would do at any given day, such as making a pot of coffee or navigate through a supermarket. The clinician, who is able to see how the patient interacts with the environment through their device, can analyze the patient's memory, general motor skills, balance, reflexes etc. This can enable them to gain a holistic understanding of the patient's objective cognitive condition and enable them to provide a diagnosis or to rule it out. The use of VR to detect MCI and dementia is newly budding and while there is evidence that it is an effective method, there is a lot of room for improvement. The adoption of this form of technology can enhance the diagnosis process and allow patients to receive their diagnosis earlier and therefore take interventions to slow the progression of their condition.

3 LITERATURE REVIEW

Dementia is characterized by progressive decline in two or more cognitive domains, including memory, language, executive and visuospatial function, personality, and behavior, all of which affect one's ability to efficiently engage in instrumental and/or basic activities of daily living (IADL) (Weller and Budson 2018). Symptoms of dementia are gradual, persistent and progressive (Duong et al. 2017). Individuals suffering from dementia experience changes in cognition and behavior which can and does affect their ability to function. Having a neurodegenerative condition can drastically affect a patient and his/her loved one's lives. However, seeing behavioral changes that stem from said conditions and not having a definitive answer about their cause can be more troublesome. Oftentimes, patients live in this limbo in the early stages of their condition because there is no definitive physical way to diagnose these diseases in the early on. Behavioral changes that stem from cognitive changes are among the first symptoms (Bature et al.

2017). Thus, many clinicians opt to test cognitive functions as a way to gain a better understanding of the patient's cognitive condition.

3.1 DEMENTIA, MILD COGNITIVE IMPAIRMENT & ALZHEIMER'S DISEASE

Dementia presents itself uniquely in each individual; the cognitive deficits that stem from it can appear as memory loss, communication and language impairments, agnosia (inability to recognize objects), apraxia (inability to perform previously learned tasks) impaired navigation, and impaired executive function (reasoning, judgement and planning). Dementia is an umbrella term used to describe a clinical syndrome of progressive cognitive decline; the types of dementia are classified according to their cause. The 4 common types are: Alzheimer's disease, vascular dementia, Lewy body dementia and frontotemporal dementia (Duong et. al. 2017).

Cognitive impairment is a result of injury to the cerebral cortex caused by synaptic failure, inflammation and/or change in cerebral metabolism (Hildreth and Church 2015). Many individuals who suffer from mild deficits and do not meet the aforementioned criteria for dementia are considered to have mild cognitive impairment (MCI), which is defined to be an objective cognitive impairment with preserved function (Hildreth and Church 2015). Normal aging may bring about difficulties with language, memory, thinking or judgement; those with MCI may experience greater difficulty in these functions than those who experience normal aging. MCI can be assessed using cognitive testing and the impairments it presents are not sufficient to interfere with an individual's daily activities (Petersen 2016). Alzheimer's disease (AD), the most prevalent cause of dementia, refers to a particular onset of functional and cognitive decline associated with age and a particular neuropathology (Soria Lopez et al. 2019). It is a progressive condition and individuals who suffer from it may present with MCI in the early stages (Matthews et al. 2008). Those who have been diagnosed with MCI are at a higher risk of developing AD and other dementias in comparison with those who do not have AD (Bruscoli and Lovestone 2004). MCI and mild dementia are both characterized by objective evidence of cognitive impairment. The main distinction between them is that in the latter, more than one cognitive function is impaired and there is substantial interference with daily life (Knopman and Petersen 2014).

3.2 DIAGNOSING DEMENTIA & MCI

The definitive diagnosis of dementia requires post-mortem evaluation of brain tissue (Weller and Budson 2018). Nonetheless, clinicians use a combination of tests to establish a high likelihood of the presence of a neurodegenerative disease like mild-cognitive impairment and dementia. The diagnosis is confirmed when the patient’s condition declines. These tests include cognitive and neuropsychological testing, laboratory tests, brain scans, psychiatric evaluations, and genetic testing. Some clinicians opt to use laboratory testing, computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate potential loss in brain mass which can point to cognitive changes or degeneration (Jack et al. 2011) and to look for evidence of strokes from vascular dementia (Strub 2013). However, this method does not always yield accurate results, especially in the early stages of the disease when tissue loss is sparse. Instead, behavioral changes are among the first noticeable symptoms of dementia (Bature et al. 2017).

Neurodegenerative diseases affect an individual's balance, speech, memory, gait, reflexes etc. which in turn affect their ability to complete daily tasks. Many of the aforementioned tests are designed to test the patient's ability to engage in daily activities. Most clinicians do not face issues conducting psychiatric evaluations and interviewing the patient's families about their condition, instead, the larger problem lies in testing the patient's competency in engaging in instrumental activities of daily activities (IADL). Most activities designed to test cognitive function require the patient to complete some sort of task they would engage in on any given day (i.e. driving, cooking, wayfinding etc.) (Garcia-Betances et. al. 2015). Although it may seem simple, neurodegenerative diseases affect an individual's balance, speech, memory, gait, reflexes etc. and a simple task can yield volumes of data about his/her cognitive function. Additionally, clinicians take a holistic look at the data they obtain from all of the tests conducted. Ideally, every healthcare setting should have a testing space in which the clinician can set up tasks for the patient to complete; however, this is not always the case. Real estate space in hospitals is very valuable and it is not realistic to expect all healthcare institutions to have the space and means to constantly set up and dismantle props for each physical testing scenario. Transdisciplinary research in neurology and virtual reality (VR) has fostered the development of ecologically valid virtual tools for the assessment of IADL, using simulations of real life activities in VR (Allain et al. 2014). Virtual reality testing is an inexpensive form of technology that is being adopted by many healthcare settings. Although VR was readily adopted by practitioners in the mental health field, it is also newly being explored as an affordable tool for the detection and treatment of neurodegenerative diseases. García-Betances et al. 2015 briefly summarized the role of

VR technology in relation to Alzheimer's disease. They categorize VR use according to their intended purpose: diagnosis, patient cognitive training, caregivers' education etc.; focus feature: spatial impairment, memory deficit, etc.; methodology employed: tasks, games etc.; immersion level, and passive or active interaction (García-Betances et al. 2015). The diagram below delineates the categorization of current VR research as it relates to Alzheimer's disease, a type of dementia:

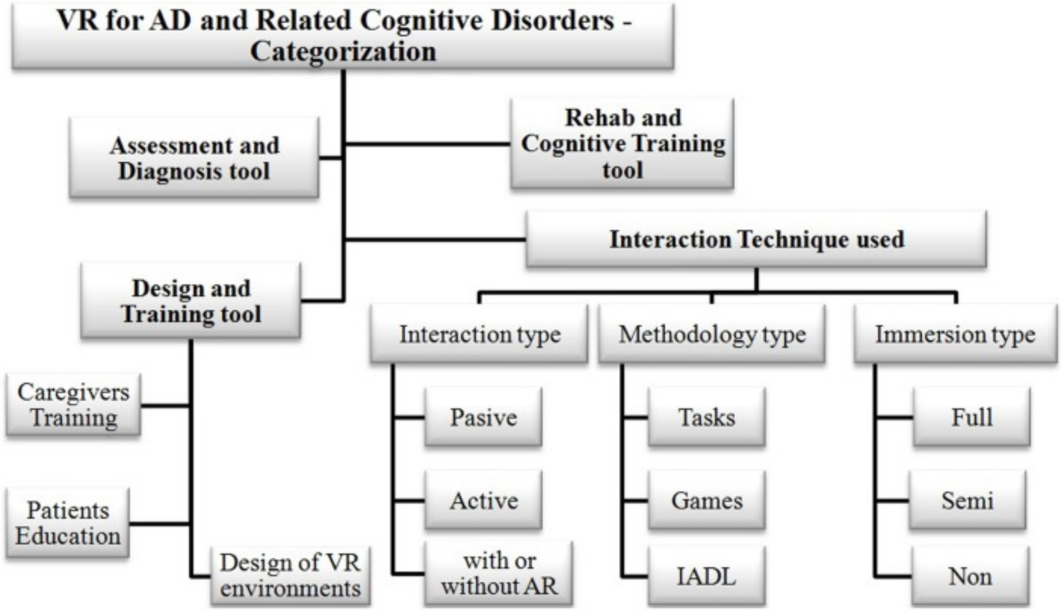

Figure 1: A Map of VR technology use in relation to Alzheimer's Disease
(García-Betances et al. 2015)

Using VR as an assessment and diagnostic tool for cognitive condition has been explored by few studies. This paper is intended to delve into the recent publications exploring VR tools for the assessment and diagnosis for dementia and MCI. It will expand upon the technology used, the cognitive features tested, the side effects and the limitations found.

4 METHODS

This systematic review was conducted based on guidelines belonging to the Cochrane Handbook for Systematic Review of Interventions and UNC's Health Science Library Systematic Review resources.

4.1 SEARCH STRATEGY

Given that VR technology is a new field, some background research was initially conducted regarding the intersection of virtual reality technology and the treatment of cognitive impairments. It was discovered that the functions that AR/VR typically serve in this field are that of a (1) diagnostic and assessment tool, (2) cognitive training tool, and (3) empathy training tool for caregivers of those who are cognitively impaired. Many papers were found to focus on the latter two and the former was thus chosen as the area of focus.

The goal of this systematic review, therefore, was to answer the following research questions: to explore how VR technology is being utilized to detect MCI and dementia, to explore the validity of using VR in this manner, and to unveil any strengths and weaknesses it may have in comparison to other forms of cognitive diagnostic testing. This background research also inspired the decision to not limit the studies based on the immersion level of the VR technology that was used, given that this is a budding field and research with fully immersive VR is scarce.

Nine databases such as PubMed, Scopus, and Web of Science were used to search for systematic reviews that fall under a similar category and SciWheel (formerly known as F100) was used to screen through these publications and build a repertoire of search terms. A health sciences librarian was consulted to help create a well-defined search strategy and build the search string to be used in the databases. See Table 1 below for search string documentation.

Database	Search Date	# of Results	Search query
PubMed	2/23/2020	180	#1: (virtual reality [mesh] or virtual reality [tw] or VRCT [tw] or head-up display [tw] OR head up display [tw] or head-mounted [tw] or head mounted [tw] or virtual environment [tw] or virtual environments [tw] or 3D environment [tw] or 3D environments [tw] or multi-sensorial interaction [tw] or virtual retinal display [tw]) #2: (Mild Cognitive Impairments [mesh] or mild cognitive [tw]or mild neurocognitive [tw] or dementia [mesh] or dementia [tw] or Alzheimer* [mesh] or Alzheimer* [tw]) #1 AND #2
Scopus	2/23/2020	527	((TITLE-ABS-KEY ("virtual reality") OR TITLE-ABS-KEY ("VRCT") OR TITLE-ABS-KEY ("head-up display") OR TITLE-ABS-KEY ("head up display")OR TITLE-ABS-KEY ("head-mounted") OR TITLE-ABS-KEY ("head mounted") OR TITLE-ABS-KEY ("virtual environment") OR TITLE-ABS-KEY ("virtual environments") OR TITLE-ABS-KEY ("3D environments") OR TITLE-ABS-KEY ("3D environment") OR TITLE-ABS-KEY ("multi-sensorial interaction") OR TITLE-ABS-KEY ("virtual retinal display"))) AND ((TITLE-ABS-KEY ("mild cognitive") OR TITLE-ABS-KEY ("mild neurocognitive") OR TITLE-ABS-KEY ("dementia") OR TITLE-ABS-KEY ("Alzheimer*")))

WoS	2/23/2020	267	((TS=("virtual reality" OR "virtual reality" OR VRCT OR "head-up display" OR "head up display" OR head-mounted OR "head mounted" OR "virtual environment" OR "virtual environments" OR "3D environment" OR "3D environments" OR "multi-sensorial interaction" OR "virtual retinal display")) AND (TS=("Mild Cognitive Impairments" OR "mild cognitive" OR "mild neurocognitive" OR dementia OR dementia OR Alzheimer* OR Alzheimer*))) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article)
CINHAL	2/24/2020	60	AB (mild cognitive impairment or mci or Alzheimer or dementia) AND AB (virtual reality OR VRCT OR head up display OR head-up display OR head-mounted OR head mounted OR hmd OR virtual environment OR virtual environments OR 3D environment OR 3D environments OR multi-sensorial interaction OR virtual retinal display) **Narrow by Language:** - english
PsyINFO	2/24/2020	97	AB (mild cognitive impairment or mci or Alzheimer or dementia) AND AB (virtual reality OR VRCT OR head up display OR head-up display OR head-mounted OR head mounted OR hmd OR virtual environment OR virtual environments OR 3D environment OR 3D environments OR multi-sensorial interaction OR virtual retinal display) **Narrow by Language:** - english
ACM DL	2/24/2020	20	[[Abstract: "virtual reality"] OR [Abstract: "vrct"] OR [Abstract: "head-up display"] OR [Abstract: "head up display"] OR [Abstract: "head-mounted"] OR [Abstract: "head mounted"] OR [Abstract: "virtual environment"] OR [Abstract: "virtual environments"] OR [Abstract: "3d environments"] OR [Abstract: "3d environment"] OR [Abstract: "multi-sensorial interaction"] OR [Abstract: "virtual retinal display"]] AND [[Abstract: "mild cognitive"] OR [Abstract: "mild neurocognitive"] OR [Abstract: "dementia"] OR [Abstract:

			"alzheimer*"]]
Embase	2/24/20	264	('virtual reality':ti,ab,kw OR vrct:ti,ab,kw OR 'head-up display':ti,ab,kw OR 'head up display':ti,ab,kw OR 'head mounted':ti,ab,kw OR 'virtual environment':ti,ab,kw OR 'virtual environments':ti,ab,kw OR '3d environments':ti,ab,kw OR '3d environment':ti,ab,kw OR 'multi-sensorial interaction':ti,ab,kw OR 'virtual retinal display':ti,ab,kw) AND ('mild cognitive':ti,ab,kw OR 'mild neurocognitive':ti,ab,kw OR dementia:ti,ab,kw OR alzheimer*:ti,ab,kw)
CochraneLibrary	2/24/2020	52+3	((("virtual reality") OR ("VRCT") OR ("head-up display") OR ("head up display")OR ("head-mounted") OR ("head mounted") OR ("virtual environment") OR ("virtual environments") OR ("3D environments") OR ("3D environment") OR ("multi-sensorial interaction") OR ("virtual retinal display"))) AND ((("mild cognitive") OR ("mild neurocognitive") OR ("dementia") OR ("Alzheimer*"))) in Title Abstract Keyword

Table 1: Search string documentation

4.2 INCLUSION & EXCLUSION CRITERIA

The following principles were drafted as inclusion criteria: (1) VR studies wherein VR is used as a diagnostic/assessment tool to screen for MCI/dementia; (2) studies that explore dementia or MCI detection must include a healthy control group opposite the VR diagnostic group, for results to be compared; (3) studies must compare the index test to a reference standard to ensure validity of results. The following were drafted as the exclusion criteria: (1) Studies conducted on individuals with multiple neurocognitive disorders (NCDs); (2) studies conducted on patients who have dementia triggered by traumatic brain injury. (3) studies exploring VR as a tool for employing computerized cognitive therapy on individuals with dementia and MCI; (4) studies that use VR technology to provide patient education.

4.3 SCREENING

A total of 1421 paper titles and abstracts were uploaded to Covidence which was utilized for the remainder of the systematic review. Covidence, a tool that is free for UNC Chapel Hill affiliates, streamlines the process of building a repertoire of relevant citations and screening through them. As such, it is typically used by researchers who are conducting systematic reviews. Two researchers separately conducted a title and abstract screening and full text screening based on the inclusion and exclusion criteria. The Cohen's Kappa was 0.33577 and 0.46712 for the title and abstract review and the full-text review, respectively. Disagreements and differences were resolved through discussion and a consensus was achieved at the end. While Covidence generally identifies and removes duplicate studies, it does not have robust artificial intelligence capabilities that yield a 100% success rate. Therefore, the deduplication process was manually conducted a second time following the full text review. In this step, many articles were removed due to language, incorrect or insufficient reference standards, and incorrect target groups. See figure 2 below for the PRISMA diagram of the systematic review screening.

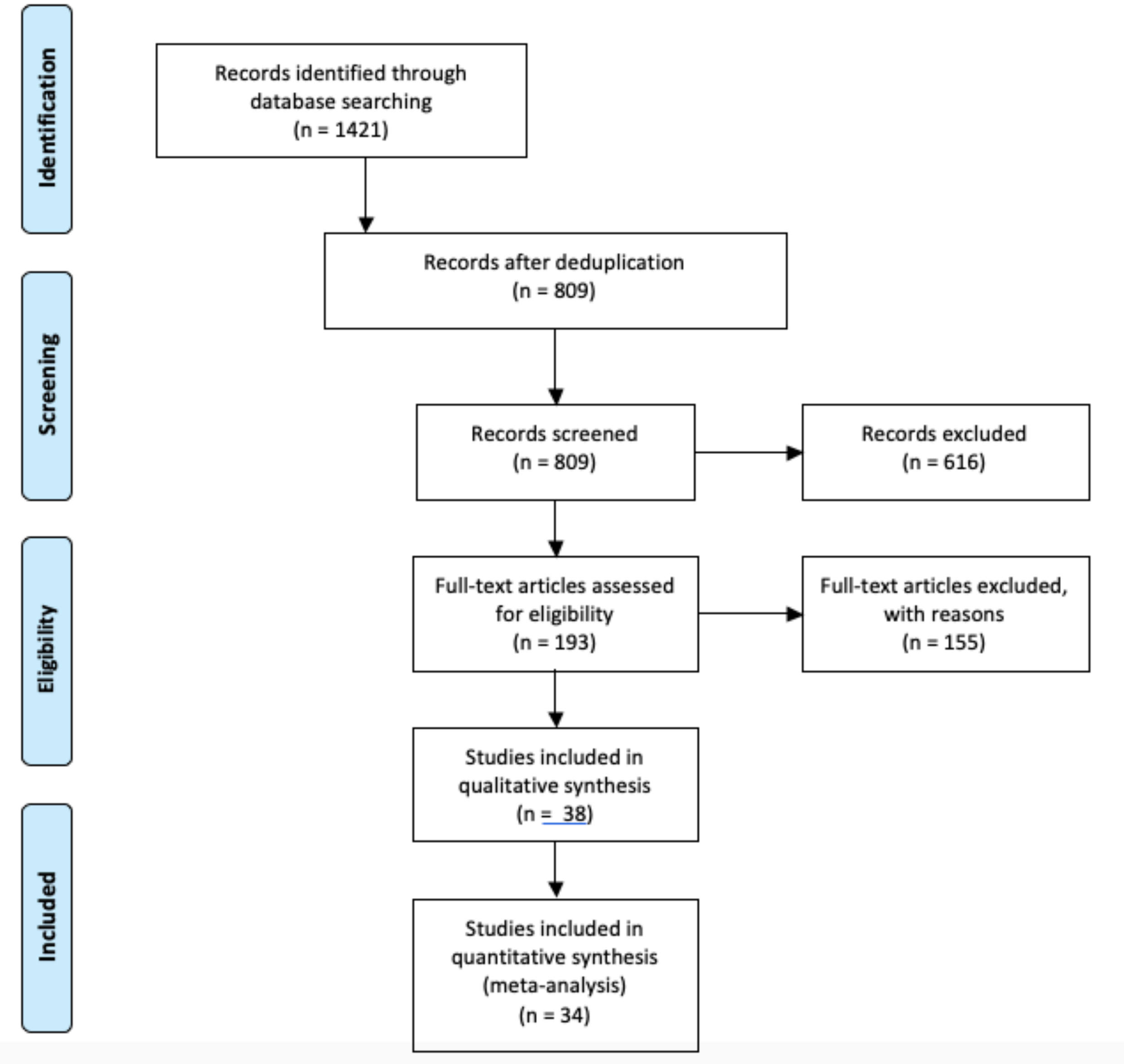

Figure 2: PRISMA diagram for paper screening

The two researchers then independently appraised the papers and disagreements were resolved among them. The quality assessment template was designed according to guidelines for diagnostic test studies as described in QUADAS-2 and Critical Appraisal

Skills Programme (CASP) (Whiting et al. 2006).[1] The template included 6 questions that attempted to shed light on potential outcome reporting bias, review bias, and verification bias. It also included questions about whether the studies included a reference standard and information about the target group. Each question was checked as yes, no, or unsure by the researchers and the results were aggregated into an Excel sheet.

5 DATA EXTRACTION & ANALYSIS

For the remaining studies, data was extracted independently by the two researchers through a Google Forms survey and were then compared for accuracy. The survey consisted of 4 parts: identification, participant information, index standard information and outcomes. Identification asked questions about the title, authors, setting, country of testing site. The second section asked about the size, gender composition and age range of the healthy controls and the target groups. Section 3 dealt with matters such as the name, immersion level, description, and methodologies of the index test and the focus features that were tested. Section four asked about what the outcomes were, how they were measured, if they were favorable and what the limitations were.

After the two researchers' results were compared, the data was compiled into a single spreadsheet and color coded based on focus feature and immersion level. See appendix 3 for data extraction template.

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[1] "CASP Checklist: 12 Questionsto Help You Make Sense of a Diagnostic Test Study." *Critical Skills Programme*, CASP, casp-uk.net/wp-content/uploads/2018/03/CASP-Diagnostic-Checklist-2018_fillable_form.pdf.

6 RESULTS

Of the 34 studies, 12 focused on assessing MCI alone, 8 focused on Alzheimer's disease only, and only 1 concentrated on those with general dementia. The remaining studies tested several target groups with two or three of the conditions listed above. After analyzing their results, all of the authors considered their tool to be a valid testing tool for diagnosing MCI and/or dementia (depending on the condition they tested). Although it cannot be said that there is a direct and complete match between the index test and the reference test results, all studies reported a very high correlation between the two results. One study even conducted a virtual hospital navigation tool in real life and via simulation (Cushman et al. 2008). The virtual hospital was designed to be identical to the real one for increased validity and the authors reported that participant performance revealed similar profiles of impairment in real-world and virtual testing across all groups.

The most commonly used reference test was the Mini Mental Status Examination (MMSE), however, most of the papers utilized a few reference tests including a battery of neuropsychological testing, interviewing, and other paper and pencil tests such as Functional Activities Questionnaire, Geriatric Depression Scale (GDS), Clinical Dementia Rating Scale (CDR). One paper used CSF biomarkers as one of the reference standards (Allison et al. 2016). The studies were conducted in various countries including but not limited to the USA, South Korea, France, Turkey, Spain and Greece. While there was no specific age range listed in the inclusion and exclusion criteria, the papers were required to test 'elderly participants.' The age range that was tested across all papers ranged from 50 to 90. A few of them even tested a younger age group in addition to a control and target elderly group for more robust age and health data (Zakzanis et al.

2009) (Sauzéon et al. 2016). Varying results were noted regarding the outcomes linked to demographics (age, gender, education level, computer literacy etc.). Most of the studies indicated that there was no correlation between performance and demographic data, while some indicated that age had the highest correlation with performance, although it was not very significant (Pengas et al. 2010); (Kim et al. 2018); (Zakzanis et al. 2009). One study indicated that there might be a small correlation between high performance and education level, but it highlighted that age was more strongly correlated (Baez et al. 2015). All of the studies emphasized a strong correlation between cognitive health and index and reference test performance. See table 2 below for study characteristics.

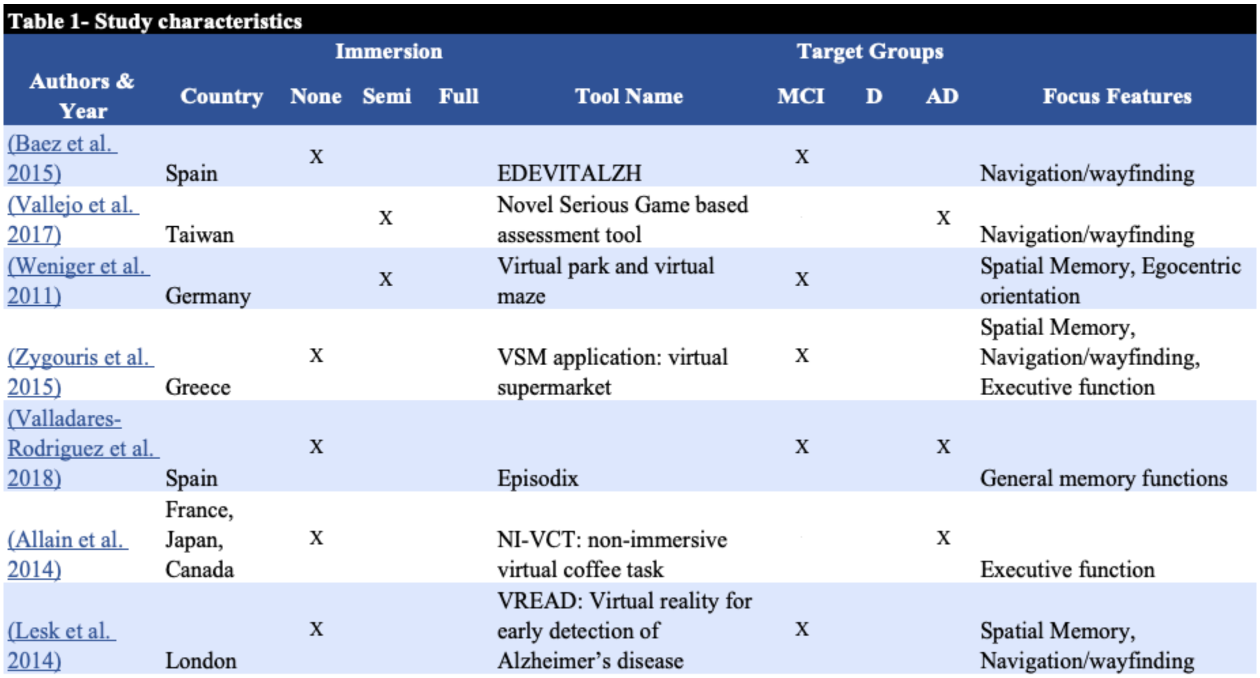

Table 1- Study characteristics

Authors & Year	Country	Immersion			Tool Name	Target Groups			Focus Features
		None	Semi	Full		MCI	D	AD	
(Baez et al. 2015)	Spain	X			EDEVITALZH	X			Navigation/wayfinding
(Vallejo et al. 2017)	Taiwan		X		Novel Serious Game based assessment tool			X	Navigation/wayfinding
(Weniger et al. 2011)	Germany		X		Virtual park and virtual maze	X			Spatial Memory, Egocentric orientation
(Zygouris et al. 2015)	Greece	X			VSM application: virtual supermarket	X			Spatial Memory, Navigation/wayfinding, Executive function
(Valladares-Rodriguez et al. 2018)	Spain	X			Episodix	X		X	General memory functions
(Allain et al. 2014)	France, Japan, Canada	X			NI-VCT: non-immersive virtual coffee task			X	Executive function
(Lesk et al. 2014)	London	X			VREAD: Virtual reality for early detection of Alzheimer's disease	X			Spatial Memory, Navigation/wayfinding

(Lecouvey et al. 2019)	France		X		-			X	Navigation/wayfinding, General memory functions
(Kubota et al. 2017)	Japan	X			VR-IADL: Virtual Reality based Instrumental Activities of Daily Living	X			General memory functions, Executive function
(Yeh et al. 2012)	Taiwan			X	VAPS: Virtual action supermarket VAP-S: Virtual action planning supermarket		X		General memory functions, Executive function
(Mohammadi et al. 2018)	Iran	X			VRNT - virtual reality navigation task	X		X	Spatial Memory, Navigation/wayfinding
(Serino et al. 2015)	France		X		-	X		X	Spatial Memory, Navigation/wayfinding
(Werner et al. 2009)	France	X			VAPS: Virtual action supermarket VAP-S: Virtual action planning supermarket	X			General memory functions, Executive function, Motor skills/ Psychomotor slowing
(Tarnanas et al. 2012)			X		VAP-M: virtual action planning museum (VAP-M)	X			Spatial Memory, Executive function
(Allison et al. 2016)	USA	X			-			X	Spatial Memory, Navigation/wayfinding
(Pengas et al. 2010)	UK		X		VRLT: the Virtual Route Learning Test & Heading Orientation Test	X	X	X	Spatial Memory, Navigation/wayfinding
(Zakzanis et al. 2009)	Canada			X	-			X	Spatial Memory, Navigation/wayfinding
(Plancher et al. 2012)	France		X		-	X		X	Spatial Memory, Navigation/wayfinding
(Tu et al. 2017)	UK, Australia	X			VSM: Virtual Supermarket		X	X	Spatial Memory, Egocentric orientation, Navigation/wayfinding, General memory functions
(Howett et al. 2019)	UK			X	Immersive virtual reality path integration task	X			Navigation/wayfinding
(Lee et al. 2014)	Korea	X			VraM task	X		X	Spatial Memory, Navigation/wayfinding
(Tarnanas et al. 2015)	France		X		DOT: Day out task & NAV: navigation task	X		X	Spatial Memory, Navigation/wayfinding, Executive function
(Eraslan Boz et al. 2020)	Turkey	X			VSM: Virtual Supermarket	X			Spatial Memory, Navigation/wayfinding, Executive function
(Montenegro and Argyriou 2015)	UK			X	VOM: Virtual Objects Memorisation test & VRS: Virtual vs Real Sounds test			X	General memory functions, Executive function
(Tarnanas et al. 2013)	Switzerland	X			VR-DOT: Virtual Reality Day-Out Task(	X		X	Navigation/wayfinding, General memory functions, Executive function
(Shamsuddin et al. 2012)	UK	X			VREAD: Virtual reality for early detection of Alzheimer's disease	X		X	Spatial Memory, Navigation/wayfinding

(Tarnanas et al. 2015)	Greece		x		VAP-M: Virtual Museum system	x		Navigation/wayfinding, General memory functions, Executive function
(Kim et al. 2018)	Korea			x	SEMPT: Social Event Memory Test	x	x	General memory functions, episodic and associative memory
(Richard et al. 2010)	France	x			Virtual Kitchen		x	General memory functions
(Cushman et al. 2008)	USA	x			-	x	x	Navigation/wayfinding, General memory functions
(Tarnanas et al. 2014)	Greece, Switzerland	x			VR-DOT: Virtual Reality Day-Out Task(	x		General memory functions, Executive function
(Martono et al. 2017)	Japan	x			Virtual Kitchen			
(Sauzéon et al. 2016)	France			x	HOMES virtual apartment- Human Object Memory for Everyday Scenes		x	Spatial Memory, Navigation/wayfinding, General memory functions
(Seo et al. 2017)	Korea			x	VDLT: Virtual daily living test	x		General memory functions, Executive function

- = the VR systems where not given specific names

Table 2: Study characteristics chart

6.1 IMMERSION

Although the majority of these tests can theoretically be conducted in real life, the biggest strengths of VR testing is that it offers increased accessibility for disabled and elderly patients. In addition, VR environments can promote ‘presence,’ or the feeling of truly being in a real-world situation, instead of a simple VR environment. The system’s depth of immersion and level of fidelity determine the level of presence experienced by the user. Slater et al. (2009) use the term ‘fidelity’ to describe the degree to which a system stimulates replicates real-world sensory experience (Slater et al. 2009). Immersion level is determined based on ‘(i) number of stimulated senses, (ii) quantity and level of interactions, (iii) synthetic stimuli fidelity, and (iv) system’s ability to isolate the user from external stimuli’ (García-Betances et al. 2015). VR simulations can be categorized roughly into 3 groups: fully immersive, semi-immersive, and non-immersive. Non-immersive immersive systems involve the use of a typical workstation including a desktop monitor with conventional graphics, a keyboard, mouse and/or joystick. A fully immersive system involves the use of 3D displays such as head-mounted displays (HMD), 3-4 surrounding projection surfaces and either a glove or another form of a high capacity input device (Costello 1997). Tarnasas et al. 2013 used a unique example of a fully immersive setup: it involved a curved rear projection screen and a split belt treadmill with force plates (Tarnanas et al. 2013).

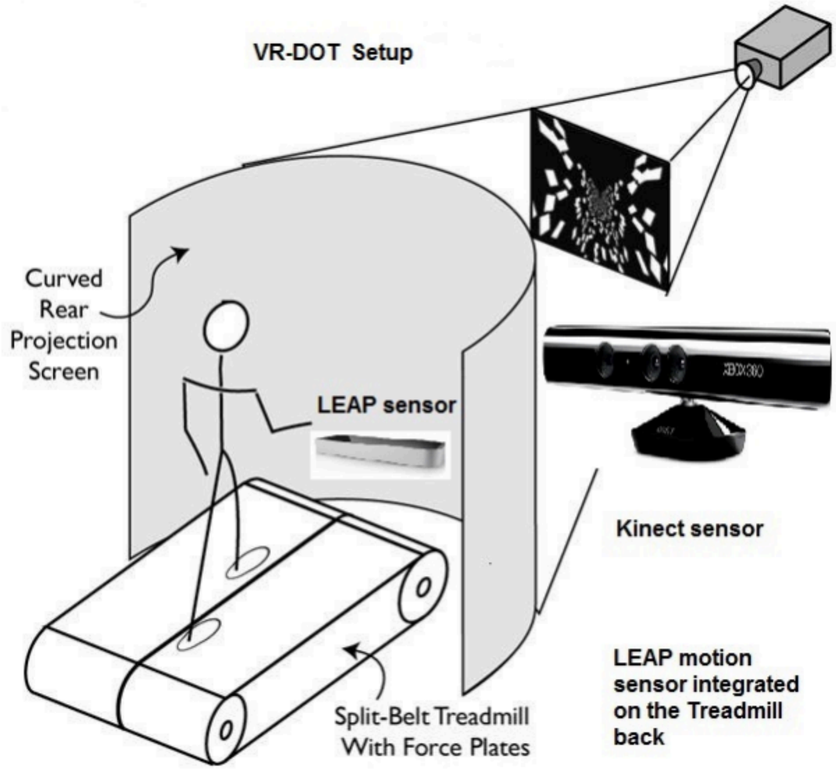

Figure 3: VR-DOT, a fully immersive VR system (Tarnanas et al. 2013).

Semi-immersive environments fall in between the two; they typically use a system with slightly more sophisticated graphics along with either a larger screen monitor, large screen projector, and/or multiple projection systems. They also involve the use of a keypad and mouse or joystick. The higher the immersion level of a system, the higher the fidelity and the feeling of 'presence.' HMDs usually provide the highest level of immersion.

According to Ma and Zheng 2011, the two most crucial features of a VR system are (i) the users' ability to control their movement in the virtual environment and (ii) the users' ability to interact with objects or interfaces in the environment through the use of an input device. These devices can be a mouse, gamepad, joystick, glove etc.; they are chosen based on the immersion level of the system. One characteristic they have in common is they provide responses (i.e. signals, haptic feedback etc.) from the system to the user when the user engages with the environment (Ma and Zheng 2011). The more immersive the system, the more complex the input device is.

While more immersive devices have the ability to increase 'presence,' they can also lead to side effects such as cyber sickness or visually induced motion sickness (VIMS) either during or after the test. Garcia-Betances et al. 2015 refer to the term 'virtual reality induced sickness symptoms and effects' (VRISE), which emphasizes that this VR induced motion sickness is correlated to the immersion level of the device. Typically, more immersive devices can yield higher VRISE rates (García-Betances et al. 2015).

6.2 INTERACTION TECHNIQUES

VE methodologies and modalities varied across the studies; nonetheless, they all focused on a task, activity or game. García-Betances et al. 2015 define tasks as particular actions that are intended, designed, and utilized to test a specific cognitive function;

activities encompass performing high-level sustained cognitive actions and processes such as: eating, cooking, shopping, etc.; and games refer to activities that are defined by rules and user engagement (García-Betances et al. 2015). Moreover, they specifically define some VE activities as IADL tasks that test aptitude for activities that are engaged in on a daily basis. Many of the studies that tested spatial navigation and orientation involved tasks, which focused on navigating through an environment or a maze and locating objects. Those that tested executive function and general memory typically involved an activity- particularly an IADL activity. These categories are not absolute, in fact the lines between them can be fuzzy depending on the simulation. For example, Tarnanas et al. 2014 created a fire evacuation simulation where participants are required to follow the rules to exit a building that has caught fire (Tarnanas et al. 2014). Given the abundance of rules, this would be considered a game, but it can also arguably be an IADL activity as it simulates a real-life situation.

6.3 FOCUS FEATURES

Persons with dementia (PWDs) experience a variety of symptoms stemming from cognitive impairment; many of the papers chose to test either those that are most widespread or those that appear earliest in individuals with cognitive decline. The main focus features that were tested across the papers were attention, general memory, orientation, and kinematic irregularities. For the purposes of comprehension, the focal aspects can be further summarized as follows: (1) Attention (i.e. ability following directions, focus), (2) executive functions (cognitive functions that are needed to accomplish complicated tasks), (3) general memory (i.e. non-verbal episodic, allocentric, egocentric, temporal order memory, prospective, short-term, working memory, associative memory), (4) orientation (i.e. allothetic, visuospatial, wayfinding, spatial navigation, topographical disorientation, spatial memory, route recall), (4) kinematic behavior (i.e. motor skills).

The brain is very complex and different regions dictate certain behaviors and cognitive functions. Similarly, given that many of these features and their sub-features work hand in hand, there is no definitive way to categorize them. For example, a system that is designed to test a patient's orientation ability may rely on testing other features such as egocentric and/or allocentric memory as well as attention and spatial memory. Some tests, like the one developed by Zakzanis et al. 2009, are even designed to test multiple focus features at a time for more robust and accurate assessment (Zakzanis et al. 2009). It is imperative to note that almost two-thirds of the papers focused mainly on orientation and/or orientation along with another focal aspect. This may be because it is one of the first forms of impairments experienced by those with dementia; spatial navigation performance can even predict pre-dementia syndromes in aging (Verghese et al. 2017).

6.3.1 ORIENTATION & SPATIAL MEMORY

As mentioned above, most of the studies tested orientation and spatial memory. Studies that fall into this category are designed to test sub focus features such as: egocentric memory, allocentric memory, wayfinding, visuospatial memory, and route learning ability.

Wayfinding and navigation are the main sub-features that are used to test orientation. Typically, wayfinding is tested by allowing the participants to navigate freely through an environment while paying attention to salient landmarks in their environment. They are then asked to recall some of the objects they saw. Allison et al. 2016 asked participants to recall as many landmarks as they could remember and then locate them on a 2D map of the environment. They also tested the participants' route learning ability by asking them to replicate the route they followed on a 2D map (Allison et al. 2016). Shamsuddin et al. 2012 also tested route learning ability, but asked the participants to replicate a pre-learned route in the VE (Shamsuddin et al. 2012). Unlike the previous study, this one did not comment on whether the skill could be transferred from a 3D to a 2D environment.

Wayfinding and navigation are also tested by first giving directions to the location of the objects and testing whether the participants are able to find them in the VE. Tarnasas et al. 2012 designed a test wherein the participants were asked to roam around a virtual museum and become familiar with its layout; the participants were then given pictures of 5 archeological artifacts and directions on how to locate them. They were given a few minutes to try and memorize the pictures and directions and then asked to locate the objects (Tarnanas et al. 2012). This test was designed to characterize cognitive profiles in an ecological fashion, which involves analyzing memory as it relates to central and perceptual details. Allison et al. 2016 followed a similar test design in which they indicated a landmark in a VE; their approach differed in that they encouraged their participants to find the shortest distance to the landmark from their current location (Allison et al. 2016).

Pengas et a. 2010 and Shamsuddin et al. 2012 attempted to test topographical memory by assessing participants' wayfinding ability, visuospatial ability and ability to follow directions. Topographical memory is characterized as the ability to recall the design, shape, or structure of a previously experienced environment or landmark. In the former study, participants were asked to follow a set of directions to find a landmark in a VE; once familiar with the environment they were asked to find another landmark by using visual cues. Once at the landmark they were asked to delineate its direction respective to themselves by using cardinal egocentric pointers (ahead, behind, to the left, or to the right) (Pengas et al. 2010) (Shamsuddin et al. 2012).

Lee et al. 2014 attempted to assess spatial working memory, which refers to short-term memory that is concerned with immediate conscious perceptual and linguistic processing. They designed a maze consisting of one room with 6 identical hallways attached to it forming an asterisk shape. The participants were asked to find various objects located in these hallways and their working memory was tested based on how frequently they entered the same incorrect hallways and doors (Lee et al. 2014).

Sauzeon et al. 2016 devised a very comprehensive test which examined participants' orientation, attention, free recall and episodic memory, which is "the ability to learn, store, and retrieve information about unique personal experiences that occur in daily life" (Dickerson and Eichenbaum 2010). A route was demonstrated in a virtual hospital; the participants were tested on their ability to (1) recall the route and (2) recall relevant objects. With regards to the former, subjects were asked to recall the route from an egocentric perspective, they were asked to replicate it on a 2D map, and when shown a series of objects that they saw in the virtual hospital, they were asked to 'point in the direction of the location depicted as if there were no walls between themselves and the object' (Sauzéon et al. 2016). With regards to the second portion, participants were asked to list the objects they saw in the environment, recall the salient landmark objects, and determine where they saw each object.

In a similar fashion, Cushman et al 2008 also designed their test in such a way where the computer passively led the participant through a virtual house. Their test was intended to examine executive functioning (EF) and episodic memory. Objects were placed in certain locations around the virtual house and subjects were asked to be attentive throughout the exploration process. They were then asked to complete a free-recall of the objects Cushman et al. 2008).

6.3.2 EGOCENTRIC & ALLOCENTRIC MEMORY

Allocentric or 'world-centered' navigation, refers to utilizing environmental features (i.e. buildings, monuments) external to the self, in order to navigate through a place. Egocentric navigation refers to the mental understanding of the route being travelled including direction, the distance that has been travelled, the time that has passed etc. (Weniger et al. 2011). Serino et al. 2015 compared the results of two tests that focused on ego and allocentric memory. They asked participants to indicate the position on a map of an object they had seen in a room in real life (allocentric memory); they were then asked to retrieve the position from an empty version of the same virtual room, starting from a different position (egocentric) (Serino et al. 2015);

Weniger et al. 2015 and Mohammadi et. al. 2018 asked participants to participate in a virtual park and neighborhood navigation task, respectively, to test allocentric memory. They then asked participants to participate in a virtual maze wayfinding task to test egocentric memory. The results were compared and it was found that those who suffer from MCI and dementia performed relatively worse than healthy control in both these features (Weniger et al. 2011) (Mohammadi et al. 2018). Mohammadi et al. 2018 also indicated that performance on the maze was significantly worse than the neighborhood navigation task amongst the test group.

Tu et al. 2017 chose to test these two features through the employment of a virtual supermarket task, in which participants were asked to find specific items from a shopping list. Initially the participants navigated through the market in first person (egocentric navigation); after maneuvering for a bit they were then asked to locate their current location on a map of the supermarket (allocentric memory) and were checked for accuracy (Tu et al. 2017).

6.3.3 EXECUTIVE FUNCTIONS & GENERAL MEMORY

Executive functions are complex cognitive functions that are needed to accomplish complicated tasks. Executive function disorders include “attention deficit, planning, problem-solving, multi-task, monitoring and behavior control”(Yeh et al. 2012). Many of the studies tested executive function alongside orientation and general memory. These tests typically involved IADL tasks and they tested several cognitive elements that would be affected in patients with MCI or dementia.

One of the most popular IADL tasks in this category is the virtual supermarket (VSM). While Eraslan Boz et al. 2020, Zygouris et al. 2015, Werner et al. 2009, Yeh et al. 2012 and Yeh et al. 2012 all used some form of a VSM, the focus features they tested were not identical. Most VSM studies ask participants to find and purchase specific items from the VSM. They are often judged based on whether they bought the correct product types and quantities, if they bought anything they were not supposed to and whether or not they conducted the financial transaction accurately (Eraslan Boz et al. 2020) (Zygouris et al. 2015) (Yeh et al. 2012). Because this is also a navigation task, the VSM also tests visual and verbal memory, executive functions, attention, and spatial navigation.

Some studies chose to test cognitive function by focusing mainly on the participants' general memory (comprising of verbal, visual, and episodic and associative memory). One study in particular asked participants to watch a short clip that simulated a real-life social event (i.e. a scene from a birthday party where the guests casually chat about their lives). They were then asked to recall the seating arrangement, information about a randomly chosen guest (name, relationship to host, city of residence, occupation, hobby etc.) and match the name of the guests to a picture of their face (Kim et al. 2018).

Associative memory, the ability to learn and remember the relationship between unrelated item, is another sub focus feature that is tested under general memory. Montenegro and Argyriou 2015 designed a simulation in which participants were asked to memorize a list of objects and locate them in a simulation; they were then show object pairs, asked to memorize their interaction and then accurately indicate the pairs and their functions (Montenegro and Argyriou 2015). The key feature of this test is that the objects displayed are everyday objects the subjects might interact with in real life and the interaction feature was chosen at random. In other words, the object pairs did not follow a pattern (i.e. teacup and saucer, plate and fork etc.); otherwise the purpose of testing associative memory would be defeated.

6.3.4 KINEMATIC BEHAVIOR

Among the studies analyzed, kinematic movement analysis was not a popular assessment method for MCI and dementia. However, unlike questionnaires and computer based tests, they can yield complex, objective performance data. Seo et al. 2017 asked their participants to complete two tasks: (1) withdraw money from the bank and (2) take a bus to a specific location. Because the test was fully immersive, they were able to see a great deal of body movement. As the participants interacted with the environment, eight motion tracking cameras collected the position of both their dominant hand and head movement. Not only were the participants assessed based on the accuracy of the tasks they completed, but the cameras yielded extra information about their head trajectory: total distance of head movement during the task, their time to completion, and head speed: mean velocity of the head while taking a bus. Interestingly, in this study neither of the two kinematic measures (hand and head speed) correlated with the results on the neuropsychological testing. They did, however, uniquely discriminate between MCI and healthy controls (Seo et al. 2017).

The study that tested the most comprehensive list of focus features tested the efficacy of VR-DOT, a module that requires multitasking in a fire evacuation drill setting, in detecting MCI. Not only did they collect behavioral data to compute EF, orientation, and memory, but they also used LEAP motion and Microsoft Kinect camera sensors inside the headset to collect quantitative kinematic behavior like grip strength and finger tapping (Tarnanas et al. 2013).

7 LIMITATIONS

There are few limitations in the current study. The first is that due to the heterogeneity regarding the test location, there was no standard language that was used in the testing portion of the studies. While this may not seem like a critical issue, languages have different semantic rules and users may react differently with systems based on the wording or phrasing of some of the rules they are provided. A second limitation was that there was a wide range of focus features tested and devices used. As a result, the authors collected different types of data using different measures that cannot be quantitatively compared across studies. Future research should target papers with similar task designs and focus features for comparable robust quantitative results. A few of the articles were eliminated from the quantitative analysis because they were not open access and could not be located even with help from an HSL librarian. Finally, the biggest limitation of this study was the scarcity of research in this field; as the field grows, reviews of this nature will produce more fruitful results.

8 CONCLUSION

This study used the systematic review method was undertaken to screen through literature that used virtual reality technology to assess cognitive condition and provide diagnosis for MCI, dementia or Alzheimer's disease. The standard battery of testing that is used to detect MCI, dementia, and Alzheimer's is not perfect. It can be invasive, yield subjective data about the patient from their loved ones, and often times is not efficient in forming early prognoses. VR is an effective alternative to physical cognitive testing that can offer objective data regarding a patients' cognitive condition. The studies examined in this review were modeled according to tasks or activities that would easily indicate areas of cognitive decline in the brain. Many of the authors emphasized that specific cognitive dysfunctions like spatial impairment can be one of the first forms of impairments experienced by those with dementia (Verghese et al. 2017). These impairments can sometimes be missed by loved ones of MCI and dementia patients, but a physical test can easily discriminate a healthy control from an individual who suffers from MCI or dementia. VR assessment tests are low-cost, computerized, and a noninvasive way to assess for cognitive condition. They also provide eye tracking capabilities which can provide valuable insight into a patient's memory, attention, and gaze- all parameters that are used to assess dementia (Davis and Sikorskii 2020). Given that the research in this area is still very new, there is a lot of room for improvement. Future research should focus on targeting more and multiple focus features, increased immersion, enhanced usability, and decreased side effects.

9 APPENDIX 1

Key Terms:

#1 AND (#2 OR #3)
#1: (virtual reality [mesh] or virtual reality [tw] or VRCT [tw] or head-up display [tw] or head-mounted [tw] or head mounted [tw] or virtual environment [tw] or virtual environments [tw] or 3D environment [tw] or 3D environments [tw] or multi-sensorial interaction [tw] or virtual retinal display [tw])
#2: (Mild Cognitive Impairments [mesh] or mild cognitive [tw]or mild neurocognitive [tw] or dementia [mesh] or dementia [tw] or Alzheimer* [mesh] or Alzheimer* [tw])
(TS=("virtual reality" OR "virtual reality" OR VRCT OR "head-up display" OR head-mounted OR "head mounted" OR "virtual environment" OR "virtual environments" OR "3D environment" OR "3D environments" OR "multi-sensorial interaction" OR "virtual retinal display")) AND ((TS=("Mild Cognitive Impairments" OR "mild cognitive" OR "mild neurocognitive" OR dementia OR dementia OR Alzheimer* OR Alzheimer*)) OR (TS=(Aging OR ageing OR geriatric OR older OR elder OR senior OR seniors OR "middle aged")))

Table 3: Search Key terms & combinations used in database search

10 APPENDIX 2

• Was there a clear question(s) for the study to address?	☐ Yes ☐ No ☐ Unsure
• Was there a comparison with an appropriate reference standard?	☐ Yes ☐ No

○ **Reference Standard:** Expert clinical diagnosis, MRI scans, Biomarkers etc. anything that is normally used for diagnosis.	☐ Unsure
• **Verification Bias:** Did all patients get the same diagnostic test and reference standard? ○ HINT: Consider •were both received regardless of the results of the test of interest	☐ Yes ☐ No ☐ Unsure
• **Review Bias:** Could the results of the test have been influenced by the results of the reference standard? ○ HINT: Consider •was there blinding, randomization • were the tests performed independently •	☐ Yes ☐ No ☐ Unsure
• Is the disease status of the tested population clearly described? ○ HINT: Consider • presenting symptoms • disease stage of severity • co-morbidity • differential diagnoses (spectrum bias)	☐ Yes ☐ No ☐ Unsure
• **Outcome reporting bias:** Were all test results reported, including uninterpretable or intermediate test results? Did the authors mention not reporting some results? ○ Did they avoid the **selective reporting** of some outcomes but not others, depending on the nature and direction of the results.	☐ Yes ☐ No ☐ Unsure

Table 4: Qualitative Assessment Template.

11 APPENDIX 3

Identification
1. List the authors 2. What is the title of the publication? 3. What is the country of publication? 4. Where was the test conducted?

5. What is the year of publication?
6. What is the purpose of the study?

Population

Control Group

1. What was the size of the control group?
2. What is the age range of the control group?
3. What is the gender composition of the control group?

Target Group

4. Which target groups were tested? Check all that apply.
    a. ‘MCI, AD, Dementia, Other’ were listed as options
5. What was the size of the target group?
6. What is the age range of the target group?
7. What is the gender composition of the target group?
8. Is there anything else noteworthy you would like to mention about the participant group(s)?

Intervention

1. Were the target and control groups given the same reference and index standards?
    a. ‘Yes, No, Unsure’ were listed as options
2. What was the name and acronym of the intervention?
3. What was the duration of the intervention testing? Skip if not applicable.
4. Which reference standards were used to test for cognitive ability?
    a. ‘MMSE, blood test, Neuroimaging, Neuropsychological testing, medical history, Laboratory testing, other’ were listed as options
5. Which VR methodology(s) was used?
    a. ‘Task, IADL, Game,’ were listed as options
6. Please describe the methodology(s) setup briefly.
7. What measurements were taken (i.e. time on task, cursor movement etc.)?
8. What was the immersion level?
    a. ‘Full, semi, none’ were listed as options
9. Which focus feature(s) were tested?
    a. ‘Spatial Memory, Allothetic orientation, egocentric orientation, Navigation/wayfinding, Topographical disorientation, General memory functions, executive functions, Motor skills/ Psychomotor slowing, Strategic and critical thinking, other’ were listed as options
10. Can you briefly describe the focus features tested?

Outcome

1. What were the outcomes of the test?
2. Outcome 1: How were the results of the index test measured? (i.e. unit of

measurement if relevant etc.)

3. Outcome 2: Is there a notable difference in outcome that the authors associated to age, gender, education level, computer literacy etc.? (If, yes, explain.)
4. Outcome 1: According to the authors are these results favorable?
    a. 'Yes, no' were listed as options
5. Did the authors highlight any future research that needs to be conducted to validated this test? (I.e. did they refer to these: from whom, what and when). Skip if irrelevant.
6. What were some limitations?

Table 5: Data Extraction Template.

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