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Comparison of BICAMS and ARCS for assessment of cognition in multiple sclerosis and predictive value of employment status

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ABSTRACT

Background: Cognitive impairment is common in multiple sclerosis (MS) but not adequately monitored by EDSS. The Audio Recorded Cognitive Screen (ARCS) and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) are easy-to-use tools in clinical practice.

Objective: To compare the sensitivity of ARCS to BICAMS and their predictive value for employment status.

Methods: MS patients and healthy controls were assessed using the BICAMS and the ARCS consecutively. Receiver Operating Characteristic (ROC) curve analyses were used to compare the two tests. A step-wise, logistic regression analysis was used to identify the cognitive test(s) that best predicted employment status and quality of life.

Results: Total ARCS, memory and attention domain scores were moderately correlated with all BICAMS tests (r= 0.3-0.5; P ≤ 0.05). Total ARCS predicts cognitive impairment with good sensitivity and specificity relative to the BICAMS tests (AUC=0.8; P=0.00045). Total ARCS detects higher levels of impairment than BICAMS in MS patients (44% versus 21%). The memory domain of the ARCS and the BVMT-R were the best predictors of employment status (OR = 1.12 and 1.14, P<0.05).

Conclusion:

BICAMS and ARCS have comparable sensitivity for cognitive impairment in MS. Memory assessment is the best predictor of employment status.

INTRODUCTION:

Cognitive impairment (CI) is common in multiple sclerosis (MS) with rates of 40-70%, throughout the course of the disease and is independent of age (1, 2). Processing speed, episodic memory and executive functions are most commonly affected (3, 4). A recent systematic review evaluated the literature on CI and employment status and found that MS patients who are unemployed or have reduced work hours score lower in cognitive assessments (5). Loss of employment is a major concern for MS patients, particularly as disease onset mostly occurs in people of working age, who are just establishing careers and families. Unemployment amongst MS patients has been associated with depression, loneliness, anxiety and reduced participation in social and community activities (6, 7). Despite this, cognitive functioning is often not routinely tested in many clinics, due to resource issues or prohibitive costs (8).

The Expanded Disability Status Scale is insensitive to cognitive decline, which often occurs independently of physical deterioration (9). The Symbol Digit Modalities Test (SDMT) has been proposed as the best single psychometric measure available for screening cognition in MS patients, but is limited in the scope of domains that it assesses (10). By contrast, the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) and the Audio Recorded Cognition Screen (ARCS) (8, 11) are instruments that address some of these practical and methodological concerns. Both tests are relatively brief to administer (15-35 minutes), can be administered by health-care professionals with no specialised training required, and have been previously validated against other neuropsychological tests (8, 11). BICAMS has been recommended as the "gold standard" in cognitive testing and has been validated in 12 languages and 15 cultures, although it has not yet been validated in an Australian population (12-27). The ARCS is administered via an audio device; thus, technician time is minimal (11). The ARCS has been validated in an Australian MS population and was more sensitive in detecting cognitive deficits than the PASAT (28).

The aim of this study was to compare the sensitivity of BICAMS and the ARCs for the assessment of cognition in MS patients, including how well they predicted quality of life (QoL) and employment status.

METHODS:

Study participants:

A total of 49 MS patients were matched to 49 healthy controls on age, gender, and education. Patient demographics are listed in Table 1. All patients were recruited from the John Hunter Hospital MS clinic, and healthy controls were recruited from the community. Patients were diagnosed with MS according to the 2017 McDonald criteria and were all relapse-onset patients according to the revised Lublin definitions (29). Exclusion criteria were if the patient: 1) had other neurological conditions that affected their ability to undergo the described tests 2) had impaired dexterity in their hands that impeded their ability to write 3) had impaired visual or auditory functioning that limited their ability to undertake cognitive testing or 4) had corticosteroid treatment in the preceding 3 months.

Table 1: Cohort Characteristics

Demographics	**MS (n=49)**	**HC (n=49)**
Female	40 (82%)	40 (82%)
Age (yrs)*	50 ± 13	49 ± 14
Highest Education Level		
Junior High School (≤10 years education)	8 (16%)	8 (16%)
Senior High School (10-13 years education)	25 (51%)	25 (51%)
University (≥13 years education)	16 (33%)	16 (33%)
Disease characteristics		
Progressive disease	10 (20%)	
Disease duration (yrs)*	11.4 ± 9.3	-
EDSS*	2.8 ± 1.9	-
MSSS*	3.3 ± 2.3	-
Treatment		
Copaxone	9	-
Tecfidera	9	-
Gilenya	5	-
Betaferon	1	-
Tysabri	6	-
Rebif	1	-
Not on treatment	14	-
Treatment duration (yrs)*	2.1 ± 2.2	-

*****mean ± SD, RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; EDSS: expanded disability status score; MSSS: multiple sclerosis severity score

Procedures:

The Hunter New England Health Research Ethics Committee approved this study (16/07/20/4.01), and methods were carried out in accordance with institutional guidelines on conducting human subject experiments. Written and informed consent was obtained from all subjects prior to study procedure. All subjects underwent the ARCS, the BICAMS battery and the Depression, Anxiety and Stress assessment (DASS-21), consecutively. A single researcher administered all tests in the same fixed order (ARCS followed by BICAMS (SDMT, CLVT-II learning tests, BVMT-R)

Fifteen control participants returned for a follow-up session one to three weeks later to allow for test-retest reliability of the BICAMS. Tests were administered in the same manner and order on retesting; however, alternate forms were employed to reduce practice effects from prior exposure to the stimuli.

We measured mental health indices using the Depression, Anxiety, and Stress Scale DASS-21, a freely available, self-report questionnaire (https://www.blackdoginstitute.org.au/). Quality of life (QoL) was measured using the MusQol-54, a self-report questionnaire validated for the MS population which derives two summary scores: physical health and mental health (30). Work productivity and employment status was measured using the Work Productivity and Activity Impairment Questionnaire validated for multiple sclerosis (WPAI-MS), a self-report questionnaire which quantifies absenteeism (missing work because of health issues), 'presenteeism' (reduced on-the-job effectiveness), work productivity loss (absenteeism plus presenteeism) and daily activity impairment (31).

Brief International Cognitive Assessment for MS (BICAMS):

A detailed description of the BICAMS has been previously published and is described briefly in the supplemental methods (8). Raw scores (total number correct answers) were normalized by age and education (SDMT), age and gender (CVLT) or age only (BVMT-R) to generate T-scores and determine impairment (adjusted scores) according to the product manuals. We used the adjusted scores to determine impairment based on existing normative data in the product manuals. Impairment was defined by a T-score more than 1.5 standard deviation (SD) below the mean.

Audio Recorded Cognitive Screen (ARCS) components:

Patients were administered the alternate version of the ARCS to the one most recently administered in the clinic. For each domain, raw scores were adjusted to account for age, gender and education (scaled scores) (11). Patients were defined as impaired if their scaled score was 1.5 SD below the mean of the reference population in any given test (11). Total ARCS score is based on a cumulative result of the scaled domains (28).

Statistical analysis:

Associations between ARCS and BICAMS test scores were explored using linear bivariate (Pearson's) correlations. Receiver Operating Characteristic (ROC) curve analyses were conducted to assess the performance of the ARCS, relative to the BICAMS as the reference.

Multifactor analysis of ARCS and BICAMS results was done using a step-wise logistic regression model to assess the best predictors (from ARCS and BICAMS) of outcomes relating to work and QoL in MS patients and healthy controls. For this model, raw scores from each of the cognitive tests (rather than scaled scores) were used. Age, education, gender, depression score, anxiety score and stress score were included as covariates. The outcomes assessed were i) employment (employed (y) or not employed (n)), ii) % work productivity lost due to MS symptoms (low/high), iii) Mental QoL (low/high) and iv) Physical QoL (low/high). Outcomes ii, iii, and iv were dichotomised at the median score because a) they were not conducive to quantitative analysis (ie. skewed) and b) of the need to keep analysis method consistent across all variables (ie. logistic regression). The magnitude of the main predictor effects are reported as odds ratios (ORs).

RESULTS:

Validity of the BICAMS in an Australian population

The BICAMS has not been previously validated in an Australian population. Therefore, we endeavoured to validate the BICAMS according to the international standards for validation for the purpose of comparing it to the ARCS. The ARCS has been previously validated against a full neuropsychological assessment in the Australian MS population (28, 32). MS patients performed worse on all three tests compared to healthy controls ($p<0.001$) (Table 2). Using the previously reported criteria of "impairment on one or more tests", 69.4% (n=34) of MS patients scored within the normal range on all three tests, as opposed to 85.7% (n= 42) of the healthy controls. The scores for MS patients were statistically significantly lower on all three BICAMS tests ($p<0.001$). Impairment on one or more, two or more, or all three tests was seen in 31%, 16% and 4% respectively for MS patients. Seven percent of controls were impaired in one test, but none of our healthy controls showed impairment on two or more tests.

All three tests demonstrated good to strong test-retest correlations (CVLT r=0.74, p=0.001; SDMT r=0.84, p=0.00004 and BVMT-R r=0.83, p=0.00006).

Table 2 Differences in BICAMS domain scores in MS and control cohorts

	MS		HC		P value*
Domain	Mean ± SD	% Impaired	Mean ± SD	% Impaired	
SDMT	51.8 ± 11.3	15	60.5 ± 9.9	6	<0.001
CVLT	54.0 ± 12.8	15	58.9 ± 9.9	2	<0.001
BVMT-R	47.7 ± 13.4	21	56.8 ± 10.2	5	<0.001

Impaired is based on T score which is > 1.5 SD from HC mean; * p-value based on 2 tailed students' t-test between mean scores for MS patients and mean HC.

Comparison of ARCS and BICAMS for cognitive assessment

As with the BICAMS, patients performed worse on the ARCS compared to healthy controls (Total ARCS, Memory, Fluency, and Attention: P<0.001). There were no significant differences between MS patients and healthy controls in the visuospatial function (p=0.10) or language domains (p=0.47) (table 3). Overall, more patients were impaired on ARCs than on BICAMS, however, there was no appreciable difference between healthy controls

Table 3: ARCS domain scores in MS and control cohorts

	MS		HC		P value*
Domain	Mean ± SD	% Impaired	Mean ± SD	% Impaired	
Total ARCS	84.7 ± 20.22	44	99.1 ± 13.4	6	<0.001
Memory	83.2 ± 25.7	37	98.9 ± 12.7	10	<0.001
Fluency	85.5 ± 16.1	37	98.7 ± 12.1	8	<0.001
Visuospatial function	100.3 ± 12.4	6	103.6 ± 7.9	2	0.10
Language	92.4 ± 21.9	21	95.7 ± 20.5	16	0.47
Attention	89.4 ± 13.2	33	98.4 ± 14.3	14	0.001

Impaired is > 1.5 SD from HC mean; * p-value based on 2 tailed students' t-test between mean scores for MS patients and mean HC.

We undertook correlation analyses comparing ARCS and BICAMS test performances. Total ARCS showed moderate but statistically significant positive correlations with all BICAMS domains as did the ARCS memory domain and attention domain scores. None of the fluency, visuospatial function or language domains correlated with any of the BICAMS domains (Table 4).

Table 4: Correlation of ARCS and BICAMS measures in an MS cohort

ARCS Domain	SDMT	CVLT-II	BVMT-R
Total ARCS	0.34*	0.42**	0.41**
Memory	0.30*	0.53**	0.48**
Fluency	0.20	0.21	0.13
Visuospatial function	0.14	0.04	0.20
Language	0.07	0.14	0.12
Attention	0.44**	0.41**	0.34**

Values are Pearson's correlation (r) values,* P<0.05, **P<0.01

The verbal learning test component of the ARCS, modelled on the Hopkins Verbal Learning Test, is most similar to the CVLT-II used in BICAMS. However, the ARCS memory domain represents a composite score of immediate recall, delayed recall and yes/no recognition test components. The scoring document of the ARCS provides scaled scores for each of these tests, in addition to the domain score. However, the CVLT-II score is based upon immediate recall scores (i.e. learning trials) only. For consistency of relating ARCS *domain* scores against BICAMS measures, Table 4 reports correlations between the ARCS memory domain (i.e. the composite score) and CVLT-II and BVMT-R. Not surprisingly, however, when analyses compared the results of the summed learning trials of the ARCS with those of the CVLT- II the correlation was substantially higher. (r=0.8, p≤0.001).

Accuracy of ARCS for measuring cognitive impairment against BICAMS as reference

Based on the previously reported criteria for impairment with the BICAMS of "impairment on one or more tests" we conducted a ROC curve analysis of Total ARCS to estimate the area under the curve (AUC) as an index of accuracy to predict any impairment using BICAMS as a reference (Figure 1). The AUC indicated that Total ARCS score accurately predicts "Any Impairment" on the BICAMS tests with good sensitivity and specificity (AUC=0.80, p<0.001).

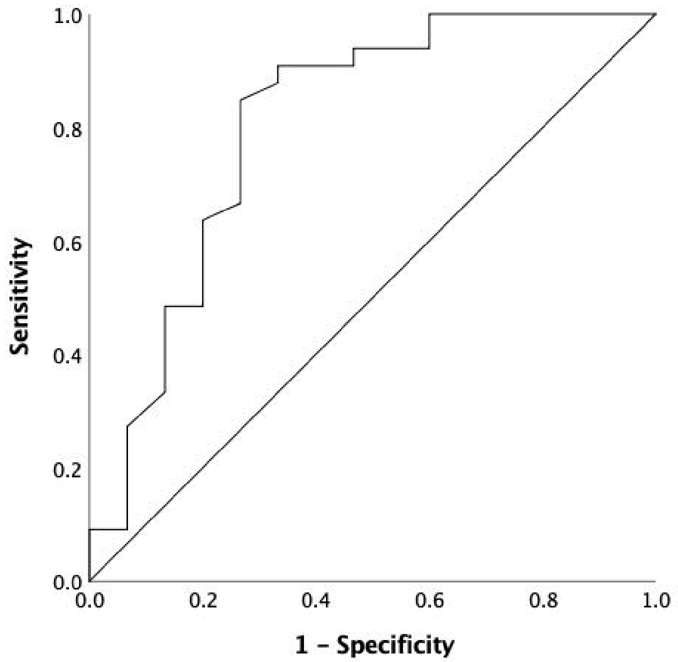

Figure 1:

Receiver Operating Characteristic (ROC) curve analysis for Total ARCs to predict impairment on any test in the BICAMS.

Mental Health Indices

Since both depression and anxiety negatively influence cognitive performance in MS patients (33, 34), the cohort also completed the DASS-21. MS patients reported higher depression and anxiety compared to healthy controls, but similar levels of stress (Table S1). We calculated Pearson's correlation coefficient for each of the domains with DASS scores in the MS patients. Depression and anxiety were the most highly correlated with cognition score, both having a statistically significant negative correlation with total ARCS, memory, attention, SDMT and BVMT-R. Anxiety was also negatively correlated with the CVLT-II (Table 5). Stress was correlated with the attention domain of the ARCS, but none of the BICAMS domains.

Table 5: Correlation of cognitive performance measures in MS patients with mental health indices

Instrument	Domain	DASS	Depression	Anxiety	Stress
ARCS					
	Total ARCS	-0.35*	-0.36**	-0.39**	-0.23
	Memory	-0.28*	-0.29*	-0.34*	-0.16
	Fluency	-0.18	-0.19	-0.15	-0.16
	Visuospatial function	-0.23	-0.18	-0.26	-0.21
	Language	-0.12	-0.16	-0.19	<0.01
	Attention	-0.47**	-0.45**	-0.47**	-0.38**
BICAMS					
	SDMT (total)	-0.30*	-0.29*	-0.34*	-0.22
	CVLT	-0.25	-0.25	-0.29**	-0.17
	BVMT-R	-0.30*	-0.32*	-0.36*	-0.17

Values are Pearson's correlation (r) values,* P<0.05, **P<0.01

Cognitive dysfunction in relation to employment status and quality of life outcomes

Cognitive dysfunction in MS affects many aspects of life, including employment status and health-related QoL. In our cohort, MS patients were more likely to report unemployment compared to healthy controls (P=0.03), and had higher rates of activity impairment (daily activities) (P=0.03), presenteeism (P<0.001) and work productivity loss (P<0.001) (Table S2). There were no statistically significant differences between patients and controls with respect to absenteeism. MS patients who were unemployed, were more likely to record an impaired score on the ARCS, fluency and attention domains, and all three BICAMS domains (Table S3).

MS Patients also reported lower QoL, both physical (P<0.0001) and mental (P<0.0001) state (Table S5). QoL physical status scores were correlated with the ARCS attention domain and the BICAMS SDMT and CVLT-II (Table 6). QoL mental status scores were correlated with the total ARCS, memory, and attention domains and the BICAMS SDMT and CVLT-II (Table 6).

Table 6: Correlation between QoL and cognitive scores

Instrument	QoL Physical Status	QoL Mental Status
ARCS		
Total ARCS	0.14	0.33*
Memory	0.05	0.27*
Fluency	0.07	0.19
Visuospatial	0.08	0.17
Language	0.06	0.13
Attention	0.32*	0.42*
BICAMS		
SDMT	0.46**	0.40**
CVLT	0.14*	0.38**
BVMT-R	0.16	0.29

Values shown are Pearson's Correlation coefficients (r), * P<0.05 **P<0.01

The ARCS and BICAMS as predictors of employment and Quality of Life

We performed a multifactor, linear regression analysis of each of the cognitive domain tests to assess the best predictor of outcomes relating to employment status and QoL in MS patients. Because each of the tests are scaled to a slightly different set of parameters (age, gender and education), we used the raw scores in a step-wise, linear regression model using demographic factors, as well as individual DASS21 domain scores as covariates in the model. For the ARCS, the memory domain was the best predictor of employment status and QoL (physical and mental state). Each of these outcomes had a moderate, but statistically significant OR. Including age, education and mental health indices in the model, increased the predictive power of these tests for detecting both employment and QoL outcomes (Table 7).

The BICAMS tests showed moderate but statistically significant values for all outcomes measures, with the SDMT being the best and only predictor of work activity (OR:0.92, P=0.027). The SDMT is also a moderate predictor of Physical QoL (P<0.001). The BVMT-R was the best predictor of employment status and the CVLT-II was a moderate but statistically significant predictor (P<0.001) of QoL mental status. Similar to the ARCS domains, age, and mental health indices increased the predictive power of these tests (Table 7).

Table 7: Cognitive domain predictors of employment and quality of life outcomes

Instrument	Outcome[1]	Predictors[2]	Odds Ratio	P-value	R^2	Covariates[3]
ARCS	Employment (y/n)	Memory	1.12	0.005	0.33	age+edu.
	Work productivity loss (low/high)	Nil	NA	NA	0.11	anx.
	QoL-Physical (low/high)	Memory	1.04	0.016	0.24	dep.
	Qol-Mental (low/high)	Memory	1.04	0.05	0.4	dep. + str.
BICAMS	Employment (y/n)	BVMT-R	1.14	<0.001	0.32	age
	Work productivity loss (low/high)	SDMT	0.92	0.027	0.12	nil
	QoL-Physical (low/high)	SDMT	1.1	<0.001	0.29	dep.
	Qol-Mental (low/high)	CVLT	1.07	0.012	0.42	dep. + str.

[1]key outcomes were unscaled and dichotomised into yes/no or low/high categories. [2]Domain variables retained in the model. [3]covariates retained in the model

DISCUSSION:

Loss of employment has a negative impact on mental health and QoL (7). Given that most MS patients are diagnosed at an age when they are establishing careers and families, the inability to work is a major concern. Globally, MS patients who are unemployed, or work reduced hours, have lower cognitive scores than those who are employed (5). Furthermore, employment has been demonstrated to have positive effects on general well-being, including self-esteem, self-efficacy and perceived social inclusion in both the general population and MS patients (6, 7). Given these implications there is a strong need for routine cognitive testing in clinics and for this to be included into the No Evidence of Disease Activity (NEDA) assessment that directs treatment decisions. This study aimed to compare the ARCS to the BICAMS. Our secondary aim was to evaluate both of these assessment tools for their ability to predict employment status and QoL in MS patients.

To compare the ARCS and the BICAMS, the BICAMS needed to be validated in an Australian population (32). The BICAMS tests identified cognitive impairment in 31.6% of our MS patients, which is consistent with the German validation study (32.6% impairment) (15). It is slightly lower than the rate of impairment determined by most of the ARCS domains including Total ARCS (44%), despite the fact that both tests detected similar levels of CI among healthy controls. The higher sensitivity of ARCS could reflect the fact that the ARCS is scaled according to education, age and gender for all domains, whereas the BICAMS tests are not. Furthermore, the two ARCS domains with highest impairment (fluency and attention) do not have a similar test in the BICAMS, which may result in a broader assessment of impairment by the ARCS. Finally, we were able to show good correlation between the ARCS verbal learning test and the CVLT-II, particularly when limited to the most comparable elements of the tests. The ARCS learning test word list has been validated in an Australian population, so this suggests that the CVLT-II word list is culturally appropriate (11).

In our experience, the BICAMS takes 15-30 minutes to administer, however this seems too much time for a busy clinic with minimal staff. In our clinic, we routinely use the ARCS to assess cognitive function, because patients can be left on their own for the duration of the test and staff time is minimal (5 minutes to score, which can be done at the end of the day). However, the BICAMS is routinely used as the “gold standard” cognitive screen for clinical trials. Therefore, the main aim of this study was to show that the ARCS was an equal cognitive assessment tool to the BICAMS. The results of the ROC analysis in combination with the correlations between scores on comparable cognitive domains, indicate that both instruments can be used to identify cognitive deficits. Differences were found on the tests for visuospatial function. The ARCS clock face drawing, which tests visuospatial function, had the lowest incidence of impairment, with only 6% of patients showing deficits. The visuospatial component of BICAMS, the BVMT-R, had the highest impairment of all BICAMS tests (25%). The BVMT-R tests both memory and visuospatial awareness. Consistent with this, we found good correlation between the BVMT-R and ARCS memory domains. Comparatively, the clock drawing task does not probe memory and direct comparison may not be appropriate for these tests.

Our comparison between the BICAMS and the ARCS supports the use of either test as a tool for measuring cognitive function of MS patients, but not interchangeably. In some clinics, ARCS may provide a practical advantage over BICAMS as it does not require a technician to be present during testing. The time needed from a technician/scorer to obtain the scaled ARCS score is 4-5 minutes, making it more time efficient for staff than the BICAMS. Additionally, the ARCS provides an overall cognitive score as well as information on language function and tests for executive function. These can be adjusted for education level and therefore may be more sensitive to individual decline, as suggested by the higher rates of CI from ARCS testing. Conversely, ARCS requires the capacity to write, so patients who have impaired dexterity in their hands may be better suited to testing via the BICAMS.

Depression and anxiety are common among MS patients, and negatively influence cognitive performance (33, 34). Consistently, our study found anxiety and depression were negatively correlated with many of the cognitive tests performed. Memory, attention and processing speed were the most affected. Consistent with previously published literature, we found visuospatial function (clock face) and visuospatial memory (BVMT-R) were not affected by depression (35).

While there are numerous studies validating the BICAMS or other cognitive tools, these studies are meaningless if they do not include an assessment of the impact that cognitive score has on patient lifestyle. To determine this we assessed the impact of the different cognitive domains on both QoL and employment status. Our findings highlight memory as the most predictive domain for both QoL and employment status. The CVLT-II and the BVMT-R have clear memory components; however, the SDMT also tests an element of incidental memory (36). The inclusion of mental health indices increased the predictive power of these tests. This is consistent with previous studies, which show mental health to be predictive of QoL (37, 38). These findings highlight the need to use depression and anxiety testing in parallel to cognitive testing in the clinic.

Clemens and Langdon (2018) recently performed a systematic review investigating how cognition relates to employment in MS patients (5). Interestingly, all of the studies they identified are European and North American and none were from Australasia. Different employment types (skilled, unskilled, or manual) may be affected differently by cognitive difficulties. Presumably there is a different spread of employment type between countries so we wanted to investigate the relationship between cognition and employment in Australia. We found the memory domain of the ARCS, and the BVMT-R were the only tests able to discriminate between employed and unemployed patients. Previous studies have found memory tests, including the BVMT-R (17, 39), CVLT-I or CVLT-II (19) and the Brown Peterson Short Term Memory Test (STM) (40) were able to discriminate between employed and unemployed MS patients. Age was a common covariate retained in our linear regression model; however, this is not surprising given that a limitation of our study is that the WPAI dichotomizes employment by yes/no and does not consider part-time employment or retirement which undoubtedly vary with age. The SDMT reached statistical significance as the sole predictor of work productivity loss but the predictive power was very modest. Benedict and colleagues also demonstrated that the SDMT is the strongest predictor of work activity in MS patients, being able to discriminate between all four employment groups tested (41).

On a global level, by establishing the validity and reliability of the BICAMS in an Australian population, we have contributed to the international effort to find a tool for detecting cognitive impairment in MS that can be used across several cultures and languages. Furthermore, our study highlights the importance of memory and mental health testing in MS patients as memory loss, depression and anxiety may be indicators of future altered employment status or QoL. The choice of tool should be what best suits the clinic, no matter how this is performed. Assessment and follow up of patients' cognitive status should be as much of a priority as any other aspect of their routine clinical care and more longitudinal studies are needed to fully assess the effect of cognitive deficit on patient lifestyle.

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ABBREVIATIONS

CI: Cognitive Impairment

SDMT: Symbol Digit Modalities Test

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis

ARCS: Audio Recorded Cognitive Screen

QoL: Quality of Life

DASS-21: Depression, Anxiety, Stress Scales

WPAI-MS: Work Productivity and Activity Impairment Questionnaire validated for multiple sclerosis

SD: Standard Deviation

ROC: Receiver Operating Characteristic

OR: Odds Ratio

AUC: Area Under the Curve

BVMT-R: Brief Visuospatial Memory Test – Revised

CVLT-II: California Verbal Learning Test II

EDSS: Expanded Disability Status Scale

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Supplementary data

Table S1: Depression Anxiety Stress Scale (DASS) Scores for MS cohort

	MS		HC		P value*
Mental Health Domain	Mean ± SD	% affected	Mean ± SD	% affected	
DASS (Overall)	23.2 ± 25.0		14.8 ± 14.0		0.05
Depression	7.5 ± 9.5	33	4.0 ± 5.5	10	0.05
Anxiety	5.5 ± 7.7	27	2.5 ± 3.6	10	0.03
Stress	10.1 ± 9.9	29	7.6 ± 6.5	10	0.1

"affected" is defined as any score other than "normal" * p-value based on 2 tailed students' t-test between mean scores for MS patients and mean HC

Table S2: Impairment of employment activity in MS patients and healthy controls.

Characteristic	**MS**	**HC**	**P-value**
Employed	57%	80%	0.030*
Of those employed:			
Activity Impairment – level of impaired activity due to general health	22.5 ± 28.9	9.5 ± 19.9	0.03
Presenteeism – impaired at work/reduced effectiveness on the job	22.9 ± 32.1	3.2 ± 6.2	<0.001
Absenteeism – work time missed	4.7 ± 11.1	2.0 ± 6.0	0.20
Work productivity loss	20.1 ± 28.6	3.1 ± 6.0	<0.001

Data are expressed as percent total time impaired over the last 7 days which were affected by general health ± SD. *Fishers exact test applied. All other P-values based on 2 tailed students' T-test between mean scores for MS patients and mean scores for HC.

Table S3: MS patients cognitive scores based on vocational status

Instrument	Employed (N=28)	Unemployed (N=21)	P-value
ARCS			
Memory	90 ± 15.4	80.0 ± 18.7	0.06
Fluency	41.25 ± 9.2	35.9 ± 7.3	0.03
Visuospatial	9.5 ± 1.9	9.2 ± 1.3	0.5
Language	9.0 ± 1.1	9.2 ± 0.9	0.1
Attention	23.6 ± 6.2	17.3 ± 7.9	0.005
BICAMS			
SDMT	56.5 ± 8.4	45.5 ± 11.8	<0.001
CVLT	57.5 ± 9.6	46.9 ± 13.1	0.004
BVMT-R	25.4 ± 6.3	18.7 ± 8.3	0.003

Data are expressed as unscaled scores ± SEM. p-value based on 2 tailed students' t-test between mean scores for MS patients and mean HC

Table S4: Quality of life scores MS patients and healthy controls

Characteristic	MS	HC	P-value
QoL Physical State	62.5 ± 20.5	82.8 ± 13.8	P<0.0001
QoL Mental State	68.2 ± 21.7	85.4 ± 14.1	P<0.0001

Data are expressed as mean ± SEM. p-value based on 2 tailed students' t-test between mean scores for MS patients and mean HC

Supplemental methods:

Brief International Cognitive Assessment for MS (BICAMS):

A detailed description of BICAMS has been previously published (1). Briefly, BICAMS consists of 3 tests: the Symbol Digit Modalities Tests (SDMT), the California Verbal Learning Test (CVLT-II) and the Brief Visuospatial Memory Test Revised (BVMT-R). There are multiple versions of each of these tests, but for the purpose of this study, all subjects were tested using the same version of each test. The exception to this was for the subjects who underwent the test-retest component who were tested using the standard form followed by the alternate form of all three tests. In all three tests, impairment was considered if the patient fell below 1.5 standard deviations (SD) from the normative scores provided in the manuals. This is according to BICAMS recommendations (2).

The SDMT presents a series of nine symbols paired with a single digit. Patients are given a key at the top of the page and asked to verbally match the symbol to the digit as rapidly as possible over 90 seconds. The score is the total number of correct answers. Impairment was considered if the patient fell below 1.5 SD from the mean of their age and education matched range in the SDMT scoring manual (3).

The CVLT-II tests the patient's verbal memory. For this study we used List A of either the standard or alternate forms (test-retest only). The examiner reads a list of 16 items and the patient is asked to recall as many of those items as possible. This is repeated five times in a row. The total score is the total points (one per correct answer less any repeated answers) over all 5 trials. Impairment was defined as patients who fell below the threshold of 1.5 SD in their age and gender matched range in the CVLT-II scoring manual (4) (T-score of < 40).

The BVMT-R is used to assess visuospatial memory. In this test, the examiner presents 6 abstract designs for 10 seconds and the patient is asked to recreate the images on a page as accurately as possible. This is repeated three times. Each design is graded by the examiner from 0 to 2 points for accuracy and location for a total possible score of 12 for each test (36 overall). Impairment was defined as patients who fell below the threshold of 1.5 SD in their age and gender matched range in the BVMT-R scoring manual (5) (T-score of < 40).

The test-retest component of the BICAMS was administered to 15 healthy subjects 1-3 weeks after the initial testing. For each BICAMS test, the Alternate Form was used.

Audio Recorded Cognitive Screen (ARCS) components:

A detailed description of ARCS has been previously published (5) and validated in an Australian MS cohort (6). Participants listen to a pre-recorded test via an audio device and headsets. During this time the examiner is free to leave the room (about 35 minutes). Participants are required to write their responses in a booklet, which is scored later (this takes approximately 5 minutes). ARCS tests 5 cognitive domains: memory, verbal fluency, language, visuospatial functioning, and attention/executive function. There are two versions of the ARCS, which are used alternately in our MS clinic to determine cognitive function. To prevent practice effects, patients were issued with the version of the ARCS which was not the most recent version they had performed in the clinic as part of their routine care.

Memory: ARCS includes a 12 word list learning task which was modelled on the Hopkins Verbal Learning Test- revised (and named 'the Newcastle Auditory Verbal Learning Test – NAVLT'). This word list is read out loud and the participant is asked to write down as many words as they can remember within the available time. This is repeated three times. The summed score of words recalled on these learning trials constitutes the immediate recall score. The other key scores from the NAVLT are the delayed recall trial and a yes/no recognition memory task. . *Fluency*: The ARCS contains three verbal fluency tests, in which participants are given one minute, for each test, to generate a list of words based on specified criteria (initial letter, category, and 'action fluency'). *Language*: Ten items are pictured in the response booklet and participants are asked to write the name of each item beside it. *Visuospatial functioning*: Participants are asked to add the numbers and a minute and second hand to a pre-drawn circle to form a clock face and set the hands at a given time. *Attention/executive functioning:* This is assessed with 2 x 30 second tests. The participant is given a list of lower case letters, and must write the capital letter beside as many as they can. In the second test, participants are given the same list, but half the letters are circled. In this test, the task is to write the capital letter beside the non-circled letters and the lower case letter beside the circled letters.

Each domain is given a score based on the total correct answers. In the case of the clock drawing, points are awarded for each component of the clock. For each test, domain scores are adjusted to account for age, gender and education using the algorithm developed in the validation trials (5). Patients were defined as impaired if their score was 1.5 SD below the mean of the reference population in any given test (5). Total ARCS is calculated based on a combination of all the scaled domains.

Supplemental References:

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