RESEARCH ARTICLE

Dementia in Individuals with Intellectual Disability; is there a Better Way to Diagnose?

The Clinical Utility of the Cognitive Computerised Test Battery for Individuals with Intellectual Disabilities and the Hopkins Verbal Learning Test

Authors:
Jordan Elliott-King[1], Sarah Shaw[2], Dr. Stephan Bandelow[1], Dr. Avinash Hiremath[3], Dr. Latha Velayudhan[4], Dr. Sarah Baillon[5,6], Shelina Kassam[1] and Prof. Eef Hogervorst[1]

Authors' affiliations:
[1] Loughborough University
[2] University of Lincoln
[3] Leicestershire Partnership NHS Trust
[4] Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, Kings College London
[5] Leicestershire Partnership NHS Trust
[6] University of Leicester

Corresponding author: Jordan Elliott-King
Loughborough University, School of Sport Exercise and Health Sciences
Sir John Beckwith, Loughborough
LE11 3TU
Email: J.Elliott-King@lboro.ac.uk
Tel:01509 222 222

ABSTRACT

Due to challenges in diagnosing dementia in individuals with an intellectual disability (ID), there is much disparity on which assessment tool should be used for diagnostics. The Cognitive Computerised Test Battery for Individuals with Intellectual Disabilities (CCIID), is validated for use within ID populations, but was not yet tested for dementia assessment. The Hopkins Verbal Learning Test (HVLT) has been extensively used for dementia assessment in the general population; however, it has rarely been tested within an ID population. This study therefore aimed to assess whether the CCIID and HVLT could be used for dementia diagnostics for individuals with ID. ID dementia cases (n=7) were compared to ID controls (n=23) using

Receiver Operating Curve (ROC) analysis to assess accuracy, sensitivity and specificity at baseline. A repeated measures analysis of variance then compared ID dementia cases (n=4) to ID controls (n=10) at 6 month follow-up. Results showed significant differences between cases and controls on total CCIID scores, CCIID Series subtest scores and total HVLT scores at baseline. ROC analysis indicated best accuracy, sensitivity and specificity for the Series test and the HVLT. However, systematic age differences within the sample showed that the HVLT was sensitive to age. This highlighted a need for further analysis into the effect of age on cognition for individuals with ID. In conclusion, this study presents evidence that suggests the Series subtest of the CCIID and the HVLT together could offer good potential in informing dementia assessment within ID populations. Future studies should seek to explore this further, as this study is limited by its small sample size.

Key words: Dementia, Diagnostics, Intellectual Disability

1 Introduction:

An intellectual disability (ID), similar to the UK specific term Learning Disability, refers to a significantly reduced ability to understand new or complex information and to learn and apply new skills. This results in impaired social functioning that begins before adulthood and sustains a lasting effect on development.[1] Life expectancy of individuals with intellectual disabilities, alongside the general population, has increased due to advances in healthcare and living circumstances.[E.g.2] With increases in age, there is greater concern for age-related disorders, such as dementia. Dementia is a cognitive impairment that gradually onsets, is progressive, and leads to interference with social and occupational functioning.[3] Currently, the greatest risk factor for dementia development is an individual's age.[4]

Individuals with ID often experience onset of ageing characteristics earlier than the general population.[5] Dementia onset is typically around 65 years old, but for individuals with intellectual disabilities onset is much earlier at around 50 years old.[6] The exact prevalence of dementia among adults with intellectual disabilities is unknown.[7] Consequently there is much disparity throughout the literature on the exact differences between individuals from the general population and those with a pre-existing intellectual disability regarding their risk for dementia. Nonetheless, individuals with ID have been shown to be at higher risk for developing dementia and at an earlier age than individuals in the general population.[8,9] Furthermore, incidence rates for dementia have been demonstrated to be up to five times higher for individuals with intellectual disabilities than older adults in the general population.[10]

Comparing onset of dementia in a survey across the US, Janicki and Dalton[6] observed differences between the general population and those with an intellectual disability in

percentage of dementia cases. At 40 years old and above 22% of individuals with intellectual disabilities were diagnosed with dementia, compared with 3% of the general population. This disparity was even greater at 60 years old and above where 56% of individuals with intellectual disabilities were diagnosed with dementia compared with 6% of the general population. Although there is still debate across the literature this further supports an increased risk for dementia if an individual has an intellectual disability, as well as an earlier age of onset in comparison to the general population.[6]

The interaction between age and dementia onset is yet to be unpicked in detail for individuals with ID. Regardless it is important to note that alongside these age related concerns for individuals with intellectual disabilities is an increasing demand for accurate and timely dementia diagnosis. Dementia diagnosis is a complicated process, but even more so for individuals with ID, as dementia and related pathology is manifested in areas of functioning that are more than likely already impaired in ID.[11] This leads to inherent difficulties in assessing cognition[e.g.12] and diagnosing dementia in populations with ID,[13] often relying on informants' report of symptoms instead.[e.g.14]

Currently, there is no consensus agreed in the literature or in practice on how to diagnose dementia in ID, but research agrees that consensus needs to be reached in order to advance assessment of dementia in ID.[15,16] The lack of standardization of diagnostic procedures for individuals with ID is impeding progress in the understanding and treatment of dementia.[17] Diagnostic efficiency and standardization is advantageous as it can facilitate communication between health professionals, decrease burden on healthcare professionals time; and lead to earlier treatment, which can result in maintaining the highest possible level of cognitive functioning while the dementia is mild.[18] Moreover, the timing of a diagnosis is important to the dementia caregiver in providing an explanation for difficulties being experienced and allowing earlier organization of care, future planning and caregiver education to mitigate the problems that are inherent when living with undiagnosed and unrecognized dementia.[19]

Diagnosis in the general population involves direct cognitive testing that reflect progressive cognitive decline in areas of functioning, such as short-term and long-term memory, orientation, communication and mood, among others. These tests should assess a range of cognitive functions in order to gain a quick overview of the individual, such as the Mini-Mental State Examination (MMSE).[20] Alternatively, tests could specifically examine a cognitive domain that has been shown to be associated with certain types of cognitive impairments, such as verbal learning and memory as tested with the Hopkins Verbal Learning Test (HVLT).[21] However, as the MMSE is highly sensitive to education and the HVLT was less,[22] so the MMSE was considered to be less useful for this population. Although there is significant debate across the literature, Crayton and colleagues[23] observed similar clinical progression in the ID participants with dementia to individuals with dementia from

the general population. Furthermore, the numerous cognitive domains affected by dementia and related cognitive disorders highlight how onset, course and progression of dementia can substantially vary from person to person, irrespective of any pre-existing cognitive impairment. Therefore, where possible, individuals with ID should complete assessments that correspond with those in the general population and vice versa. This could aid communication and understanding of dementia pathology in both populations. There are many potential improvements to diagnosis of dementia for people who have a pre-existing intellectual disability through this approach. Using a test battery that is designed for application in ID populations may be able to offer a solution to diagnostic difficulties. The Cognitive Computerised Test Battery for Individual's with Intellectual Disabilities or CCIID could be an example of a suitable test battery.

The CCIID was developed by Van der Wardt, Bandelow & Hogervorst,[24] based on theories of intelligence and research into cultural fairness for the purpose of determining an individual's level of ID. The CCIID was developed based on a non-verbal IQ test for deaf children, which makes it cross-culturally applicable. The CCIID has demonstrated high correlations with traditional longer IQ tests, such as the WAIS.[24] Overall, the CCIID examines inductive reasoning and visual-spatial abilities. Evidence has suggested, however, that verbal explicit memory is one of the earliest cognitive processes to be affected by the onset of dementia.[25] Research has also indicated that assessments of verbal memory are capable of predicting both current and future cognitive functioning.[26]

Considering recent research, highlighting a correspondence between the cognitive profiles of individuals from the general population with dementia with individuals with a pre-existing intellectual disability and dementia[27] also using a verbal memory test may prove beneficial in helping to identify dementia in individuals with ID.[28,25] Furthermore, applying an assessment that is already used in the general population, if successful, could increase inclusivity in dementia diagnostic procedures and encourage cross-disciplinary communication in order to better inform our understanding of dementia as a whole.

The Hopkin's Verbal Learning Test or HVLT,[21] has been extensively used in the general ageing population for the purpose of dementia diagnosis, and has often been shown to have high accuracy, sensitivity and specificity in discriminating between those diagnosed with dementia and controls.[29] The HVLT has also been validated cross culturally, most notably in Chinese samples[30] and Spanish samples.[31]

Despite its widespread use, the HVLT has rarely been used in research containing samples of individuals with ID. In a study of young adolescence with ID it was found that the HVLT correlated highly with other cognitive tests that have been validated in an ID population and was tolerated well.[32] However, the HVLT is yet to be validated in an ID population for the purpose of dementia diagnosis.

Hence, this study aimed to evaluate the potential for the CCIID to assess cognitive

abilities in Leicestershire service users with ID; to establish accuracy, sensitivity and specificity of HVLT and CCIID in distinguishing between ID cases and controls for dementia diagnosis; to compare accuracy, sensitivity and specificity of HVLT total score to CCIID composite and subtest scores to establish which instrument is best suited to aid clinicians during dementia diagnosis in individuals with ID; and to evaluate the feasibility of the CCIID and the HVLT to be used in support of the diagnostic process at 6 month follow- up assessment for individuals with ID.

Based on previous research and pilot data it was therefore hypothesized that the proposed cognitive assessments would be well tolerated by individuals with intellectual disabilities both with and without dementia; but controls would score more highly on the HVLT total score, CCIID subtests: Series, Odd One Out and Jigsaw, as well as the CCIID composite score than cases at both baseline and follow-up.

2. Methods

2.1. Participants

Participants for this study were recruited from Leicestershire Partnership NHS Trust ID services. Patients attending ID service out-patient clinics who met the study inclusion criteria were approached by a Consultant Psychiatrist regarding their interest in taking part in the study. Participants were included in the study if they had a diagnosis of Intellectual Disability as defined by the ICD-10 criteria; were aged between 30 and 70 years old and had a completed Dementia Questionnaire for Learning Disabilities (DLD) in their medical file. Prior to completion of the DLD potential physical complications are ruled out. Participants were excluded if they did not have an appropriate carer or person who knows the patient well enough to act as consultee, if the patient is assessed by the consultant psychiatrist to not have capacity to give informed consent; if they lacked the ability to complete the study assessments and/or could not follow the instructions required to do so; or if they did not have a carer or person willing or able to provide the informant information.

2.2. Instruments

During the testing session the participants completed the free recall section of the HVLT and then all subtests of the CCIID, starting with the Series, followed by the Odd One Out and finishing with the Jigsaw.

The tests were administered by 2 researchers who were trained in delivering the tests to individuals with ID. Testing took roughly 45 minutes in total, however, participants were offered breaks throughout resulting in variations in testing time between participants. A health questionnaire was given to carers during this time, which provided descriptive information on the participant.

Table 1 describes the assessments taken. Each subtest gave an individual score. The CCIID also gave a total score that totals all 3 subtest scores which indicates the level of overall cognitive functioning in the assessed areas.

Table 1 – Assessments to be taken

Test	Subtest	Ability tested	Description
HVLT:	Free recall section	Short and Long term Verbal Memory	The HVLT takes 10 minutes to complete. This section involves a researcher reading a list of 12 words aloud and then asking the participant to repeat as many words as they can remember. This is repeated over three trials and the amount of words recalled is noted.
CCIID:	Series	Inductive Reasoning	Three shapes are presented to the participant on a touch screen computer. There is a large range of items, which vary in degree of difficulty, therefore some items may be all the same shape whereas others are transforming. The participant is asked to choose the option that makes the fourth shape and completes the series.
	Odd One Out	Inductive Reasoning	The participant is presented with six shapes. Five of the shapes are either the same or share a feature that groups them together. The participant is asked to identify the shape that is the 'odd one out' or is most different from the other five shapes.
	Jigsaw	Visual-Spatial Abilities	Jigsaw is based on existing block design tests. The participant is presented with a box containing a set of geometric shapes on a touch screen computer. They are asked to replicate the geometric shapes next to the presented box using single colour or patterned squares given to them. The patterned squares can be rotated and moved into different positions, the participant is also able to change their mind as they go along, the jigsaw is only finished when the participant clicks the finished button.

2.3. Procedure

This study and its procedure received NHS ethical approval from NRES Committee East of England. The Consultant Psychiatrist approached the patient regarding the study, where they assessed if the patient had capacity to give informed consent. If the participant was deemed to not have the capacity to consent, then the carer accompanying the patient to the appointment was asked to act as Consultee, or suggest someone who was suitable and willing to do so. The Consultee Information Sheet was then given to the person identified as the Consultee.

The Consultant Psychiatrist was ethically required to obtain consent. Before doing so they explained the nature and the purpose of the study, using the participant information sheet and dementia booklet were converted to a symbol format to aid understanding of the study. If happy to

continue the participant was then required to give informed consent, if they were able to, or the Consultee was asked to sign the Consultee Assent form. The carer was also asked to give informed consent in order to participate alongside the participant.

Once a participant and their Consultee (if required) had consented to participation in the study the researchers booked an appointment with the participant and their carer for the testing session. The session took place either at the out-patient clinic at Mansion House, Leicester Frith Hospital, or in the participant's place of residence. During the testing session participants completed the HVLT and the CCIID. Participants were encouraged to take breaks throughout, therefore, testing sessions lasted approximately one hour including breaks. Participants were then thanked for participating and given a debrief form which was explained to them by the researcher, participants were able to keep this if required.

2.4. Statistical Analysis

A cross – sectional case-control study design was employed to compare ID cases that are diagnosed with dementia to ID controls. A Mann Whitney U analysis evaluated the differences between cases and controls on demographic factors and assessment scores. Spearman's rank correlations were then used to further investigate the associations between demographic variables and test scores. Following this, Receiver Operating Curve (ROC) were then used to highlight the accuracy, sensitivity and specificity of the assessments that were found to be significantly correlated to whether the participant is a case or a control. Multiple Linear Regression (MLR) models were completed to indicate which predictor variables influenced performance on each of the cognitive assessments. The sample was then matched for age statistically and analysis was repeated to see whether the assessments were still able to discriminate between dementia cases and controls.

Subsequent repeated analysis of variance was conducted on the whole sample to evaluate differences between cases and controls at baseline and 6 month follow-up on the subtests that had been completed by enough participants at both time points. This is to begin to evaluate the longitudinal potential of the selected assessments. All analyses were conducted in SPSS 23.0 and a p-value of <0.05 was applied throughout.

3. Results

30 people with learning disabilities were recruited from the Leicestershire Partnership Trust to take part in the study, 7 of whom had been diagnosed with dementia. Cases were significantly older than controls, but the groups did not differ in level of ID severity. Descriptive statistics and Mann-Whitney U tests of difference for all participants, the ID dementia cases and ID controls are presented in Table 2.

Table 2 – Descriptive Statistics:

	Case	Control	Total	Mann Whitney U (p value)
N	7	23	30	-
Mean Age in years (SD)	54.17 (6.70)	44.83 (9.40)	46.76 (9.64)	**27.00 (p=0.02)***
Severity (n):				65.00 (p=0.80)
Mild	2 (33.3%)	7 (30.4%)	9 (31.0%)	
Moderate	3 (50.0%)	15 (65.2%)	18 (62.1%)	
Severe	1 (16.7%)	1 (4.3%)	2 (6.9%)	
Mean Total CCIID Score (SD)	7.50 (1.29)	18.53 (11.19)	16.43 (10.96)	**12.00 (p=0.05)***
Mean Series Score (SD)	3.00 (0.00)	8.21 (5.00)	7.30 (4.95)	**8.00 (p=0.01)***
Mean Odd One Out Score (SD)	4.00(1.15)	10.73(9.94)	9.57 (9.37)	31.00 (p=0.54)
Mean Jigsaw Score (SD)	1.00(0.00)	1.5 (0.65)	1.41(0.62)	12.00 (p=0.18)
Mean HVLT Total (SD)	0.57 (1.51)	4.57 (5.12)	3.63 (4.82)	**34.50 (p=0.02)***
Gender (n):				77.50 (p=0.86)
Male (%)	4 (57.1%)	14 (60.9%)	18 (60%)	
Female (%)	3 (42.9%)	9 (39.1%)	12 (40%)	

*** indicates a significant result (p≤0.05)**

Cases and controls differed significantly in Series scores, total CCIID scores and total HVLT scores. The Odd One Out and Jigsaw subtests, however, did not show any significant differences between groups. Therefore, further analysis were conducted using only the Series subtest, total CCIID and total HVLT scores.

Table 3 shows correlational analysis that was undertaken to further investigate the associations between descriptive statistics and outcome variables. Significant Spearman's rank correlation confirmed the association between diagnosis and age, indicating that cases are older than controls. Being a case or control was also significantly associated with Series, total CCIID and total HVLT scores. ID Severity was correlated with total CCIID score, highlighting a sensitivity of the CCIID to different levels of severity. The HVLT was highly correlated with age, indicating a possible age bias on HVLT scores which was explored further. All three cognitive assessments were correlated with each other.

Table 3: Spearman's rank correlation matrix

	ID Severity	Age	Diagnosis	Series Score	Total CCIID	Total HVLT
ID Severity	-					
Age	rho=0.113 p=0.56	-				
Diagnosis	rho=0.048 p=0.81	**rho=0.428** **p=0.02***	-			
Series Score	rho=0.149 p=0.51	rho=-0.361 p=0.09	**rho=-0.531** **p=0.01***	-		
Total CCIID	**rho=-0.541** **p=0.01***	rho=-0.407 p=0.08	**rho=-0.443** **p=0.04***	**rho=0.723** **p≤0.00***	-	
Total HVLT	rho=-0.325 p=0.085	**rho=-0.536** **p≤0.00***	**rho=-0.443** **p=0.01***	**rho=0.432** **p=0.04***	**rho=0.551** **p=0.01***	-

*** indicates a significant result (p≤0.05)**

Table 4: ROC Analysis for Series, Total CCIID and Total HVLT

	Area	Std. Error	95% CI	P value	Cut-off	Sensitivity	Specificity
Series	0.90	0.07	0.76-1.00	0.02*	**3.5**	**100%**	**79%**
					4.5	100%	74%
Total CCIID	0.82	0.09	0.64-1.00	0.05*	**11.0**	**100%**	**65%**
					13.5	100%	59%
Total HVLT	0.79	0.08	0.62 – 0.95	0.02*	**4.5**	**100%**	**53%**
					5.5	100%	35%

*** indicates a significant result (p≤0.05)**

Table 4 shows Receiver Operating Curve (ROC) analysis that was conducted to investigate the accuracy, sensitivity and specificity with the suggested cut-off scores for the Series subtest scores, CCIID total scores and HVLT total scores. The ROC curves were produced by plotting the sensitivity against the specificity for each cognitive assessment in discriminating between dementia cases and controls.

Figure 1 shows the ROC curve for the Series subtest, a large area under the curve of 0.90 was shown and a cut-off score of 3.5 would detect 100% of the cases and identify 79% of the controls correctly.

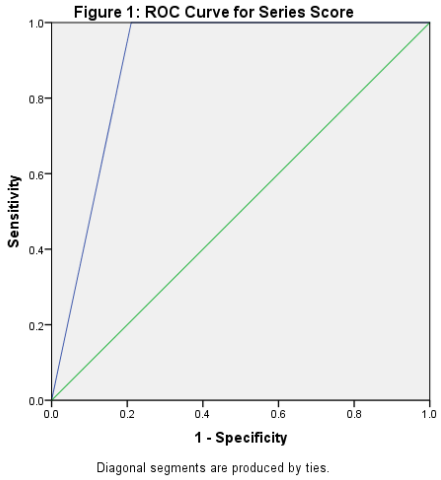


Figure 2 shows the ROC curve for the total CCIID scores, showing a large area under the curve (0.82). A cut-off score of 11.0 showed the highest sensitivity and specificity within this sample of 100% and 65%, respectively.

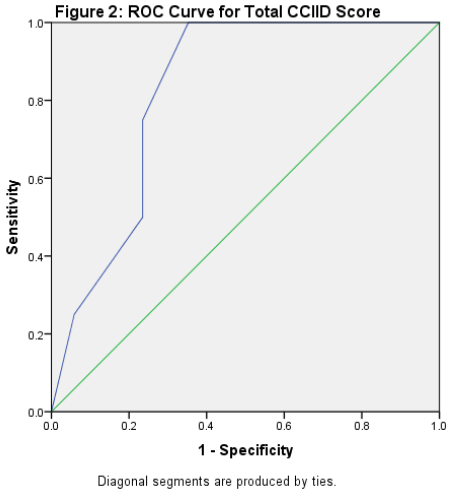
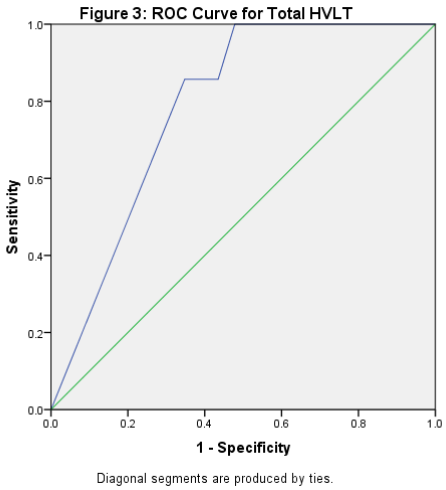


Figure 3 shows the ROC curve for the total HVLT scores, showing an area under the curve of 0.79. A cut-off score of 4.5 showed the highest sensitivity and specificity within this sample of 100% and 52%, respectively.



Following ROC analyses, three multiple linear regression analyses were run, applying a stepwise backward method to establish the variance in Series, total CCIID and HVLT scores. Stepwise backward method involves starting with all candidate variables, which in this case was gender, age, diagnosis and severity of intellectual disability, and removing non-significant variables from the model.

Table 5 shows the results of the first MLR seeking to explain variance in Series subtest scores. Entering all of the variables incurred a determination coefficient of 0.479 (R square). The statistical parameters associated with the final step of the multiple linear regression, which represented the best explanatory independent variables were significant ($F_{(4,17)} = 3.91$, p=0.02) and explained 69% of the variance in Series scores. The final variables included in the model were age, gender and ID severity. Age and ID severity significantly contributed to the model. Older participants achieved lower scores than younger participants.

Table 5 –Multiple Linear Regression for Series Subtest

	Beta	95% CI	P value
Constant		9.10 – 30.64	≤0.00*
Age	-0.48	-0.52 – -0.06	0.02*
Gender	-0.33	-7.07 – 0.61	0.61
ID Severity	0.40	0.13 – 6.19	0.04*

*** indicates a significant result (p≤0.05)**

Secondly, a MLR was conducted to assess the variance in Total CCIID scores, see Table 6. Entering all variables incurred a determination coefficient of 0.464 (R square). The statistical parameters associated with the final step of the multiple linear regression, which represented the best explanatory independent variables

were significant ($F_{(2,17)}$ = 6.53, p=0.01) and explained 66% of the variance in total CCIID scores (R square). The final variables included in the model were Dementia diagnosis and ID severity. The model excluded age and gender. Only ID severity significantly contributed to the model, whereas Dementia diagnosis did trend towards significance.

Table 6 – Multiple Linear Regression for Total CCIID Scores

	Beta	95% CI	P value
Constant		22.58 – 46.28	≤0.00*
Diagnosis	-0.36	-22.43 – 0.64	0.06
ID Severity	-0.56	-15.75 – -2.88	0.01*

*** indicates a significant result (p≤0.05)**

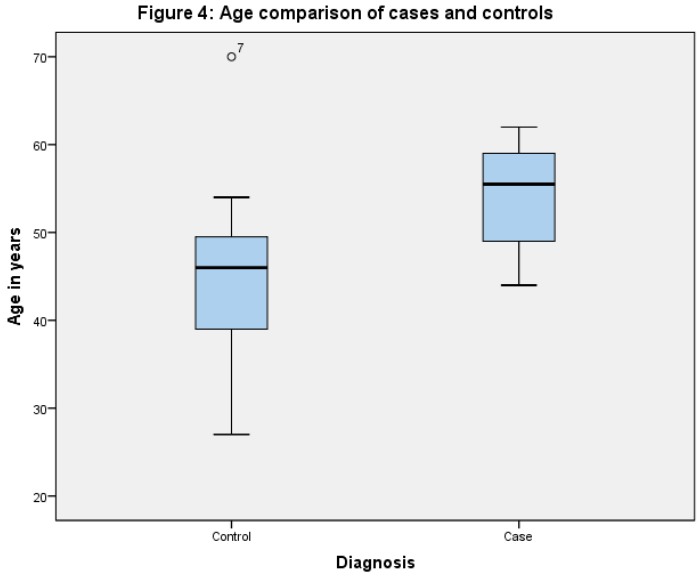
Lastly, a MLR was conducted to assess the variance in Total HVLT scores, see Table 7. Entering all of the variables incurred a determination coefficient of 0.280 (R square). The statistical parameters associated with the final step of the multiple linear regression, which represents the best explanatory independent variables were significant ($F_{(1,27)}$ = 6.06, p=0.02) and explained 18% of the variance in total HVLT scores (R square). Only age was left as the final variable included in the model. The model therefore excluded diagnosis, gender and ID severity.

Table 7 – Multiple Linear Regression for Total HVLT Scores

	Beta	95% CI	P value
Constant		5.27 – 22.44	0.003*
Age	-0.43	-0.40 – -0.04	0.02*

*** indicates a significant result (p≤0.05)**

The models shown in tables 5, 6 and 7 were not consistent with correlations carried out earlier in the analysis. This could be due to the small sample size included in the study potentially making the models unstable. Therefore, further inspection of the groups was conducted. The age range of cases, 27 to 70 years old, differed from controls, 44 to 62 years old, but did not appear problematic. However, on further inspection of box plots cases were much older as a group than controls, highlighting a systematic age difference between the groups. See figure 4.



In order to match for age in subsequent analysis, a filter was applied to exclude participants with an age less than or equal to 44 years old or greater than or equal to 62 years old. Descriptive statistics for the age matched sample are displayed in table 8 below. In this sub-sample age was no longer significantly different between cases and controls. Series scores remained significantly different, regardless of sample alterations but HVLT and total CCIID were no longer significant. This suggests an age bias for these assessments.

Table 8 – Descriptive Statistics for Age matched sample:

	Case	Control	Total	Mann Whitney U (p value)
N	6	12	18	-
Mean Age in years (SD)	54.17 (6.70)	49.42 (3.26)	41.00 (5.15)	21.00 (p=0.16)
Severity (n):				33.00 (p=0.74)
Mild	2 (33.3%)	2 (16.7%)	4 (22.2%)	
Moderate	3 (50.0%)	9 (75.0%)	12 (66.7%)	
Severe	1 (16.7%)	1 (8.3%)	2 (11.1%)	
Mean Total CCIID Score (SD)	8.00 (1.00)	14.55 (8.82)	13.14 (8.24)	11.00 (p=0.39)
Mean Series Score (SD)	3.00 (0.00)	6.64 (3.61)	5.86 (3.53)	**4.50 (p=0.05)***
Mean HVLT Total (SD)	0.67 (1.63)	2.25 (3.05)	1.72 (2.72)	23.00 (p=0.17)
Gender (n):				33.00 (p=0.74)
Male (%)	3 (50.0%)	5 (41.7%)	8 (44.4%)	
Female (%)	3 (50.0%)	7 (58.3%)	10 (55.6%)	

*** indicates a significant result (p≤0.05)**

Descriptive statistics were then further analysed using Spearman's rank correlation analysis, as shown in table 9. Interestingly, total HVLT remained correlated with Age, despite the age match alterations, suggesting an independent effect of age on HVLT assessment scores in this sample.

Table 9: Spearman's rank correlation matrix for age matched sample

	ID Severity	Age	Diagnosis	Series Score	Total CCIID	Total HVLT
ID Severity	-					
Age	rho=0.118 p=0.64	-				
Diagnosis	rho=-0.082 p=0.75	rho=0.342 p=0.16	-			
Series Score	rho=0.157 p=0.59	rho=0.067 p=0.82	**rho=-0.541 p=0.05***	-		
Total CCIID	rho=-0.328 p=0.25	rho=-0.017 p=0.96	rho=-0.240 p=0.41	**rho=0.776 p≤0.00***	-	
Total HVLT	rho=-0.059 p=0.86	**rho=-0.523 p=0.03***	rho=-0. 363 p=0.17	rho=0.386 p=0.17	rho=0.36 5 p=0.20	-

*** indicates a significant result (p≤0.05)**

In the age matched sample the Series subtest was the only assessment that showed a significant correlation with Dementia diagnosis. ROC analysis for the Series subtest indicated an area under the curve of 0.86. A cut-off score of 3.5 showed the highest sensitivity and specificity within this sample of 100% and 73%, respectively. When a cut-off of 4.5 was applied the sensitivity remained at 100% but the specificity dropped to 64%, so the most effective cut-off was 3.5.

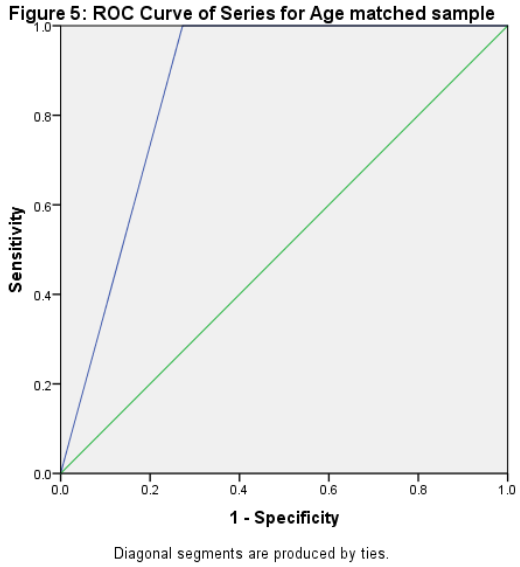


Table 10 shows results of an MLR seeking to explain variance in Series subtest scores within the age matched sample. Entering all of the variables incurred a determination coefficient of 0.244 (R square). The statistical parameters associated with the final step of the multiple linear regression, which represented the best explanatory independent variables were not significant ($F_{(4,9)}$ = 0.726, p=0.60). Neither diagnosis, age, gender or ID severity significantly explained the variance in Series scores. However, the sample due to matching was most likely too small to run these analyses.

Table 10 –Multiple Linear Regression for Series Subtest in Age matched sample

	Beta	95% CI	P value
Constant		-32.63 – 43.73	0.75
Diagnosis	-0.40	-0.906 – 2.50	0.23
Age	-0.02	-0.69 – 0.66	0.96
Gender	-0.06	-6.34 – 5.50	0.88
ID Severity	0.24	-2.57 – 5.15	0.47

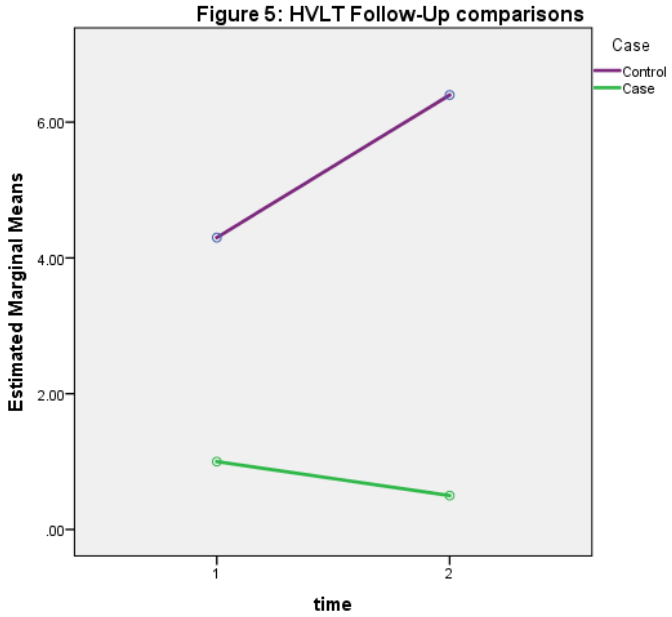
*** indicates a significant result (p≤0.05)**

Following assessment of baseline scores comparing cases to controls, 6 month follow-up assessments were examined on the full sample. Due to various reasons including illness, death, sleep patterns and lack of availability due to other activities and family visits not all participants could be followed up. Table 11 below shows the descriptive statistics of the follow-up data collected 6 months after baseline assessment.

Table 11 – Descriptive Statistics for Follow-up analysis

	Case	Control	Total
N	1	2	3
Series	7.00	8.50 (6.36)	8.00 (4.58)
N	0	2	2
Total CCIID	-	12.5 (6.36)	12.5 (6.36)
N	4	10	14
Total HVLT	0.50 (1.00)	6.40 (5.85)	4.71 (5.62)

Two-way repeated measures ANOVA were conducted to evaluate the differences between cases and controls at baseline and 6 month follow-up on the total HVLT scores. It was not possible to examine the other subtests due to small numbers of responses to follow-up assessments. The ANOVA for HVLT indicated no significant difference on total HVLT score at baseline and 6 month follow-up ($F_{(1,12)}$ = 0.49, p=0.50). The interaction between time point and diagnosis also revealed a non-significant difference ($F_{(1,12)}$ = 1.30, p=0.28). As seen in Figure 5, Dementia case mean HVLT scores declined from baseline to 6 month follow-up but due to low numbers in this analysis (n=14), these effects did not reach significance. This suggests that the HVLT does detect a reduction in cognition for participants with dementia. Controls appeared to improve on the HVLT, which could be explained by the participants' repeat exposure to the test format.



4. Discussion

The present study aimed to assess and compare the accuracy, sensitivity and specificity of the Computerised Cognitive test battery for Individuals with Intellectual Disabilities (CCIID) and the Hopkins Verbal Learning Test (HVLT). The study further aimed to evaluate the potential for utility of proposed cognitive tests at follow-up assessment. Performance on the CCIID and total HVLT for 7 dementia cases with ID, were compared to 23 ID controls at baseline and for the HVLT 4 cases and 10 controls at 6 month follow-up. The results of this comparison show dementia cases achieving significantly lower scores on the Series subtest of the CCIID, the total CCIID score and the total HVLT score than ID controls at baseline. Unfortunately, numbers of participants able to complete follow-up assessments was limited, so statistical significance was not achieved with follow-up analysis. However, on inspection of the means, ID dementia cases declined on total HVLT score. Results of this study are consistent with previous findings, which indicate that dementia cases score lower on cognitive assessments compared to controls in both individuals with ID and individuals without.[22,33] This is unsurprising considering the progressive nature of cognitive decline associated with dementia. This is also similar to other studies, as people with ID and no dementia showed an average improvement of the HVLT at follow-up.[34]

Jamieson-Craig and colleagues highlighted a current reliance on informant reporting in dementia diagnostics in ID.[35] For instance, The Dementia Screening Questionnaire for Individuals with intellectual disabilities. which has been heavily advocated in place of cognitive assessments.[14] Our study, however, has shown that it is possible to effectively use direct cognitive test batteries to support clinicians in dementia diagnostic procedures, if the correct tests are employed and cut-offs pertinent to individuals with ID are applied. This study shows the potential for the CCIID, Series subtest and total HVLT scores to have good clinical use to inform clinical judgment.[36]

Many direct tests that have been previously used incurred floor effects when participants were classed as having severe ID, meaning cognitive tests are frequently limited in their potential for practical usage (e.g: PCFT[37]; MMSE[33]; CAMCOG[38]). This, however, was not the case with the CCIID and HVLT. This can be attributed to the suitability of using the CCIID and HVLT to assess the cognition of individuals with ID. The CCIID was designed to be cross-cultural and has been validated in numerous ID populations.[24] The HVLT, on the other hand, has rarely been utilized in an ID population. Yet, by using just the free recall section in this study, the HVLT was suitable for ID participants and was found to be tolerated well by both ID dementia cases and ID controls.

Out of the subtests completed for this study the Series and the HVLT showed the most promise for clinical utility. The Series subtest score, which examines inductive reasoning, showed a significantly high accuracy and could detect 100% of dementia cases and identify 79% of controls. This suggests that the Series subtest alone could be extremely useful to

clinicians for diagnostics. When the sample was matched for age, the Series subtest still identified 100% of dementia cases and 73% of controls. This suggests that the series is accurate at detecting cases and controls regardless of age, highlighting its potential for clinical use.

Additionally, this study supported the use of the HVLT within this population. The HVLT gave a sensitivity of 100%, with a lower specificity of 52%. Previous research in the general population has shown the HVLT to have good diagnostic utility, be tolerated well and applicable across cultures. However, demographic factors, such as age, can alter the accuracy of the HVLT.[39] Moreover, prior studies have shown severity of intellectual disability to influence scores on cognitive assessments.[37] The sample examined in this study did not differ between dementia cases and controls in ID severity, gender or education level, indicating a well matched sample. Similar to previous findings[40] dementia cases in this study were significantly older than controls. The systematic age differences observed in this sample therefore influenced outcomes observed on the HVLT. In order to account for the age specific effects adjusted cut-off norms for the HVLT could be applied. The application of age specific cut-offs could be important for those with early onset Alzheimer's disease, who are under sixty-five years old, as well as for those who have advanced age of above eighty years old.[41] Previous research has applied age specific cut-offs to the HVLT.[30] This has resulted in up to a four point difference in total HVLT score used to obtain maximum discriminative capacity.

Considering that the HVLT has been rarely employed in samples of individuals who have an intellectual disability, age specific cut-off's for the purpose of dementia diagnostics are yet to be explored. The evidence provided in this study, however, suggests that investigating age specific cut-offs during dementia diagnostics for individuals with ID may be more accurate than applying a general cut-off score. This was unfortunately beyond the scope of this study, due to the small sample size. Nevertheless, to achieve maximum clinical use of the HVLT in both the general population and those with a pre-existing intellectual disability age specific cut-offs should be more heavily scrutinized.

Additionally the HVLT and the Series present the opportunity to apply a more inclusive approach to dementia diagnostics. The HVLT has been consistently utilised for dementia diagnostics in the general population. Utility for individuals with ID as well could offer an avenue for memory clinics and ID specialists to synchronize their diagnostic procedures. This in turn, could incur benefits in communication and understanding of the course and progression of dementia across populations. The Series has been shown to have good correlations with traditional IQ tests, such as the WAIS,[24] and with further investigation could be considered for general population diagnostics as well. Future research should seek to explore the Series alone, as a potential tool to add to Dementia diagnostics for the general population.

This study, as with many in its field it is limited by the small sample size participating in the study. In a larger sample

size it would be possible to further investigate the effect of age on the various cognitive assessments and establish a definitive cut-off for both Series and HVLT to be introduced into clinical practice for dementia diagnostics. Future research should therefore seek to further validate the proposed cognitive assessments within a larger sample of individuals with ID. The potential for clinical utility demonstrated in this study suggests that it may be possible to reach a consensus on diagnostics procedures to be used for individuals with ID.

The lack of current standardized criteria and diagnostic procedures is agreed to be thoroughly impeding progress in our understanding and treatment of dementia in ID.[17] Establishing a suitable diagnostic tool that can be used throughout clinics and research could incur substantial benefits in assessment efficiency, communication between health professionals and in treatment. Studies have shown that earlier treatment can maintain the highest possible level of cognitive functioning while the dementia is mild.[18] Therefore, further study is warranted to maximize the benefit of the current findings to clinical settings.

Overall, both the CCIID and the HVLT have been shown to distinguish effectively between dementia cases and controls in an ID population and could offer great potential for clinical utility. The Series subtest was most effective as a stand-alone assessment but clinicians could consider the use of the Series and HVLT alongside each other for an efficient and well-informed diagnosis.

The authors would like to acknowledge the Leicestershire partnership trust and it's members for their support in the ethical approval and carrying out of this study.

References:

1. World Health Organization. *The world health report: 2001: Mental health: New understanding, new hope.* Geneva, Switzerland: World Health Organization. 2001
2. Ahlström G, Sandberg M, Ng N, Aging with intellectual disability: A prevalence study of older people in Sweden. *Journal of Intellectual Disability Research*. 2016;*60*(7-8): 628-628. DOI: 10.1111/jir.12305
3. American Psychiatric Association. *Diagnostic and statistical manual-text revision.* Washington, DC: American Psychiatric Association; 2000: 256.
4. Youn J C, Lee D Y, Kim K W, Woo J I, Epidemiology of dementia. *Psychiatry Invest*, 2005; 2: 28-39.
5. Lin J, Wu C, Lin P, Lin L, Chu C M, Early onset ageing and service preparation in people with intellectual disabilities: Institutional managers' perspective. *Research in Developmental Disabilities.* 2011;32(1):188-193. https://doi.org/10.1016/j.ridd.2010.09.018
6. Janicki M P, Dalton A J, Prevalence of dementia and impact on intellectual disability services. *Mental Retardation*. 2000;38(3): 276-288.
7. Janicki M P, *Dementia and Aging Adults with Intellectual Disabilities: A Handbook*. New York: Routledge. 2014

8. Nieuwenhuis-Mark R E, Diagnosing Alzheimer's dementia in Down Syndrome: Problems and possible solutions. *Research in Developmental Disabilities.* 2009;30(5):827-838. https://doi.org/10.1016/j.ridd.2009.01.010
9. Cooper S, High prevalence of dementia among people with learning disabilities not attributable to Down's syndrome. *Psychological Medicine.* 1997; 27:609-616. https://doi.org/10.1017/S0033291796004655
10. Strydom A, Chan T, King M, Hassiotis A, Livingston G, Incidence of dementia in older adults with intellectual disabilities. *Research in Developmental Disabilities.* 2013;34(6):1881-1885. https://doi.org/10.1016/j.ridd.2013.02.021
11. Holland A J, Hon J, Huppert F A, Stevens F, Incidence and course of dementia in people with Down's syndrome: findings from a population-based study. *Journal of Intellectual Disability Research*. 2000;44(2):138-146.
12. Gutman M, Moskovic E, Jeret J S, Computerised cognitive testing of individuals with Down's syndrome and Alzheimer's disease. *Journal of Intellectual Disability Research*. 2016;60(2):179-181. https://doi.org/10.1111/jir.12227
13. Holland T, *Intellectual disability and dementia: Research into practice.* London: Jessica Kingsley Publishers. 2014.
14. Gomiero T, Bertelli M, Deb S, et al. A multicentre Italian validation study in aging adults with Down syndrome and other forms of Intellectual Disabilities: Dementia Screening Questionnaire for Individuals with Intellectual Disabilities. *Current Alzheimer research*. 2017; 14(7): 709-721. https://doi.org/10.2174/1567205014666170117094757
15. Zeilinger E L, Stiehl K A, Weber G, A systematic review on assessment instruments for dementia in persons with intellectual disabilities. *Research in Developmental Disabilities.* 2013; 34(11): 3962-3977. https://doi.org/10.1016/j.ridd.2013.08.013
16. Elliott-King J, Shaw S, Bandelow S, Devshi R, Kassam S, Hogervorst E, A critical literature review of the effectiveness of various instruments in the diagnosis of dementia in adults with intellectual disabilities. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2016;4:126-148. https://doi.org/10.1016/j.dadm.2016.06.002
17. Aylward E H, Burt D B, Thorpe L U, Lai F, Dalton A, Diagnosis of dementia in individuals with intellectual disability*. *Journal of Intellectual Disability Research.* 1997;41(2):152-164. https://doi.org/10.1111/j.1365-2788.1997.tb00692.x
18. Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, Richardson S, Efficacy of donepezil in early-stage alzheimer disease: A randomized placebo-controlled trial. *Archives of Neurology.* 2004;61(12):1852-1856. doi:10.1001/archneur.61.12.1852

19. Ng K K, Martin-Khan M, Farrow M, Beattie E, Pachana N A, The implications of the timing of aiagnosis of Dementia on the Dementia caregiver. *Advances in Alzheimer's Disease*. 2016;5(04):143. doi: 10.4236/aad.2016.54010
20. Folstein M F, Folstein S E, McHugh P R, Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research.* 1975;12: 189-198.
21. Brandt J, The Hopkins Verbal Learning Test: Development of a new memory test with six equivalent forms. *The Clinical Neuropsychologist.* 1991;5(2): 125-142.
22. Hogervorst E, Combrinck M, Lapuerta P, Rue J, Swales K, Budge M, The Hopkins verbal learning test and screening for dementia. *Dementia and geriatric cognitive disorders*. 2002;13(1):13-20. https://doi.org/10.1159/000048628
23. Crayton L, Oliver C, Holland A, Bradbury J, Hall S, The neuropsychological assessment of age related cognitive deficits in adults with Down's syndrome. *Journal of Applied Research in Intellectual Disabilities.* 1997;11(3):255-272. https://doi.org/10.1111/j.1468-3148.1998.tb00066.x
24. Van Der Wardt V, Bandelow S, Hogervorst E, *Development of the cognitive computerized test battery for individuals with intellectual disabilities (CCIID) for the classification of athletes with intellectual disabilities.* New York: Nova Science Publishers. 2011.
25. Krinsky-McHale S J, Devenny D A, Silverman W P, Changes in explicit memory associated with early dementia in adults with Down's syndrome. *Journal of Intellectual Disability Research.* 2002; 46(3):198-208. https://doi.org/10.1046/j.1365-2788.2002.00365.x
26. Gross AL, Rebok GW, Unverzagt FW, Willis SL, Brandt J, Word list memory predicts everyday function and problem-solving in the elderly: Results from the ACTIVE cognitive intervention trial. *Aging, Neuropsychology, and Cognition.* 2011;18(2):129-46.
27. Dick MB, Doran E, Phelan M, Lott IT, Cognitive Profiles on the Severe Impairment Battery Are Similar in Alzheimer's Disease and Down Syndrome with Dementia. *Alzheimer disease and associated disorders*. 2016;30(3):251. doi:10.1097/WAD.0000000000000132
28. Fox LS, Olin JT, Erblich J, Ippen CG, Schneider LS. Severity of cognitive impairment in Alzheimer's disease affects list learning using the California Verbal Learning Test (CVLT). *International Journal of Geriatric Psychiatry*. 1998;13(8):544-9. https://doi.org/10.1002/(SICI)1099-1166(199808)13:8<544::AID-GPS821>3.0.CO;2-N
29. de Jager C A, Hogervorst E, Combrinck M, Budge M, Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's

disease. *Psychological Medicine.* 2003;33(06):1039-1050. https://doi.org/10.1017/S0033291703008031

30. Shi J, Tian J, Wei M, Miao Y, Wang Y, The utility of the Hopkins Verbal Learning Test (Chinese version) for screening dementia and mild cognitive impairment in a Chinese population. *BMC Neurology.* 2012;12:136-2377-12-136. doi:10.1186/1471-2377-12-136.
31. González-Palau F, Franco M, Jiménez F, Parra E, Bernate M, Solis A, Clinical utility of the Hopkins verbal test-revised for detecting Alzheimer's disease and mild cognitive impairment in Spanish population. *Archives of clinical neuropsychology*. 2013;28(3):245-53. https://doi.org/10.1093/arclin/act004
32. Rinehardt E A, The role of verbal memory, intelligence, and achievement scores in adolescents with learning disabilities. (ProQuest Information & Learning). *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2007;67(10-):6074-6074.
33. Deb S, Braganza J, Comparison of rating scales for the diagnosis of dementia in adults with Down's syndrome. *Journal of Intellectual Disability Research.* 1999;43(5):400-407. https://doi.org/10.1046/j.1365-2788.1999.043005400.x
34. Schrijnemaekers A M, de Jager C A, Hogervorst E, Budge M M, Cases with mild cognitive impairment and Alzheimer's disease fail to benefit from repeated exposure to episodic memory tests as compared with controls. *Journal of Clinical and Experimental Neuropsychology*. 2006;28(3):438-55. https://doi.org/10.1080/13803390590935462
35. Jamieson-Craig R, Scior K, Chan T, Fenton C, Strydom A, Reliance on carer reports of early symptoms of dementia among adults with intellectual disabilities. *Journal of Policy and Practice in Intellectual Disabilities*. 2010;7(1):34-41. https://doi.org/10.1111/j.1741-1130.2010.00245.x
36. Sheehan R, Sinai A, Bass N, Blatchford P, Bohnen I, Bonell S, Courtenay K, Hassiotis A, Markar T, McCarthy J, Mukherji K, Dementia diagnostic criteria in Down syndrome. *International journal of geriatric psychiatry.* 2015;30(8):857-63. https://doi.org/10.1002/gps.4228
37. Kay DW, Tyrer SP, Margallo-Lana ML, Moore PB, Fletcher R, Berney TP, Vithayathil E, Preliminary evaluation of a scale to assess cognitive function in adults with Down's syndrome: the Prudhoe Cognitive Function Test. *Journal of Intellectual Disability Research.* 2003;47(3):155-68. https://doi.org/10.1046/j.1365-2788.2003.00451.x
38. Hon J, Huppert F A, Holland A J, Watson P, Neuropsychological assessment of older adults with Down's syndrome: an epidemiological study using the Cambridge Cognitive Examination (CAMCOG). *British Journal of Clinical Psychology.* 1999;38(2):155-65. https://doi.org/10.1348/014466599162719

39. Hogervorst E, Xin X, Rahardjo T B, Shifu X, The Hopkins Verbal Learning Test and detection of MCI and mild dementia: A literature review. *J Alzheimers Dis Parkinsonism*. 2014;4(166):2161-0460. http://dx.doi.org/0.4172/2161-0460.1000166
40. Sinai A, Hassiotis A, Rantell K, Strydom A, Assessing specific cognitive deficits associated with dementia in older adults with Down syndrome: Use and validity of the Arizona Cognitive Test Battery (ACTB). *PLoS One.* 2016;11(5):e0153917. https://doi.org/10.1371/journal.pone.0153917
41. Vanderploeg R D, Schinka J A, Jones T, Small B J, Borenstein Graves A, Mortimer J A, Elderly norms for the Hopkins verbal learning test-revised. *The Clinical Neuropsychologist*. 2000;14(3):318-24. https://doi.org/10.1076/1385-4046(200008)14:3;1-P;FT318