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Clinical Study

Compromised visually guided motor control in individuals with Alzheimer's disease: Can reliable distinctions be observed?

William J. Tippett [a,b,c,d,*], Lauren E. Sergio [e,f], Sandra E. Black [b,c,d,g]

[a] Department of Psychology, University of Northern British Columbia, 3333 University Way, Prince George, British Columbia, Canada V2N 4Z9
[b] Sunnybrook Health Sciences Centre and Sunnybrook Research Institute, Toronto, Ontario, Canada
[c] Heart and Stroke Foundation Centre for Stroke Recovery, Toronto, Ontario, Canada
[d] L.C. Campbell Cognitive Neurology Research Unit, Sunnybrook, Toronto, Ontario, Canada
[e] School of Kinesiology and Health Science, York University, Toronto, Ontario, Canada
[f] Centre for Vision Research, York University, Toronto, Ontario, Canada
[g] Department of Medicine (Neurology), University of Toronto, Toronto, Ontario, Canada

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ABSTRACT

Identifying the multitude of deficits associated with dementia-related illnesses such as Alzheimer's disease (AD) presents a significant challenge for many health care facilities, particularly as current screening procedures may lack the sensitivity to highlight all the relative functional deficits within these populations. Although quick assessment screening tools, such as the Mini Mental State Exam (MMSE), have been the mainstay in screening patients worldwide, there are limitations to their ability in identifying visuomotor (VM) impairment. Thus, the primary objective of this research was to evaluate the presence and level of VM ability/deficits in healthy normal controls (NC) and populations with AD. The research also aimed to demonstrate that a VM measure can be utilized successfully in a busy health care setting. Results showed a clear distinction between the AD and NC groups on the VM measure. Large effect size differences were observed between groups, particularly as the VM task progressed through its varying conditions. In addition, this novel VM assessment measure demonstrated good presentation and speed and was appropriate for frontline staff in a primary healthcare setting to undertake further examination of an individual's overall visually guided ability/control.

1. Introduction

In clinical settings, mental status assessments are frequently utilized, along with the neurological exams and imaging data, for the diagnosis of probable Alzheimer's disease (AD).[1,2] Quick, easy-to-use assessments are always desired for screening individuals to determine the presence of deficits in one or more cognitive domains, which together with evaluation of functional capacities, determine if the patient meets the criteria for dementia.[2–4] Formal neuropsychological testing in a clinical setting requires clinically trained personnel and has limited availability in many jurisdictions. Current research suggests that neuropsychological tests of visuospatial (VS) or visuomotor (VM) ability (for example, Rey–Osterrieth Complex Figure [Rey–O] and Benton Judgement of Line Orientation)[5,6] are limited by static procedures (e.g. paper and pencil), which arguably is contrary to everyday experiences[7] that involve dynamic and shifting visual environments. Dynamic testing procedures may improve interpretation of clinical findings, especially when examining VS and VM ability,[7] and could provide valuable insight into cognitive and functional ability in neurodegenerative patient populations. VM/VS ability is very relevant to daily function because individuals with VM/VS difficulties have significant problems navigating the world around them (including driving, walking, and climbing stairs).[8,9] In particular, driving can be problematic in individuals in the early stages of AD with increased levels of car accidents, traffic violations and traffic fatalities.[10–13] Unsafe driving behaviour is not well predicted by the Mini Mental Status Exam (MMSE) score,[14] reflecting that a test emphasizing language and memory does not provide a good predictor of driving ability and therefore VS/VM ability. Given that significant VM control deficits may occur early in dementia,[15,16] a quick and reliable way to evaluate this ability that goes beyond traditional neuropsychological measures could be clinically valuable.

Patients with AD have difficulty completing VS tasks including: angle discrimination, mental rotation, visual search, visual attention, depth and motion, and saccadic inhibition.[17–21] Although this is not an exhaustive list of observed VS deficits, it highlights common processing deficits that could contribute to poor performance by participants with AD in completing visually-guided activities. In

* Corresponding author. Tel.: +1 250 960 6504; fax: +1 250 960 5744.
E-mail address: tippett@unbc.ca (W.J. Tippett).

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particular, patients with AD have significant problems handling non-standard mapping procedures (e.g. working on a horizontal plane to move items in a vertical plane), resulting in speed/velocity reductions and increased movement and planning errors.[8,16,22]

Prior research[16,17] has postulated that a breakdown of VM ability in patients with AD may reflect pathology in the parietofrontal network, and in particular, the posterior parietal cortex.[13,16] Early assessments of VM performance in AD populations have demonstrated the potential to identify functional deficits that relate to everyday life, which not only identify disease presence, but may also detect disease progression.[23,24]

The purpose of this study was to examine the extent that VM control is affected and detectable in patients with AD compared with healthy normal control (NC) participants and to demonstrate the potential of this VM method as an accessible, reliable, and quick measure in a busy healthcare setting. The objective is to provide clinicians with additional information about functional VM ability not observed on traditional measures. The secondary goal of this research was to evaluate elements of this proposed VM procedure to reliably identify dementia presence (e.g. AD), and in particular compare it to traditional screening measures (e.g. MMSE, Rey–O).

2. Methods

2.1. Participant characteristics

A total of 61 participants was recruited from the Sunnybrook Dementia Study at the L.C. Campbell Cognitive Neurology Research Unit, at the Sunnybrook Health Sciences Centre (SHSC), a University of Toronto academic healthcare institution, including 25 NC and 36 participants with probable AD. The demographic and clinical information for the population samples is provided in Table 1.

In this study, patients with AD met the original National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders criteria for probable or possible AD[1] and the clinical core criteria for the new demographic criteria,[2] and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition[25] criteria for dementia. All patients received a comprehensive clinical evaluation, including detailed medical history review, neurological examination, routine laboratory and imaging investigation, as well as neuropsychological testing with a standardized test battery, including the Dementia Rating Scale (DRS) and the MMSE. Participant's volumetric MRI and single photon emission CT (SPECT) findings were compatible with AD. Participants were excluded if they displayed or reported any uncorrected visual disability or if any medical condition hindered their task performance (such as arthritis, apraxia).

Table 1
Demographics of participants with Alzheimer's disease (AD) compared to healthy, normal controls (NC)

Characteristics	Controls (n = 25)	AD (n = 36)	p value
Age (years), mean ± SD	73.34 ± 7.87	74.37 ± 8.37	NSD
Male/female sex, n (%)	48/52	45/55	NSD
Education (years), mean ± SD	14.77 ± 2.94	13.20 ± 2.58	NSD
MMSE mean ± SD (range)	29.08 ± .94 (4)	23.09 ± 3.84 (15)	<0.001
DRS, mean ± SD (range)	140.73 ± 2.07 (8)	117.46 ± 8.13 (30)	<0.001

DRS = dementia rating scale, MMSE = Mini Mental State Exam, NSD = not significantly different, SD = standard deviation

2.2. Visuomotor Procedure and Apparatus

Visually-guided motor performance was evaluated via a modified computer-based VM procedure.[16] Data were collected using a Dell 15-inch laptop (Dell, Round Rock, TX, USA) and a clear touch sensitive screen (Keytec Magic Screen: Model KTMT-1315, sampling rate: 100 Hz; Keytech, Garland, TX, USA), under four conditions. Participants began a trial by fixating on a central start location and placing their index finger on the touch-sensitive screen. Participants became aware their finger was on the target position as the target changed colour when "touched". On condition 1, the touch screen was affixed directly over the monitor, so that the finger position following the target directly represented the cursor position. On remaining conditions 2, 3 and 4, the cursor position was only reflective of the finger position on the computer monitor. Although condition 3 involved the touch screen being placed directly over the monitor, the cursor position was 180° away from the participant's finger position. For condition 2 (finger moved cursor in the same direction) and 4 (finger moved cursor in the opposite direction), the touch screen was placed horizontally and directly in front of the keyboard (Fig. 1). Conditions 2, 3, and 4 are all non-standard mapping conditions (whereby the goal of a movement was not in direct alignment with the visual information guiding it).[26] Targets were always presented in one of four locations: 0 °, 90 °, 180 °, or 270° (0° being directly to the left, with increasing angles occurring clockwise). The task required approximately 15 minutes to 20 minutes to complete. The touch screen had the ability to move to various locations but the cursor position on the monitor always reflected the finger position on the touch screen; thus feedback of cursor position to the participants was relatively instantaneous. For a further description of the task, see.[16]

During task performance, movement times (MT), reaction times (RT), and error rates were collected and analyzed. The RT was calculated by scoring initial onset of finger movement (that is, when the participant moved out of centre target position after onscreen target presentation), and MT was calculated by the total time required to move from centre target location to outer target position. These measures were combined to create a total time (TT) score.

2.3. Data analysis

2.3.1. Error trials

An inability to complete a trial correctly was categorized in six types: (i) Type 1, failure to touch the centre target within 5000 ms of its appearance; (ii) Type 2, failure to maintain position at the centre target location prior to the "go signal"; (iii) Type 3, leaving the centre target less than 150 ms after the "go signal"; (iv) Type 4, leaving the centre target more than 1000 ms after the "go signal"; (v) Type 5, exceeding the maximum movement time to the outer target (6000 ms); and (vi) Type 6, failure to maintain the cursor at peripheral target location for 1000 ms. Error trials were not repeated.

2.3.2. Timing

For all conditions, when participants moved away from the centre target location prematurely (before the target was extinguished), their reaction time was not scored and the trial was scored as an error trial (see Section 2.3.1). If subjects maintained a centre position (for more than 150 ms) but delayed reaction movement beyond 1000 ms, this was scored as an error trial (Type 4). In this case no reaction time score was calculated and values were based on average reaction time scores. If participants displayed 100% error throughout any condition, participants received a maximum reaction time of 3000 ms and a maximum movement time score of 6000 ms. If participants moved past the outer target or did not reach the outer target within the given time, the

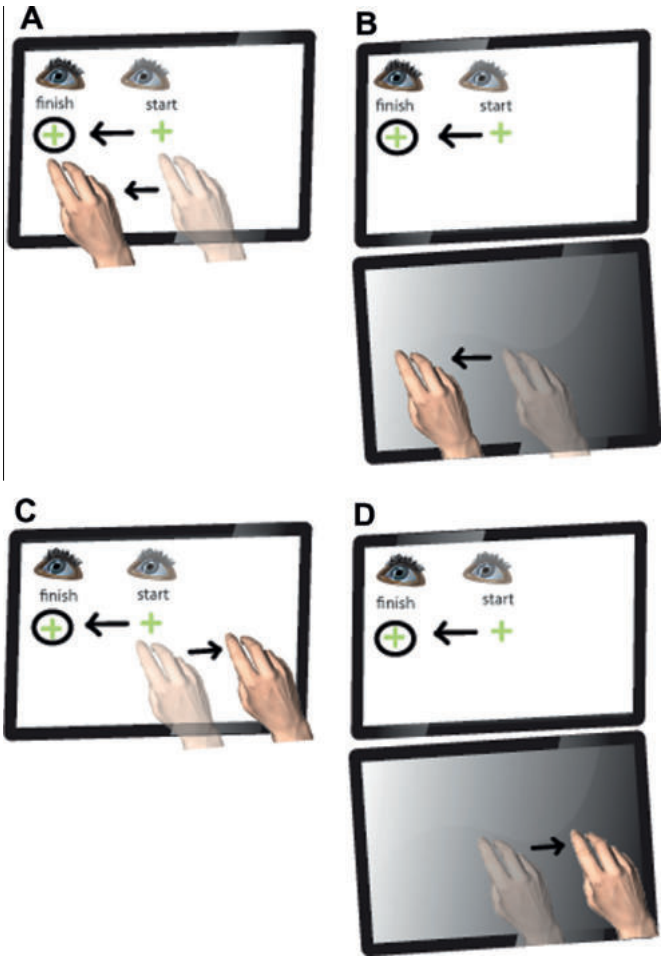

Fig. 1. Diagram of the computerized test for visuomotor performance. (A) Condition 1 – the direct 1-1 condition where finger position is the cursor position; (B) condition 2 – the touch screen was placed horizontally in front of the vertical monitor, participants move their finger on the horizontal touch screen to observe movements on the vertical screen; (C) condition 3 – the touch screen is placed over the vertical monitor as in (A), but the on-screen cursor moves 180° to the finger movement; and (D) condition 4 – the touch screen is placed horizontally as in (B) and cursor moves as in (C), 180° from the finger position. All conditions randomly display targets in 0°, 90°, 180° or 270° positions. Touch screen location is spatially altered in (B) and (D) and visual feedback of cursor position is also altered in (C) and (D). (This figure is available in colour at www.sciencedirect.com)

movement time was not calculated, and the trial was considered an error trial.

3. Results

3.1. Visuomotor Performance

A multivariate analysis (MANOVA) was conducted using the TT score between participant groups and for each condition on the VM procedure. Results showed significant main effects for Group × Condition: for condition 1, $F_{1,57} = 6.74$ ($p < 0.05$); for condition 2, $F_{1,57} = 5.28$ ($p < 0.05$); for condition 3, $F_{1,57} = 13.89$ ($p < 0.001$); and for condition 4, $F_{1,57} = 10.48$ ($p < 0.01$) (Fig. 2). Covariate analysis for age and education variables displayed no significant effects ($p < 0.05$) between sample groups.

Furthermore, a breakdown of TT was achieved by examining both MT and RT values between participant groups. A MANOVA was conducted for RT values and showed significant main effects for Group × Condition: for condition 1, $F_{1,56} = 4.37$ ($p < 0.05$); condition 2, $F_{1,56} = 7.24$ ($p < 0.05$); condition 3, $F_{1,56} = 17.10$ ($p < 0.001$); and condition 4, $F_{1,56} = 7.33$ ($p < 0.01$). A MANOVA was conducted for MT values and showed significant main effects for Group × Condition: for condition 1, $F_{1,56} = 12.41$ ($p < 0.01$); for condition 2, $F_{1,56} = 1.61$ ($p = 0.21$); for condition 3, $F_{1,56} = 2.59$ ($p = 0.113$); and for condition 4, $F_{1,56} = 4.98$ ($p < 0.05$).

3.2. Error Performance

Error performance (Fig. 3) was assessed using MANOVA, which revealed significant main effects between groups on errors for: Type 1, $F_{1,56} = 9.99$ ($p < 0.01$); Type 4, $F_{1,56} = 4.49$ ($p < 0.05$), and Type 5, $F_{1,56} = 7.60$ ($p < 0.01$).

3.3. Effect Size

Effect sizes were calculated between each participant group for each testing condition using TT values. The results demonstrated that effect sizes between the control and AD groups were generally large (range: 0.74–1.2), suggesting that this tool could be helpful distinguishing groups (Table 2).

3.4. Receiver Operator Characteristic Analysis

Receiver operator characteristic (ROC) analysis was conducted on the MMSE (as the "gold standard" since it is one of the most utilized frontline tools) and the combined TT values for conditions 3 and 4 (the two conditions with the greatest observable differences). Not surprisingly the MMSE performed well with an area under the curve (AUC) value of 0.92, (95% confidence interval [CI]: 0.86–0.99). The VM procedure displayed an AUC value of 0.78 (95% CI: 0.68–0.89) (Fig. 4). The best cut-off score for the MMSE was at 27.5 points, suggesting that individuals scoring below 28 on the MMSE should be classified as impaired (that is, as having mild cognitive impairment [MCI] or AD). The best cut-off value for the VM procedures was 3689 ms, indicating that individuals slower than this value could be classified as having AD (Table 3).

3.5. Correlation

Bivariate correlation was conducted between the MMSE and the VM procedures. Results showed a moderate correlation between the MMSE and the VM procedures (Pearson $R = 0.44$, for a two-tailed test, $p < 0.0005$). Thus, shared variance between these measures was only 19%, suggesting these procedures assessed two distinct areas of processing.

Interestingly, we also examined correlational relationships between four common VS neuropsychology measures: Benton Line orientation, Rey Complex Copy Figure, Trails A and Trails B and the proposed VM task on all conditions against all RT and MT values (Fig. 5). Results indicated 13 significant (two-tailed) correlations between these four neuropsychological measures and RT and MT VM values. In addition, it was observed that RT scores on condition 3 demonstrated the strongest and most consistent correlations to the neuropsychological measures.

4. Discussion

Clinicians often rely on common symptoms (e.g. memory loss) to assist in the diagnosis of AD. However, compromised VM ability (e.g. falls) can be very apparent in the early stages of this disease.[27] When developing a diagnosis of possible AD, the primary focal point for many clinicians during screening includes determining the existence of a progressive memory deficit and, if possible, corroborating evidence of dysfunction on brain imaging.[28–30]

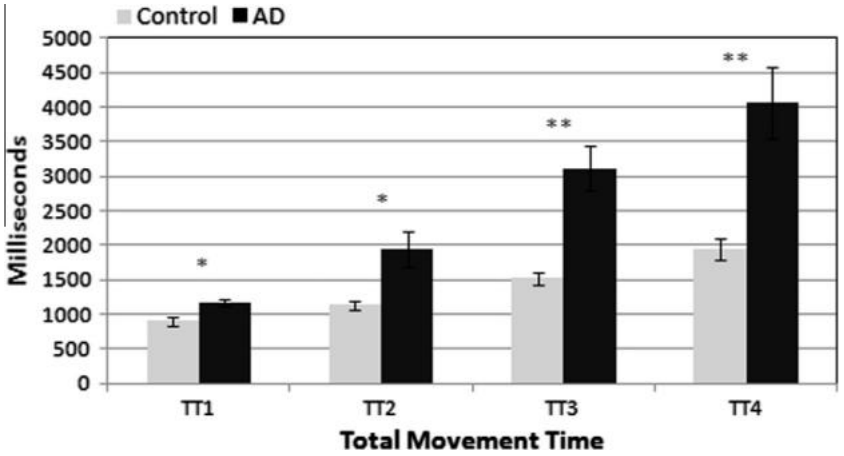

Fig. 2. Histogram showing average total time values (MT + RT = TT) for each of the participant groups, for each experimental condition (1 to 4) showing the main significant effects at the $^{*}p < 0.05$ and $^{**}p < 0.01$ level. Error bars represent standard error of the mean. AD = participants with Alzheimer's disease, control = healthy, normal control participants, MT = movement times, RT = reaction times, TT = total time.

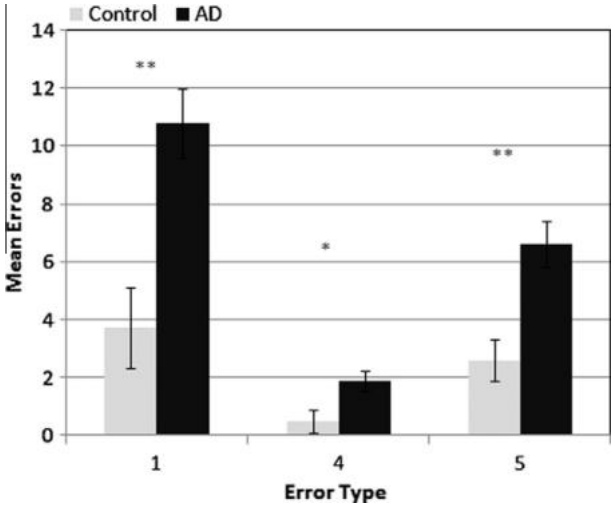

Fig. 3. Histogram showing the average error rate for participants with Alzheimer's disease (AD) and for healthy, normal participants (Control): Type 1 – failure to touch the centre target within 5000 ms of its appearance; Type 4 – leaving the centre target more than 1000 ms after the "go signal"; and Type 5 – exceeding the maximum movement time to the outer target (6000 ms). Error Types 2, 3 and 6 showed no significant effect. $^{*}p < 0.05$, $^{**}p < 0.01$.

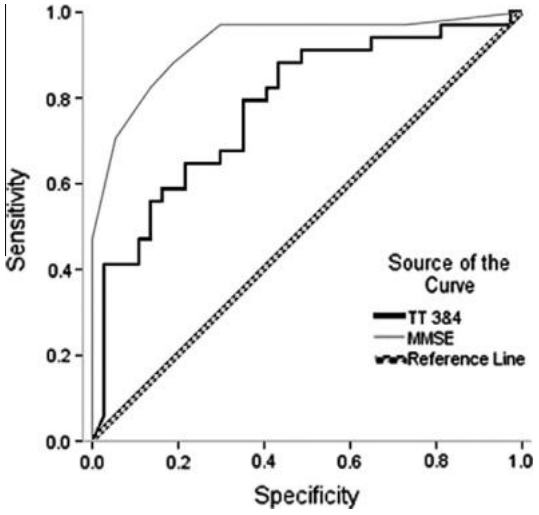

Fig. 4. Receiver operator characteristic analysis for the Mini Mental State Exam (MMSE) and the visuomotor procedure (VM; the combined total time [TT] values for conditions 3 and 4) showing that both tests had similar sensitivity but that the MMSE test had a higher specificity than the VM procedure. Note that the MMSE values were inverted (for example, 30 = 1, 29 = 2, and so on) before the analysis was applied to provide a better display of the relationship between the variables.

Table 2
Effect sizes values from the visuomotor measure are displayed between groups for each condition.

Groups	Cohen's *d* values			
	Condition 1	Condition 2	Condition 3	Condition 4
AD *versus* Control	0.74	0.75	1.2	0.94

AD = patients with Alzheimer's disease, Control = healthy, normal participants.

Table 3
Receiver Operator Characteristic values for the Mini Mental State Exam (MMSE) and the visuomotor procedure (VM)

Task	Best cut-off point	AUC	Sensitivity (%)	Specificity (%)
MMSE	28 points	0.92	97.1	29.7
VM	3689 (ms)	0.78	91.2	48.6

AUC = area under the curve.

Statistical evidence presented here, including effect size values, indicate that clear distinctions can also be found easily using non-language based procedures, which suggests that there could be several different types of deficits (e.g. VM difficulties) that are at work (or not at work) long before the most recognizable symptom (memory deficit) is manifest. This argument is bolstered by recent evidence that demonstrated that individuals with pre-symptomatic AD (identified on brain imaging and cerebrospinal fluid examination) were more likely to experience episodes of falling than individuals without this profile.[27] Thus, measuring limitations (e.g. VM ability) to the ability to operate safely within the environment, particularly in an at-risk dementia population, is of great importance.

Correlations

		RT1	RT2	RT3	RT4	MT1	MT2	MT3	MT4	Trails A	Trails B	Rey-Copy	Benton
Trails A	Pearson Correlation	-.056	.081	**.325***	.210	**.335***	.203	**.381****	.216	1	.631**	-.536**	-.376*
	Sig. (2-tailed)	.713	.591	.030	.166	.023	.176	.010	.155		.000	.000	.020
	N	46	46	45	45	46	46	45	45	46	41	45	38
Trails B	Pearson Correlation	.003	.030	**.472****	**.479****	.220	.168	**.420****	**.484****	.631**	1	-.376*	-.504**
	Sig. (2-tailed)	.984	.852	.002	.002	.168	.292	.007	.002	.000		.017	.002
	N	41	41	40	40	41	41	40	40	41	41	40	34
Rey-Copy	Pearson Correlation	-.024	**-.375***	**-.356***	-.113	**-.341***	**-.539****	-.280	-.151	-.536**	-.376*	1	.464**
	Sig. (2-tailed)	.875	.011	.018	.464	.022	.000	.065	.327	.000	.017		.004
	N	45	45	44	44	45	45	44	44	45	40	45	37
Benton	Pearson Correlation	-.018	-.316	**-.661****	-.280	**-.376***	-.185	-.294	-.287	-.376*	-.504**	.464**	1
	Sig. (2-tailed)	.916	.053	.000	.094	.020	.266	.078	.085	.020	.002	.004	
	N	38	38	37	37	38	38	37	37	38	34	37	38

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Fig. 5. Correlational relationships between four common visuospatial neuropsychology measures: Benton Line orientation (Benton), Rey Complex Copy Figure (Rey–Copy), Trails A and Trails B and the proposed visuomotor (VM) task on all conditions (1–4) against all reaction time (RT) and movement time (MT) values showing 13 significant (two-tailed) correlations (bold type) between these four neuropsychological measures and RT and MT VM values.

The MMSE was used as a comparator throughout this paper, as its use is widespread and it is one of the most common measures to determine initial disease presence, as well as to evaluate disease progression. However, the MMSE is similar to other neuropsychological measures in that it requires a trained professional to administer, can suffer from human error and bias, is susceptible to practice effects, and can be affected by coaching from loved ones, none of which influences the VM procedure. Most importantly, the MMSE has clear limitations in its ability to identify functional VM deficits that might be problematic[14] for individuals affected by dementia.

The ROC analysis indicated that the MMSE and the VM task achieved similar levels of sensitivity, with the MMSE outperforming the VM task on specificity, which one would expect as this procedure assisted in the group designations, and as such, is an obvious limitation to this research. However, it is remarkable that the VM task (a non-verbal procedure) maintained relatively the same level of sensitivity as the MMSE, given that all that was evaluated was the individual's visually guided motor control. Bi-correlation results demonstrated that these two procedures do not share a significant amount of variance, and as such, were testing different things.

However, correlation results for traditional measures (e.g. Benton, Rey-Copy) currently utilized to evaluate VS ability demonstrated a significant relationship with this simple and novel VM task. Thus, essentially, these two procedures (MMSE and the VM task) could be an effective frontline assessment for dementia patients with potentially significant VM deficits not readily recognizable on the MMSE. Support for this position, as described earlier, is founded in research that has demonstrated that driving, walking and falling accidents are more common than previously believed in the AD population.

Recent research has demonstrated the importance of examining VS/VM ability in individuals with AD; [12–14,27,31,32] but even with this evidence there has been limited progress in the development of VM tools to assist in diagnosis and assessment of VM ability. Due to the multifactorial issues that can arise as a result of AD, having additional tools to identify deficits is extremely important. The VM measure used during this project had numerous assets, which include:

(i) The task can be administered within 15 minutes to 20 minutes and is designed to provide immediate classification without trained interpretation.
(ii) The task requires minimal language ability, and can be administered to those with weaker language skills.
(iii) It is an accessible task available both for training test administrators and administering to participants.
(iv) As a computerized task it provides an unbiased performance assessment.

With increasing strain on the healthcare system it is essential to identify assessment procedures that can be readily adapted to busy clinical settings and that can provide clinicians with insight into overall functional ability. The VM measure procedure can be utilized in a fast-paced environment, and overcome many current limitations of screening procedures.

5. Conclusion

This research suggests that increasingly complex visually guided activities can provide insight into the level of an individual's dementia-related deficits. VM activities rely on a "network" of cooperative brain regions,[26,33,34] and as such reduced ability in this integrative action might suggest a complicated illness. The findings here suggest that the novel VM assessment task can identify patients with AD relatively well (and with further testing, possibly those with MCI), with a short time requirement, and with limited testing constraints.

Implementing this VM procedure is simple and requires only a touch-sensitive laptop or a touch screen add-on, and a program such as the one presented in this research that can track simple VM movements. Our results indicate that this procedure could be further simplified (e.g. time and number trials) and still identify "at risk" individuals. In addition, because the procedure is computerized, limited training is required for the administrator and results are readily available upon task completion, displaying time values and error performance.

Thus, assessment of visually guided actions in AD may alert clinicians early on to the risks associated with limited VM ability and aid in disease management. Additionally, further evaluating the link between VM control and the ability to navigate successfully, certainly appears important.

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