Accuracy of Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) when scored by Multiple Sclerosis (MS) healthcare professionals (HCPs) and impact on MS HCPs' perception of patients' cognitive impairment.

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Chapter 1: Lay summary

Multiple sclerosis (MS) is a lifelong condition once diagnosed, which affects the brain and spinal cord. More than 130,000 people in the UK have MS and it is commonly diagnosed between the ages of 20 and 40. People with MS can experience vision problems, muscle stiffness and spasticity, problems with mobility and balance, fatigue and emotional changes such as depression. Another common symptom of MS is problems with cognition, which can negatively impact quality of life. Cognition describes mental processes such as making decisions, learning something new, paying attention, remembering information and solving problems. Areas of cognition most commonly affected in people with MS include information processing speed (how quickly a person can process and respond to information), visual memory (the ability to learn and remember visually presented information e.g., images) and verbal memory (the ability to learn and remember verbally presented information e.g., words).

People with MS can find cognitive difficulties just as disabling as physical symptoms, however, it is often overlooked or not prioritised by healthcare professionals, since it is not as obvious as physical disability. As such, people with MS continue to live with hidden needs. It is important that cognition is routinely assessed and monitored in clinical practice to tackle the invisibility of cognitive difficulties and prompt further assessment and treatment. Relying on patient-reported cognitive problems may not align with cognitive performance on objective assessments due to a range of influencing factors such as depression, anxiety and fatigue. This emphasises the need to use objective cognitive testing to complement subjective measures of cognition and assess different aspects of cognitive functioning. Traditional cognitive batteries such as the Brief

Repeatable Battery of Neuropsychological Test (BRB-N), for example, are costly, time-consuming and require resources which are often scarce in clinics.

The Brief International Cognitive Assessment for MS (BICAMS) is a 15-minute screening tool to assess cognition in people with MS. It comprises three sub-tests to evaluate information processing speed, visual and verbal memory. BICAMS does not require any specific assessor training, and no special equipment is needed beyond a pen, paper and stopwatch. BICAMS was developed in 2012 as part of an international effort to routinely screen and monitor cognition in people with MS. To explore the validity and international reach of BICAMS, we conducted a systematic review to identify, evaluate and summarise the existing international validation studies on BICAMS. The review showed that BICAMS has been validated in 26 countries to date, including Argentina, Belgium, Turkey, and Japan. Furthermore, we also performed a meta-analysis to assess the results of these studies, which demonstrated that BICAMS can detect cognitive impairment in people with MS compared to healthy controls across a range of cultures, languages, and countries.

BICAMS is designed to be utilised as part of routine clinical practice by a range of healthcare professionals, but despite this, BICAMS is mainly used by psychologists. Only one study, in Germany, has explored the feasibility of BICAMS by non-psychologists and observed scoring errors in half of the cases. The authors concluded that non-psychologists must be even more intensively trained and supervised by experts in the application and scoring of BICAMS. All healthcare professionals need to address cognition within their practice, including nurses and physiotherapists, to ensure people with MS do not continue living with hidden needs. Therefore, in addition to the review, the present study aimed to investigate the accuracy of UK healthcare

professionals scoring on BICAMS to determine feasibility of BICAMS in clinical practice. This was done by using a statistical analysis to assess level of agreement on BICAMS scoring between a trainee clinical psychologist (TCP) and healthcare professionals. Our analysis indicated an excellent level of agreement and provides evidence to support the use of BICAMS by healthcare professionals, within routine MS clinical practice.

Healthcare professionals decide whether patient behaviours are related to cognitive impairment based on their observations e.g., healthcare professionals may attribute patients' difficulties to fatigue or physical disability rather than cognitive impairment. Thus, it would be useful to know if completing BICAMS and feeding back on scores impacts healthcare professionals perceptions of the patients' cognition. In light of this, the study also aimed to explore whether healthcare professionals' perceptions of patients' cognitive impairment change following BICAMS administration and feedback. To evaluate healthcare professionals perceptions, we compared an informant self-report measure of patient cognition (called the Multiple Sclerosis Neuropsychological Questionnaire-Informant; MSNQ-I), completed at three points, with patients' objective scores on BICAMS. No significant change was observed on the three MSNQ-Is, compared to objective BICAMS scores, across the three time points. Perhaps, if our study had a larger sample of people with MS, this may have generated different findings.

Taken together, the systematic review and meta-analysis highlighted the work of the international MS community at validating BICAMS, demonstrating a development in raising awareness of MS cognition as well as increasing the implementation of BICAMS into routine clinical practice. The present study demonstrated that BICAMS can be successfully completed by healthcare professionals to optimise further monitoring and management of

cognition in people with MS. Healthcare professionals are encouraged to receive training in BICAMS administration and scoring to support the assessment and monitoring of cognition in people with MS in clinics.

Chapter 2: Accuracy of Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) when scored by Multiple Sclerosis (MS) healthcare professionals (HCPs) and impact on MS HCPs' perception of patients' cognitive impairment.

Abstract

Cognitive impairment is a common clinical feature of multiple sclerosis (MS) which negatively impacts quality of life, yet it is often overlooked by healthcare professionals (HCPs). The Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) is an international cognitive screening tool for people with MS (PwMS), designed to be utilised as part of routine clinical MS practice by a range of HCPs. The primary aim of the study was to investigate the level of agreement on scoring between a trainee clinical psychologist (TCP) and UK HCPs to confirm feasibility of this measure and thus facilitate its clinical use. Our exploratory aim was to evaluate whether HCPs perceptions of patients' cognitive impairment change following BICAMS administration and feedback, using the Multiple Sclerosis Neuropsychological Questionnaire-Informant (MSNQ-I) across three time points.

Six HCPs (all female, mean age 51.33) and 18 PwMS (11 females, mean age 51, 12 diagnosed with relapsing-remitting form of MS) took part in the study. HCPs were trained on BICAMS scoring, administration and feedback before completing this assessment with PwMS. HCP scores on BICAMS were checked by the TCP and level of agreement between scorers was analysed using intraclass correlation coefficient (ICC). For the exploratory aim, HCPs completed the MSNQ-I, at three time points, which were interspersed with BICAMS completion and feedback

on BICAMS scores. Difference scores between totalled BICAMS *z*-scores and MSNQ-I *z*-scores, for the three time points, were compared using repeated measures ANOVA.

The level of agreement between scorers indicated excellent reliability on all three BICAMS subscales (intraclass correlation coefficients: SDMT= 0.999, CVLT-II= 1.000 and BVMT-R= 0.980). No significant change was observed on the statistical accuracy of MSNQ-Is, compared to patient objective cognitive tests scores, across the time points. Future research should aim to acquire a larger sample size to evaluate separately the effects of completing BICAMS and receiving feedback. Our findings suggest that BICAMS is a feasible assessment tool for MS cognition that can be successfully completed by HCPs in routine clinical practice to optimise further monitoring and management.

Introduction

Multiple sclerosis

Multiple sclerosis (MS) is a chronic, autoimmune-mediated disease of the central nervous system, involving inflammatory and degenerative processes (Dobson & Giovannoni, 2018). MS is commonly diagnosed between the ages of 20 and 40, and involves a constellation of symptoms in the motor, sensory, psychological, and cognitive domains (McGinley et al., 2021). The course of the disease is highly variable and can be categorised into different clinical phenotypes. In relapsing-remitting MS (RRMS), relapses, which are defined as neurological symptoms lasting 24 hours or more, are followed by periods of remission. RRMS may develop into secondary progressive MS (SPMS) which describes gradual worsening of symptoms and increased disability without remission. Primary progressive MS (PPMS) is diagnosed in a small

proportion of people and involves gradual accrual of progressive disability from onset of symptoms, with no relapses or remissions. Clinically isolated syndrome (CIS) is characterised by an initial, single episode of neurological symptoms, lasting 24 hours or more. CIS can be the first indication of what later becomes a diagnosis of MS but can also represent a single episode with no further neurological progression (McGinley et al., 2021). Diagnosis is based on the revised McDonald criteria (Thompson et al., 2018) and current treatment for MS involves disease-modifying drugs (DMDs), lifestyle adjustments, psychological support, and rehabilitation interventions (Dobson & Giovannoni, 2018).

MS cognition

Cognitive impairment is widely acknowledged as a prominent feature of MS, affecting approximately 34-65% of PwMS across all clinical phenotypes, including the prodromal phases (Benedict et al., 2020; DeLuca et al., 2020). Cognitive impairment can progress insidiously or suddenly during relapses and typically becomes more pronounced in the progressive forms of disease (DeLuca et al., 2020). MS-related cognitive impairment is generally circumscribed and not global, with the most prevalent cognitive deficits found in learning, memory, and information processing speed. Other compromised cognitive domains include executive functioning, complex attention, and visuospatial functioning (Benedict et al., 2020). Cognitive impairment is recognised as a debilitating symptom of MS which can have profound adverse effects on quality of life (Gil-González et al., 2020), employment (Clemens & Langdon, 2018; Kavaliunas et al., 2022), disease management (Bruce et al., 2018; Gomes et al., 2022), personality (Roy et al., 2018) and driving safety (Krasniuk et al., 2021).

MS cognition is overlooked by healthcare professionals

Cognitive impairment is considered one of the "invisible" symptoms of the disease since it has no direct tangible presence (Lakin et al., 2021). Invisible symptoms such as cognitive difficulties are often overlooked or ignored by others including family members, colleagues, and HCPs, perhaps because patients appear visibly healthy or have physical disabilities to which reduced function is wrongly attributed. Patients may find it difficult to raise concerns with HCPs which hinders assessment and treatment, and consequently, patients continue to live with hidden needs (Parker et al., 2021). There is a disparity between patient and neurologist perceptions of MS symptoms, highlighting that cognition is not considered a priority in neurology appointments. Neurologists consider physical symptoms such as ambulation issues, falls and incontinence to impact most on quality of life. Conversely, patients consider non-physical symptoms such as cognitive problems, fatigue, and pain to be more significant (Col et al., 2017; Marin et al., 2021).

HCPs' perceptions of cognition may not align with objective measures

HCPs are not accurate in predicting cognitive impairment at MS routine consultation, suggesting that standard neurological examination, alone, is not sufficiently sensitive to detect cognitive impairment (Romero et al., 2015). Instead, MS routine consultation requires objective, accurate cognitive assessment to complement routine clinical evaluation (Romero et al., 2015) and facilitate optimised, comprehensive care (Bakirtzis et al., 2018; Sumowski et al., 2018).

Patient' perceptions of cognition may not align with objective measures

A handful of reliable and validated self-report measures are available to assess cognition in MS, including the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ; Benedict et al., 2003). The MSNQ is a 15-item measure of neuropsychological competence during activities of daily living and is validated for patient-report (MSNQ-P) and informant-report (MSNQ-I). Self-

reported cognitive functioning is poorly correlated with objective test results, even on validated self-report measures such as the MSNQ-P (Eilam-Stock et al., 2021). PwMS can either underestimate or overestimate cognitive function, suggesting there is no linear bias (Davenport et al., 2022; Hughes et al., 2019). Conversely, informant reports of MS patients' cognitive functioning, from partners, family, and friends, correlate more strongly with MS patients' objective test results (Benedict et al., 2004; Jackson et al., 2023).

Confounders of self-reported cognition

Self-reported cognitive status may not accurately align with objective test performance due to several confounders such as depression (Biasi, 2023; Crouch et al., 2022), anxiety (Vissicchio et al., 2019), perceived stress (Beier et al., 2015), sleep problems (Hughes et al., 2017), self-efficacy (Hughes et al., 2015) and fatigue (Biasi, 2023; Davenport et al., 2022). Routinely screening and monitoring for mood disorders and fatigue in addition to cognition can also discriminate cognitive impairment from these modulating factors and reveal any potential interaction effects (Portaccio & Amato, 2022; Thomas et al., 2023).

Traditional cognitive assessments for MS

In addition to subjective measures of cognition, it is important to also employ objective cognitive tests to assess different aspects of cognitive functioning and provide a comprehensive picture of the patient's cognition. Traditional objective neuropsychological assessments for MS, such as the Brief Repeatable Battery of Neuropsychological Test (BRB-N; Rao et al., 1990) and the Minimal Assessment of Cognitive Function in MS (MACFIMS; Benedict et al., 2002) are some of the most widely used, traditional batteries to detect cognitive dysfunction in PwMS.

Barriers to cognitive evaluation in MS practice

Traditional neuropsychological assessments are costly, time-consuming and often require a clinical neuropsychologist, a resource which is often scarce or unavailable in many MS clinics (Meca-Lallana et al., 2021). Further, these batteries are not routinely available outside specialist centres and are not comparable across countries (Klein et al., 2018; McNicholas et al., 2020).

Routine cognitive testing is needed

There is a growing consensus, across PwMS and professionals, that objective cognitive assessments should form part of routine clinical practice to capture impaired cognition in MS (Kalb et al., 2018; Morrow et al., 2022). Both the National Institute for Health and Care Excellence (NICE, 2022) and the American Academy of Neurology (AAN, 2014) recommend an annual routine cognitive assessment to establish cognitive status in MS. PwMS, family members, clinicians and healthcare commissioners widely support the implementation of routine cognitive testing and feel that cognitive symptoms should receive equal attention to physical health difficulties (Elwick et al., 2021; Mortensen et al., 2020). HCPs recognise that cognition is not appropriately addressed in clinics and that technology to assess and treat cognitive concerns are required to deliver improved cognition services in MS clinics (Langdon et al., 2022). Despite the marked impact of cognitive difficulties on the lives of PwMS, and the widely acknowledged need to embed routine cognitive testing into MS practice, cognitive assessment remains undervalued and poorly managed in MS clinics (Langdon et al., 2022).

Importance of routine cognitive testing

Routine assessment and monitoring of MS cognition can promote awareness of cognitive concerns in health services and prompt referral for further targeted assessment and treatment,

including cognitive rehabilitation (Chen et al., 2021; Longley, 2022). HCPs can also be vigilant to increased risks associated with cognitive impairment such as driving accidents, unemployment, and poor disease management (Kalb et al., 2018). In response to identified cognitive dysfunction, HCPs can provide education to the patient and their carer about cognition in MS, as well as promoting lifestyle choices that can protect cognition. Also, since MS is a chronic disease, monitoring cognition throughout the disease course can provide a longitudinal picture of potential symptom progression (Ruet & Brochet, 2020). HCPs can also adopt an appropriate interaction style, for example, by providing concrete explanations, repeating information within and across consultations, checking understanding and remembering of information, and encouraging management and protection such as through the Brain Health initiative (Langdon & Young, 2023).

Development of BICAMS

In 2012, an international consensus committee comprising 12 leading international MS experts convened to review and select scales that could be combined to produce a valid international cognitive assessment for MS. The committee agreed that the assessment should measure information processing speed, verbal memory, and visual memory (immediate recall). This prompted the selection of the Symbol Digit Modalities Test (SDMT) in oral form, the first five learning trials of the California Verbal Learning Test-II (CVLT-II), and the first three learning trials of the Brief Visuospatial Memory Test-Revised (BVMT-R; Langdon et al., 2012).

International validity of BICAMS

The committee published an international validation protocol to guide national validations of BICAMS (Benedict et al., 2012). Subsequently, BICAMS has been embraced by the

international MS community, with 26 published national validations to date (Potticary & Langdon, 2023). These validation studies demonstrate that BICAMS is a valid and reliable measure of cognitive functioning and can detect cognitive impairment in MS compared to healthy controls, across a range of cultures, languages, and countries (Potticary & Langdon, 2023). Importantly, BICAMS has the same sensitivity to cognitive impairment as the lengthy, complex, and costly "gold standard" neuropsychological batteries (Dusankova et al., 2012).

Implementing BICAMS into routine clinical practice

BICAMS is a psychometrically sound and feasible international assessment tool for MS cognition and is applicable in a routine clinical setting. No special equipment is required beyond a pen, paper and stopwatch and does not require any specific assessor training. BICAMS is designed to be utilised as part of routine clinical MS practice by a range of health professionals and can be accessed by patients who do not attend specialist centres (Langdon et al., 2012). BICAMS has facilitated awareness of assessment and management of MS cognition by offering a cost-effective and time-efficient measurement technology to routinely monitor cognitive function in MS clinics. BICAMS is a brief screening tool for cognition, therefore, more comprehensive cognitive batteries are recommended for a full neuropsychological evaluation (Bakirtzis et al., 2018).

Experiences of using BICAMS by non-psychologists

BICAMS is designed to be used by a range of HCPs (Langdon et al., 2012), but despite this, BICAMS is still being used mainly by psychologists. One study has documented BICAMS administration and scoring by HCPs (Renner et al., 2020). In this study, nurses were provided with extensive training in BICAMS administration, however the completed test forms were

reviewed and scored by two independent psychologists. Reliability of scoring between the two psychologists were assessed using intraclass correlation coefficient (ICC). Evidence is still needed to confirm that BICAMS is a feasible tool to use within clinical practice, by HCPs. Only one study, in Germany, has explored the clinical practicability of non-psychologists using BICAMS (Penner et al., 2021). In this study, graduate medical assistants (termed "physician assistants") were trained to administer and score BICAMS and their scoring was later evaluated by neuropsychological experts. Significant mistakes in application and scoring of BICAMS were found in 50.3% of cases. The researchers concluded that non-psychologists should be more intensively trained and supervised by experts in the application and scoring of BICAMS. Taken together, these findings highlight the importance of assessing the accuracy of BICAMS administration and scoring to maximise the use of BICAMS in routine MS clinics by a range of HCPs. Investigating the feasibility of using BICAMS in routine practice could inform guidance offered to MS HCPs regarding preparation for cognitive assessment and feedback.

All MS HCPs need to address cognition

All MS HCPs need to address cognition as part of their healthcare provision, including nurses (e.g., Slough & Brownlee, 2021), physiotherapists (e.g., Ghahfarrokhi et al., 2022) and occupational therapists (e.g., Krasniuk et al., 2021). Therefore, the MS multidisciplinary team (including neurologists, nurses, psychologists, and speech therapists) are encouraged to receive training to use short MS cognitive assessment batteries such as BICAMS (Langdon & Young, 2023). With their multifaceted role, MS HCPs can play a crucial role in supporting PwMS to manage cognitive changes throughout the disease trajectory by cultivating an awareness of cognition, legitimising their experiences, providing education, routine assessment, and monitoring of cognition (Jarrett, 2022).

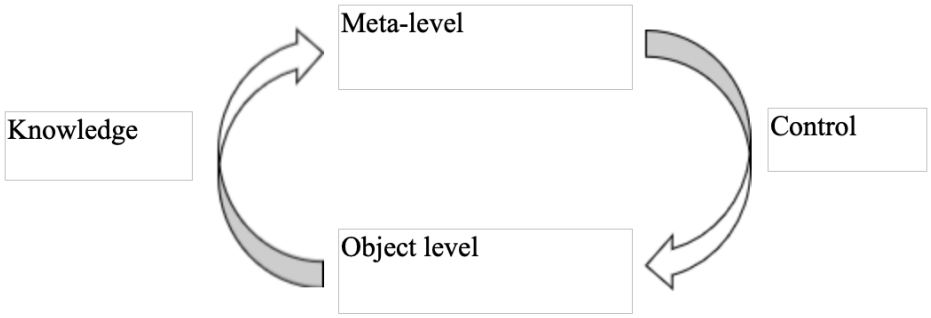
Theoretical model of metacognition

Metacognition, or "thinking about thinking", describes the ability to monitor and control one's cognitive processes – known as metacognitive knowledge and metacognitive control (Dunlosky & Metcalfe, 2009). Specifically, metacognitive knowledge is the knowledge and awareness an individual has of their own cognitive processes and their ability to introspectively monitor these. Metacognitive control is the ability to control these processes using self-regulatory mechanisms such as adapting behaviour based on outcomes (Fleur et al., 2021; Livingston, 2003).

According to the theoretical model of metacognitive processes proposed by Nelson and Naren (1977; Figure 1), metacognitive processes are split into two interrelated levels (object level and meta-level) and two relations in terms of the direction of the information flow between these levels (metacognitive knowledge and metacognitive control). Metacognitive knowledge is the processing of information from the object level to the meta-level and metacognitive control is the processing of information from the meta-level to the object level.

Figure 1

Model of metacognitive processes



Theoretical link with present study

Applying the metacognition model to the MS clinic situation and available measures, the informant-report MSNQ-I is assumed to tap into HCPs internally constructed dynamic model of the patient's cognitive status, for the purposes of this study. Applying the Nelson and Naren model (1977; Figure 1), the accuracy of the HCPs' internal model of the patient's cognitive status could be experimentally determined by comparing the subjective MSNQ-I with the patients' objective BICAMS scores. The HCPs observations and information of PwMS' cognitive competence can theoretically be compared internally by HCPs with HCPs' current evaluative internal model of the cognitive status of the patient.

Metacognition involves an internal, dynamic evaluation of one's cognitive status which is constantly updated by experience. HCPs, based on their observations, decide whether behaviours are related to the cognitive impairment of the patient – for example, HCPs may attribute PwMS' difficulties to fatigue or disability rather than cognitive impairment. As the HCP continues to observe other difficulties in PwMS, new evidence may lead them to re-evaluate the PwMS' cognition and continually adjust their internal model of PwMS' cognitive abilities. The HCPs internal model of PwMS' cognitive competence leads the HCP to alter behaviour to support cognitive competence and mitigate PwMS' cognitive impairments such as changing their interaction style by speaking in shorter sentences and slowing their speech.

Research questions

Primary research question

1. Can HCPs accurately score BICAMS?

To address this research question, the empirical study evaluated the accuracy of UK MS HCPs' scoring of BICAMS, in comparison to a trainee clinical psychologist (TCP) scoring BICAMS. Accuracy of scoring was measured using level of agreement (determined using ICC) on BICAMS scores between the HCP and TCP.

Exploratory research question

1. Do HCP perceptions of MS patients' cognitive functioning change following BICAMS administration, scoring and feeding back?

To address this research question, the empirical study explored whether MS HCPs' perception of MS patients' cognitive function changed following completing, scoring, and feeding back on BICAMS. Changes in HCP perception of MS patients' cognitive function was measured using the MSNQ-I interspersed with BICAMS completion, scoring and feedback.

Method

Recruitment and setting

PwMS were recruited by HCPs from three different settings – Brighton General Hospital under Sussex Community NHS Foundation Trust (an NHS MS community service in Sussex), Darent Valley Hospital MS Clinic under Dartford and Gravesham NHS Trust (a district general hospital in Dartford) and The Samson Centre (a registered MS charity organisation in Guilford providing physiotherapy).

Eligibility criteria

Inclusion criteria

1. Adults aged 18-60, diagnosed with MS by a consultant neurologist using the latest McDonald criteria (Thompson et al., 2018).
2. Capacity to provide informed consent.

Exclusion criteria

1. Any significant psychiatric condition which could impact performance on BICAMS.
2. Any other medical condition which could impact on cognition.
3. Recent cognitive assessment or cognitive rehabilitation within the last 6 months.

Sampling

Prior to any statistical analyses, a power analysis was performed to calculate how many PwMS would be required to generate statistically significant results where agreement is measured using ICC (Bonett, 2002; Walter et al., 1998). Based on an alpha level of 0.05, a power of 0.8 (Cohen, 1992) and a minimum acceptable reliability between 0.5 and 0.75 (Koo & Li, 2016), the power analysis specified a sample size of 18 PwMS. To account for attrition, with an estimated drop-out rate of 10%, a recruitment sample of 20 PwMS was planned to ensure complete data on 18.

Design

A longitudinal repeated measures design was employed (Table 1).

Table 1

Table of longitudinal repeated measures design

Time	T0								+1 week	+2 weeks		+3 weeks
Contact		Contact 1 (phone interview)	Contact 2 (face-to-face)					After contact 2		Contact 3 (phone interview)		After contact 3
MS Patient	Receive patient study pack 1 week in advance of phone interview	MS HCP reads information sheet and consent form to patient and discuss	Reviews information sheet and signs consent form		Disease and demographic questionnaire, PDDS, HADS and FSS	Complete BICAMS with MS HCP				Receive feedback on BICAMS from MS HCP		
MS HCP	Email patient study pack to patient 1 week in advance of phone interview	Read information sheet and consent form to patient and discuss	Give patient information sheet and consent form to sign and answer questions	MSNQ-I 1	Demographic questionnaire	Complete BICAMS with MS Pt	MSNQ-I 2	Send letter to GP	BICAMS scoring and feedback check with TCP	Give feedback on BICAMS to MS Pt	MSNQ-I 3	Complete qualitative survey of experience
TCP									BICAMS scoring and feedback check with MS HCP			

Note.
HCP= Healthcare Professional; TCP= Trainee Clinical Psychologist; MSNQ-I= Multiple Sclerosis Neuropsychological Questionnaire-Informant; BICAMS= Brief International Cognitive Assessment for MS; PDDS= Patient determined disease steps; HADS= Hospital Anxiety and Depression Scale; FSS= Fatigue Severity Scale

Measures

Experimental measures

1. Brief International Cognitive Assessment for MS (BICAMS; Langdon et al., 2012)

BICAMS has been established as a clinically feasible tool with good psychometric properties for assessing cognition in PwMS worldwide (Potticary & Langdon, 2023). This 15-minute screening tool comprises the SDMT (Smith, 1982) to assess information processing speed, the CVLT-II (Delis et al., 2000) to assess immediate verbal recall and the BVMT-R (Benedict, 1997) to assess immediate visual recall.

2. Multiple Sclerosis Neuropsychological Questionnaire-Informant (MSNQ; Benedict et al., 2003)

The MSNQ is a 15-item validated measure of subjective cognitive deficits related to MS. For the purposes of the exploratory aim, the MSNQ-I was used. Cut-off scores of >22 on the MSNQ-I correctly classified 85% of the corresponding patients in terms of cognitive impairment, with a sensitivity of 0.87 and a specificity of 0.84 (Benedict et al., 2003).

3. A brief qualitative survey exploring HCPs' perceptions of cognitive impairment

This is a study-specific, non-validated qualitative survey designed by the researchers to evaluate HCPs' experiences of BICAMS and how it has impacted their perceptions of the individual patient's cognitive impairment.

Other measures

1. Patient disease and demographic questionnaire

Patient disease and demographic data was collected using a brief, non-validated, study-specific questionnaire. This data was collected to establish typicality of the sample.

2. HCP demographic questionnaire

Demographic data was collected using a brief, non-validated, study-specific questionnaire to gather information about the HCP such as their age, ethnicity, years of education, and years of experience working as an MS HCP.

3. Patient determined disease steps (PDDS; NARCOMS; Hohol et al., 1995; Hohol et al., 1999)

The PDDS is a patient-reported outcome of disability in MS and consists of 9 ordinal levels ranging between 0 (normal) and 8 (bedridden; Learmonth et al., 2013). There is a strong correlation between the objective, gold standard Expanded Disability Status Scale (EDSS; Kurtzke, 1983) and PDDS scores (p = .783; Learmonth et al., 2013). PDDS scores can be converted into EDSS scores as well as classifications of mild, moderate, or severe disability (Marrie et al., 2006).

4. Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)

The HADS is a widely used screening instrument to identify anxiety and depressive symptoms in medical populations. For major depressive disorders, cut off scores of ≥8 gave a sensitivity of 0.82 and a specificity of 0.74 and cut off scores of ≥11 gave a sensitivity of 0.56 and a specificity of 0.92 (Brennan et al., 2010). The HADS has been validated and extensively used in MS (Pais-Ribeiro et al., 2018).

5. Fatigue Severity Scale (FSS; Krupp et al., 1989)

The FSS is a unidimensional Likert scale consisting of 9 statements evaluating the severity but also the impact of fatigue in PwMS. The FSS has acceptable reliability, internal consistency, sensitivity, and responsiveness for PwMS (Krupp et al., 1989; Learmonth et al., 2013).

Expert by Experience (EbE) involvement

Discussions with a recent panel of interested partners and survey, which included an EbE as a panel member, was reviewed to give a broad context to the design and inform study planning (Langdon et al., 2022). For the precise details of the study, a service user diagnosed with MS was asked to review our drafted study protocol and comment on the study objectives, design, and procedures. The service user noted that the PWMS were to be asked to complete a demographic questionnaire, but the HCPs were not. They suggested that researchers record HCPs' years of experience and demographics. We devised a demographic questionnaire for HCPs including their years of experience working as an MS HCP. The service users suggested that researchers ensure BICAMS does not preclude other aspects of the patients' care being discussed. In the BICAMS training, it was therefore explained to the HCPs that other aspects of the patients' care should be prioritised in their clinic appointment prior to completion of study measures. Another suggestion was around ensuring that the TCP is adequately trained and supervised in BICAMS administration and scoring. The service user was reassured that the TCP will have familiarised themselves with BICAMS administration and scoring prior to training the HCPs and will be regularly supervised by Professor Dawn Langdon who has extensive experience of using BICAMS and training psychologists to use BICAMS. Finally, the service user suggested patients should receive an incentive for their participation in the study. In response to this, all patients who consented to participate in the study were entered into a prize draw for the chance to win a £50 Amazon gift voucher.

Integrated Research Approval System (IRAS) application

An NHS ethics application was submitted via IRAS. A proportionate review from the London Bridge Research Ethics Committee (REC) was subsequently held in June 2022. In response to the committee's comments, changes were made to several study materials including the participant and HCP information sheets, and consent forms. Having reviewed our proposed document amendments and other responses to their comments, the London Bridge REC gave a favourable ethical opinion in August 2022 (Appendix 5).

Local Research and Development (R&D)

Sussex Community NHS Foundation Trust R&D confirmed capacity and capability of the study in November 2022. Sussex R&D required HCPs to complete informed consent training via the National Institute for Health and Care Research (NIHR), prior to recruiting patients. As per Sussex R&D guidance, a local collaborator from the HCP team agreed to support the study locally and co-ordinate any queries with the RHUL researchers. Sussex R&D also required the researchers and local collaborator to store and manage study-related paperwork in a secured site file. The paperwork included documents provided by R&D such as a delegation of duties log, a training log, and an error log.

Dartford and Gravesham NHS Trust R&D confirmed capacity and capability of the study in May 2023. They did not require any amendments to the study documents and did not require HCPs to undergo any additional training.

The therapy lead at The Samson Centre presented the study to the Centre Director and Chair for their agreement. The Samson Centre confirmed capacity and capability of the study in May 2023. They did not require any amendments to the study documents and did not require HCPs to undergo any additional training, other than that specified in the study protocol.

IRAS non-substantial amendments

A total of three IRAS non-substantial amendments (Appendix 6) were submitted to London Bridge REC between December 2022 and May 2023. The amendments are detailed below.

IRAS non-substantial amendment 1

An IRAS non-substantial amendment was submitted to London Bridge REC in December 2022 and was approved in January 2023. The original IRAS permission specified that MS nurses would be recruited. However, upon meeting with the site team, it emerged that physiotherapists were also working in the MS support team, fulfilling the same general MS support worker role as MS nurses. Thus, an amendment was submitted to include the recruitment of physiotherapists as well as MS nurses as site investigators.

The original IRAS permission specified that MS patients would meet with the HCPs via three face-to-face clinical appointments. Having met with HCPs, they felt that the burden on patients and themselves could be reduced if the first and third contact were via telephone. An amendment was submitted to change the first and third contact to a telephone interview and provide patients with the information sheet and consent form a week in advance of the first telephone contact (via email) to allow patients a week between reading the information sheet and providing consent.

IRAS non-substantial amendment 2

An IRAS non-substantial amendment was submitted to London Bridge REC in April 2023 and was approved in May 2023. The original IRAS permission was to collect data in the period between June 2022 and April 2023. However, recruitment and retention of MS HCPs posed the biggest challenge for the study. MS HCPs were initially recruited from Sussex Community NHS Foundation Trust and had consented to take part in the study at the BICAMS training session at Brighton General Hospital in

December 2022. The Brighton HCPs were unable to start data collection due to a combination of illness, bereavements, and increasing workload. The disruption caused by the NHS strikes also posed a challenge to recruitment. An amendment was submitted to request that the data collection period was extended to 31st December 2023.

IRAS non-substantial amendment 3

An IRAS non-substantial amendment was submitted to London Bridge REC in May 2023 and was approved in June 2023. The original IRAS permission was to collect data from Sussex Community NHS Foundation Trust. However, the Brighton HCPs were unable to start data collection within the scheduled timeframes due to a combination of illness, family bereavements and NHS strikes. Since Brighton HCPs were delayed in collecting data, three other trusts/centres were approached – Dartford and Gravesham NHS Trust, Wye Valley NHS Trust, and The Samson Centre. An amendment was submitted to request involvement of these three other participating organisations.

The original IRAS permission was for the first and third patient contact to be via telephone call, with the second being face-to-face, to reduce the burden on patients and HCPs. Having met with the collaborator at The Samson Centre, it was felt that all three contacts could be completed via telephone call or face-to-face since they regularly see patients face-to-face. An amendment was submitted to request that, for The Samson Centre, the first and third contact could be completed face-to-face or via telephone call.

Ethical considerations

Patients were allocated a study number in accordance with the BPS Code of Ethics and Conduct (BPS, 2018). The local collaborator recorded patient names and study numbers in a table, stored at the clinic site. The patients' disease, and demographic data relating to their lifetime history of MS, type of MS, current medications, and other mental health/neurological/medical conditions, and research data

relating to the study, were the only patient information documented and shared with the researchers for the purposes of the study.

The researchers discussed patient confidentiality and anonymity with the MS HCPs to ensure there would be no identifying information on the batteries or outcome measures. HCPs asked patients who completed the batteries and outcome measures to refrain from sharing identifiable information. However, their names were documented on the consent form at the beginning of the study and the consent forms were only seen by the clinical team and stored at the clinic site. All study documents were screened for personal information by the HCPs before sharing them with researchers. These documents were electronically stored on an encrypted USB stick and were accessible to the researchers involved in the study, and a back-up was stored on the RHUL server.

Procedure

Study preparation with HCPs

In preparation for training the HCPs, patient packs and HCP packs were created and printed. The patient packs contained the patient information sheet (Appendix 1) and consent form (Appendix 2) which would be sent out to them one week in advance of the first telephone contact. The HCP pack was created to ensure that all study materials were kept neatly together and in order of completion. The HCP pack contained the HCP information sheet (Appendix 3), consent form (Appendix 4), study measures (Appendix 7), and a checklist at every contact point (three checklists altogether). Two sets of training slides were also prepared in advance of the training sessions – one on the study which outlined the background, aims, hypotheses, sampling, recruitment, procedure as well as guidance on feeding back results to patients. The other set of slides were specifically on BICAMS and went through the development of BICAMS, administration, scoring and faux responses for HCPs to practice administration and scoring with each other in the training session.

Researchers (HP and DL) met with the HCPs to present the study and provide training on BICAMS administration, scoring, feeding back, and related procedures. Two in-person training sessions were delivered to HCPs from Sussex Community NHS Foundation Trust – one in July 2022 by DL and one in December 2022 by HP and DL jointly. HCPs commented on guidance relating to introducing cognitive assessment, feeding back, and accommodating cognitive impairment in routine clinical practice. An in-person training session was delivered to HCPs from Dartford and Gravesham NHS Trust in April 2023 by DL, with HP joining the training online via MS Teams. An in-person training session was delivered to HCPs from The Samson Centre in June 2023 by DL and HP jointly. At The Samson Centre training, HCPs requested stamped envelopes to send patient letters to the GP since they were not able to email letters. They also requested that HCP packs and patient packs for each MS patient were printed out and posted to them by the researchers, because they did not have adequate printing facilities.

The procedure involved three patient contacts with the HCP, across a three-week period, with two telephone calls and one face-to-face clinic appointment, for each MS patient. A schematic of the study design can be found in Table 1.

Contact 1

The HCPs emailed PwMS the information sheet and consent form one week in advance of the first telephone contact. A week later, the HCP read and discussed the information sheet and consent form with the patient in a telephone interview, answering any questions the patient had relating to the study. It was made clear that patients were free to withdraw at any stage, without providing a reason and with no impact on their healthcare.

Contact 2

In the face-to-face routine clinic appointment, the information sheet was reviewed with the HCP and informed written consent was provided by the patient. The HCP completed MSNQ-I 1 and the demographic questionnaire. The patient completed the disease and demographic questionnaire, PDDS, HADS, FSS and BICAMS. After BICAMS testing, the HCP completed MSNQ-I 2. At the appointment, the HCP provided the patient with the stamped addressed envelope to complete after contact 3. Following the appointment, the HCP sent a letter to the patients' GP, informing them of the patient's study involvement. The HCP scored BICAMS and emailed an anonymised pdf of the study pack to the TCP. The TCP scored all questionnaires and second scored the BICAMS responses. The HCP then received feedback on BICAMS scoring from the TCP (via telephone or email), and advice regarding feedback to the patient.

Contact 3

The patient received feedback on BICAMS over the telephone with the HCP. The HCP completed MSNQ-I 3 and the qualitative survey.

Statistical analysis plan

Normality of all data will be explored, and descriptive statistics calculated for all variables. Assuming normality, correlations of BICAMS scores with fatigue, anxiety, depression, and disability would be calculated using Pearson's correlation coefficients, to identify potential confounders.

Impairment on BICAMS was defined according to Langdon et al (2012) as scoring -1.5 SD or below compared to healthy controls. Scores obtained from HCPs on BICAMS will be compared with scores from the TCP using ICC. ICC will be used to calculate the extent of agreement among raters when the ratings are in the form of at least two quantitative measurements (Shrout & Fleiss, 1979).

Difference scores between BICAMS and MSNQ-I will be calculated to determine statistical accuracy of perceived cognition status (after Davenport et al., 2022). To investigate how HCPs' perception of MS patients' cognitive impairment is affected by experiential and objective data, difference scores between MSNQ-I *z*-scores and totalled BICAMS *z*-scores will be compared using repeated measures ANOVA (totalled BICAMS versus MSNQ-I 1, 2, 3).

The brief qualitative surveys completed by HCPs will be analysed using thematic analysis (Braun & Clarke, 2006). Thematic analysis was considered the most appropriate qualitative research method for identifying, analysing, organising, describing, and reporting on insightful themes that emerged from the surveys (Braun & Clarke, 2006).

Results

Descriptive and clinical characteristics of sample

Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (SPSS) Version 28. No missing values were detected. Boxplots were visually inspected, and no outliers were detected. Descriptive statistics were produced based on the demographic and clinical characteristics of the PwMS sample (Table 2). MS patients were recruited from Darent Valley Hospital (5), Brighton General Hospital (10) and The Samson Centre (3).

Table 2

Demographic and clinical characteristics of PwMS sample

		M (*SD*)	Min – Max	N (%)
Gender	Male Female			7 (38.9) 11 (61.1)
Age		51 (9.85)	30 – 60	
Ethnicity	White British			16 (88.9)

	Mixed			2 (11.1)
	Asian/Asian British			0 (0)
	Black/Black British			0 (0)
	Arab			0 (0)
	Other			0 (0)
Years of education		13.22 (2.88)	10 – 18	
Employment	Full time			7 (38.9)
	Part time			5 (27.8)
	Full time education			0 (0)
	Homemaker			1 (5.6)
	Medically retired			3 (16.7)
	Unemployed			2 (11.1)
Living status	Married			9 (50)
	Living with partner			3 (16.7)
	Living with other family			1 (5.6)
	Living with children			1 (5.6)
	Living alone			4 (22.2)
MS phenotype	CIS			0 (0)
	RRMS			12 (66.7)
	PPMS			0 (0)
	SPMS			6 (33.3)
Years since diagnosis		11.50 (10.29)	1 – 33	
Hauser Ambulation Index		3 (2.14)	1 – 8	

Note.
M= Mean; *SD*= Standard deviation; N= Percent frequency; CIS= Clinically Isolated Syndrome; RRMS= Relapsing-Remitting MS; PPMS= Primary Progressive MS; SPMS= Secondary Progressive MS

Additional information such as MS medication was also self-reported. Five PwMS (27.8%) reported taking no medication for MS. Nine PwMS reported taking DMDs such as Natalizumab (1), Alemtuzumab (1), Fampridine (1), Fingolimod (1), Glatiramer acetate (1), Ofatumumab (2), Dimethyl Fumarate (1), and Interferon Beta-1a (1).

A total of six UK MS HCPs took part in the study (2 physiotherapists from Brighton General Hospital, 2 MS nurses from Darent Valley Hospital and 2 physiotherapists from The Samson Centre). Descriptive statistics were produced based on the demographic characteristics of the HCP sample (Table 3).

Table 3

Demographic characteristics of HCP sample

		M (*SD*)	Min – Max	N (%)
Gender	Male			0 (0)
	Female			6 (100)
Age		51.33 (8.66)	42 – 65	
Ethnicity	White British			4 (66.67)
	Mixed			1 (16.67)
	Asian/Asian British			0 (0)
	Black/Black British			1 (16.67)
	Arab			0 (0)
	Other			0 (0)
Years of education		14.83 (1.94)	11 – 16	
Years of experience as an MS HCP		8.17 (7.31)	2 – 21	
Living status	Married			4 (66.67)
	Living with partner			1 (16.67)
	Living with other family			0 (0)
	Living with children			1 (16.67)
	Living alone			0 (0)

Note.
M= Mean; *SD*= Standard deviation; N= Percent frequency

PwMS associated factors

Descriptives of patient-reported depression and anxiety (HADS-D and HADS-A), disability (PDDS) and fatigue (FSS) were calculated (Table 4).

The mean depression score fell within the normal range (5.44, *SD* = 3.55). The mean anxiety score fell within the borderline range (8.33, *SD* = 3.60*).* The mean FSS score was 43.50 (*SD* = 14.68). The mean PDDS score was 3.17 (*SD* = 1.98), indicating gait disability. This means that PwMS can find walking and athletic or physically demanding activities difficult. This stage of disability does not typically require a cane or other forms of assistance to walk, however, this may be required during a relapse.

Table 4

Associated factors in PwMS sample

PwMS associated factors	M (*SD*)	Min – Max
HADS-D	5.44 (3.55)	1 – 10
HADS-A	8.33 (3.60)	1 – 16
PDDS	3.17 (1.98)	1 – 7
FSS	43.50 (14.68)	14 – 59

Note.
M= Mean; *SD*= Standard deviation; HADS-D= Hospital Anxiety and Depression Scale-Depression; HADS-A= Hospital Anxiety and Depression Scale-Anxiety; PDDS= Patient Determined Disease Steps; FSS= Fatigue Severity Scale

Pearson's correlations of BICAMS scores

Normality of the variables were assessed using the Shapiro-Wilk test. The Shapiro-Wilk test was considered the most appropriate test of normality due to the small sample size i.e., $n<50$ (King & Eckersley, 2019). The results showed that all the variables were normally distributed ($p > .05$) except for depression and fatigue. Further analysis was conducted to check normality by obtaining the skewness for depression (-0.91) and fatigue (-1.60) which fell between -1.96 and 1.96 (Kim, 2013). Hence, all the variables were considered to be normal.

Since the assumption of normality was met, correlations of BICAMS sub-test scores with depression, anxiety, disability, and fatigue were calculated using Pearson's correlation coefficients to identify potential associated factors (Table 5).

The results showed a significant negative correlation between depression and BVMT-R (r (16) = -.52, p = .026), a significant negative correlation between anxiety and CVLT-II (r (16) = -.51, p = .031), and a significant negative correlation between anxiety and BVMT-R (r (16) = -.49, p = .038). For BICAMS scales intercorrelations, the results showed a significant positive correlation between the SDMT and

BVMT-R (r (16) = .698, p = .001) and a significant positive correlation between the CVLT-II and BVMT-R (r (16) = .50, p = .034), as expected.

Table 5

Pearson's correlations of BICAMS scales with potential confounders

	1	2	3	4	5	6	7
1 HADS-D	-	.720**	.014	.267	-.408	-.190	-.523*
2 HADS-A		-	-.322	.010	-.376	-.510*	-.491*
3 PDDS			-	-.023	-.287	.210	.232
4 FSS				-	-.356	.168	-.365
5 SDMT					-	.429	.698**
6 CVLT-II						-	.503*
7 BVMT-R							-

Note.
* p < .05, ** p < .01, *** p < .001
HADS= Hospital Anxiety and Depression Scale; HADS-D= Hospital Anxiety and Depression Scale-Depression; HADS-A= Hospital Anxiety and Depression Scale-Anxiety; PDDS= Patient Determined Disease Steps; FSS= Fatigue Severity Scale; SDMT= Symbol Digit Modalities Test; CVLT-II= California Verbal Learning Test; BVMT-R= Brief Visuospatial Memory Test-Revised

Intraclass correlation comparing MS HCP scores with TCP

To determine the level of agreement between scorers, HCP raw scores on BICAMS sub-tests were compared with TCP raw scores using ICC. Table 6 illustrates the HCPs' and TCP's mean scores for each sub-test and level of agreement.

The level of agreement between scorers was numerically highest for the CVLT-II and lowest for the BVMT-R. The HCP and TCP scores on all three sub-tests attained ICC values between 0.98 and 1.00, which suggests excellent reliability between scorers (Koo & Li, 2016).

Table 6

Level of agreement between scorers on BICAMS

BICAMS sub-test	HCP raw scores M (*SD*)	TCP raw scores M (*SD*)	Level of agreement (ICC)
SDMT	46.78 (12.63)	46.61 (12.81)	0.999
CVLT-II	52.67 (10.99)	52.50 (10.84)	1.000
BVMT-R	20.00 (8.87)	18.67 (9.22)	0.980

Note.
M= Mean; *SD*= Standard deviation; BICAMS= Brief Cognitive Assessment for Multiple Sclerosis; ICC= Intraclass correlation coefficient; SDMT= Symbol Digit Modalities Test; CVLT-II= California Verbal Learning Test; BVMT-R= Brief Visuospatial Memory Test-Revised

Calculating BICAMS and MSNQ z-scores

Raw scores on the BICAMS sub-tests (Table 7) were converted into *z*-scores (Table 9) based on the normative mean and standard deviation data obtained from a UK control population (Orchard, 2013). The *z*-scores from the three individual sub-tests were then added together to produce a totalled BICAMS *z*-score.

Table 7

Raw scores on BICAMS

	Min	Max	M	*SD*
SDMT	20	65	46.61	12.81
CVLT-II	33	68	52.50	10.84
BVMT-R	6	35	18.67	9.22

Note.
M= Mean; *SD*= Standard deviation; SDMT= Symbol Digit Modalities Test; CVLT-II= California Verbal Learning Test; BVMT-R= Brief Visuospatial Memory Test-Revised

According to published UK norms for BICAMS subscales (Orchard, 2013), seven PwMS were impaired on the SDMT, six were impaired on the CVLT-II and eight were impaired on the BVMT-R.

Raw scores on the three MSNQ-Is (Table 8) were converted into *z*-scores (Table 9) based on the normative mean and standard deviation data from a recent control population (Thomas et al., 2023).

Table 8

Raw scores on MSNQ-Is

	Min	Max	M	*SD*
MSNQ-I 1	1	42	18.22	11.11
MSNQ-I 2	4	37	17.00	9.79
MSNQ-I 3	3	36	20.33	10.18

Note.
MSNQ-I= Multiple Sclerosis Neuropsychological Questionnaire-Informant

Table 9

Z-score descriptives for BICAMS and MSNQ-Is

	Min	Max	M	*SD*
SDMT	-4.31	.29	-1.59	1.31
CVLT-II	-3.01	1.59	-0.45	1.43
BVMT-R	-4.32	1.48	-1.79	1.84
BICAMS total	-11.64	2.06	-3.82	3.84
MSNQ-I 1	-1.65	1.93	-0.15	0.97
MSNQ-I 2	-1.38	1.49	-0.25	0.85
MSNQ-I 3	-1.47	1.40	0.04	0.89

Note.
M= Mean; *SD*= Standard deviation; BICAMS= Brief Cognitive Assessment for Multiple Sclerosis; SDMT= Symbol Digit Modalities Test; CVLT-II= California Verbal Learning Test; BVMT-R= Brief Visuospatial Memory Test-Revised; MSNQ-I= Multiple Sclerosis Neuropsychological Questionnaire-Informant

Differences between BICAMS and MSNQ-I

Difference scores between BICAMS and MSNQ-Is were calculated to determine statistical accuracy of HCPs perception of patients' cognitive status. Difference scores were produced by subtracting MSNQ-I 1, 2, 3 *z*-scores from totalled BICAMS *z*-scores (after Davenport et al., 2022).

To investigate how HCPs' perception of MS patients' cognitive impairment is affected by experiential and objective data, difference scores between totalled BICAMS *z*-scores and MSNQ-I *z*-scores were compared using a repeated measures ANOVA (totalled BICAMS *z*-scores versus MSNQ-I 1, 2, 3).

Table 10

Differences between BICAMS and MSNQ-Is

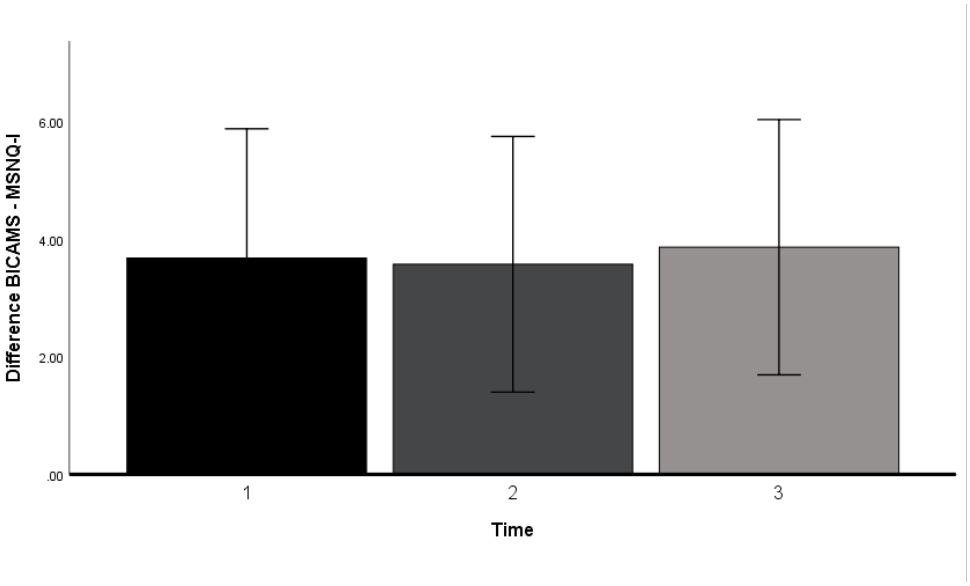
	M	*SD*
BICAMS and MSNQ-I 1	3.68	4.42
BICAMS and MSNQ-I 2	3.57	4.37
BICAMS and MSNQ-I 3	3.86	4.36

Note.
M= Mean; *SD*= Standard deviation; BICAMS= Brief Cognitive Assessment for Multiple Sclerosis; MSNQ-I= Multiple Sclerosis Neuropsychological Questionnaire-Informant

A repeated measures ANOVA was conducted to compare difference scores between totalled BICAMS *z*-scores and MSNQ-I *z*-scores. The results showed that there is no significant difference after experiential evidence or objective tests scores, F (2,34) = 2.79, p = .076. Hence, we fail to reject the null hypothesis. Figure 2, below, visually illustrates the means of the difference scores between BICAMS and MSNQ-Is across three time points – before completing BICAMS, after completing BICAMS and after feedback.

Figure 2

Bar chart comparing means of difference scores between BICAMS and MSNQ-Is



Thematic analysis of qualitative surveys from MS HCPs

The brief qualitative surveys completed by HCPs were analysed using thematic analysis (Braun & Clarke, 2006). Braun and Clarke's six-phase guide to performing thematic analysis was firmly followed. Firstly, HCP survey responses were read and re-read, making note of initial ideas during the process. Secondly, relevant codes were identified from the data set. Next, pertinent codes were organised into overarching themes (Table 11). These themes were checked against the codes to generate a thematic map of the analysis. The specifics of each theme were refined and verified by DL.

Table 11

Emerging themes from HCP surveys

HCP survey items	Overarching themes
Experience of administering BICAMS	a. Time-consuming b. Easier with experience and familiarity c. Preparation helped
Experience of scoring BICAMS	a. Difficulty scoring BVMT-R b. Built confidence
Experience of feeding back on BICAMS	a. Difficult when impairment is present b. Guidance from TCP was helpful

Impact of BICAMS on HCP perceptions of cognitive impairment	a. Awareness of cognitive difficulties in PwMS b. Understanding of confounders

Experience of administering BICAMS

There was a general consensus that BICAMS administration became "easier" and "smoother" as HCPs became more familiar and experienced with administration. After their first time administering BICAMS, one HCP reported "it felt fiddly and difficult to get things running smoothly". After their fifth BICAMS, the same HCP reported "I now feel more confident administering BICAMS. It runs smoothly and generally feels easy to administer". Similarly, another HCP initially described the administration process as "complicated" and "time-consuming". After administering BICAMS to a few patients, this HCP reported "it was easier and felt more fluid as I was more confident with what I was doing". HCPs also reflected that BICAMS administration felt easier if they were "better prepared" for administration beforehand. One HCP reflected that they were initially "disorganised", with another reporting it "took some time".

Experience of scoring BICAMS

One HCP thought the SDMT was the easiest of the subtests to score. Four out of the six HCPs shared that BVMT-R scoring was "difficult", with one HCP describing this subtest as "the hardest one to score". One HCP spoke about this subtest having the "most variability" compared to the other sub-tests and several other HCPs had not realised how "accurate" the BVMT-R scoring had to be. Several HCPs reflected that they were "overgenerous" with their scoring on the BVMT-R in particular. One HCP acknowledged "I may have given the patient a bit of leeway with BVMT-R".

Similar to BICAMS administration, HCPs reflected on how their confidence in scoring has grown as they have gained more experience with scoring BICAMS. After scoring three BICAMS, one HCP

said, “I feel more confident at scoring now”. A few HCPs reported that receiving feedback on previous scoring made it easier. However, there was a sense that several HCPs thought they still struggled with scoring on the BVMT-R. One HCP noted that while BICAMS became easier to administer and score, the BVMT-R was “still a struggle”. Likewise, another HCP said they “still hesitate with the visual memory test scoring”.

Experience of feeding back on BICAMS

HCPs found feeding back more difficult if the patient had shown impairment in any of the domains (“I found this difficult as the patient was impaired across all three domains”). One HCP noted that “finding the right wording is challenging” when feeding back to patients with impairment. While several HCPs spoke about the difficulty in feeding back when impairment was present, another HCP noted how useful it was to provide feedback as the patient felt “justified” and “had strategies they could employ”. Another expressed that feedback guidance from the TCP was helpful when it came to HCPs feeding back results to patients (“receiving guidance on feeding back was useful”). Another HCP expressed “I felt confident giving feedback due to the detailed feedback I received”.

Impact of BICAMS on HCP perceptions of cognitive impairment

All six HCPs acknowledged that BICAMS had impacted on their perceptions of cognitive impairment. HCPs reported that BICAMS had increased their awareness of cognitive difficulties and are now “sensitive to subtle changes”. One HCP expressed they have “picked up on issues that were not necessarily apparent in everyday interactions”. Another noted “it has given me greater awareness of how patients are impacted by cognitive impairment and how we can support them”. Another HCP said she is now more aware of how “complex” and “nuanced” MS cognition can be.

BICAMS had also improved HCPs’ knowledge and understanding of confounders of subjective cognitive complaints. One HCP said the patient expressed concerns about their cognition even though

BICAMS showed no impairment across the three sub-tests, reporting that this could potentially be "fatigue-related". This HCP shared "I have realised how fatigue and other factors can mimic cognitive impairment". Similarly, another HCP said, "I think people feel their cognitive impairment is worse than what it is".

Discussion

Interpretation of findings

Prevalence of impairment in sample

The mean BICAMS scores on each subscale were similar to other published means (e.g., Drulović et al., 2022; Gaughan et al., 2021). According to published UK norms (Orchard, 2013), seven PwMS were impaired on the SDMT, six were impaired on the CVLT-II and eight were impaired on the BVMT-R. The prevalence of cognitive impairment across the three subscales were in line with prevalence rates reported in other studies (e.g., Ozakbas et al., 2017; Walker et al., 2016). It is fair to conclude that our MS sample was broadly comparable to other studies. The apparent overrepresentation of females with MS (11 out of 18) is not concerning. It is important to consider that this female recruitment bias is a reflection of how common MS is in females compared to males, with a female to male sex ratio of approximately 3:1 (McGinley et al., 2021).

Correlations of BICAMS scales with potential confounders

Correlations of BICAMS sub-test scores with depression, anxiety, disability, and fatigue were calculated to identify potential associated factors. Several studies highlight the importance of accounting for depression, anxiety and fatigue in PwMS given they are all potential confounders of objective impairment (Davenport et al., 2022; Thomas et al., 2023). Our findings showed a significant correlation between reported depression symptoms and visual memory function. Furthermore, reported

anxiety symptoms were significantly correlated with both visual and verbal memory function. Collectively, these findings were, in part, unsurprising given that the association between depression, anxiety and objective cognitive test performance is highly reported in the evidence base (Kalron et al., 2018; Marrie et al., 2020; Morrow et al., 2016). However, depression did not correlate with the SDMT or CVLT-II. This is inconsistent with previous findings (e.g., Biasi et al., 2023; Leavitt et al., 2020) reporting an association between depression and information processing speed. The lack of association could be explained by the sample falling within the normal range for HADS depression, which is considered atypical as depression is a prevalent mental health problem in PwMS (Boeschoten et al., 2017). HCP selection of MS patients may have skewed the sample towards good mental health status. Furthermore, a small sample size may have resulted in an underrepresentation of mood disorders, suggesting that perhaps a larger, more comprehensive sample may have generated different findings.

Our findings showed that fatigue did not correlate with cognitive performance on the three BICAMS scales. Since high levels of fatigue were reported in the sample, it was expected that this would yield an association between subjective fatigue and objective cognition in line with previous findings (Bellew et al., 2022; Eizaguirre et al., 2020). In addition, no association was found between physical disability and performance on BICAMS. Cognitive impairment is thought to manifest in progressive forms of the disease (Johnen et al., 2017; Peres et al., 2022), yet these phenotypes were underrepresented in our sample and may have explained this lack of association. Or perhaps the small numbers did not provide adequate power to illustrate these associations.

Importantly, several recent studies have outlined factors associated with cognitive impairment in MS which were not explored in this study e.g., pre-morbid IQ, lesion location, neuroendocrine factors, potential side effects of DMDs (Margoni et al., 2023; Stein et al., 2023). For example, premorbid cognitive functioning (Stein et al., 2023) and perceived social support (Rafizadeh et al., 2023) are considered protective factors against cognitive decline. Thus, with so many unseen processes

contributing to cognitive impairment, it is difficult to determine cognitive status in the broader context of the disease and account for all associated factors involved in the complex picture of MS cognition.

Primary research question

Assessing MS-related cognition is crucial given the breadth of literature indicating a host of poor outcomes relating to cognitive impairment in PwMS. In response to this, BICAMS was developed as a brief tool to assess and monitor cognition in MS clinics and was designed to be used by a range of HCPs (Langdon et al., 2012), but despite this, cognitive evaluation is often performed by neuropsychologists (Bakirtzis et al., 2018). Ideally, all MS HCPs should be addressing cognition as part of their healthcare provision, including nurses (e.g., Slough & Brownlee, 2021) and physiotherapists (e.g., Ghahfarrokhi et al., 2022). In light of this, the primary aim of the study was to assess the accuracy of BICAMS when scored by UK MS HCPs.

The HCP and TCP scores on all three BICAMS sub-tests revealed ICC values between 0.98 to 1.00 which indicates excellent reliability between scorers. The level of agreement between scorers was numerically highest for the CVLT-II, followed by the SDMT, but overall, the ICC's were similar. The six HCPs had no previous experience of using BICAMS prior to this study, so an excellent reliability was a surprising but positive statistical finding. This was the first study to assess the accuracy of scoring on BICAMS by HCPs. In one study, MS HCPs completed BICAMS having been provided with extensive training in BICAMS administration. However, the completed test forms were reviewed and scored by two independent psychologists (Renner et al., 2020). Thus, evidence was still needed to confirm clinical practicability of HCPs using BICAMS. To our knowledge, only one study has explored the feasibility of using BICAMS with investigators who were neither psychologists nor medical doctors (Penner et al., 2021), although a number of research studies have reported successful data collection by neurology research fellows (e.g., Campbell et al., 2016). However, other HCPs such

as nurses, physiotherapists and occupational therapists are the target users for BICAMS in routine MS clinic settings. Penner et al (2021) trained physician assistants to administer and score BICAMS and their BICAMS use was subsequently evaluated by neuropsychological experts. Contrary to our finding, serious mistakes in application and scoring of BICAMS were found in 50.3% of cases.

In our study, HCPs were MS specialists with considerable clinical experience of MS (8 years of experience working as an MS HCP, on average, with one HCP reporting 21 years of experience). They also had clinical knowledge and experience of MS cognition. HCPs were provided with BICAMS training in small groups of three to four, which allowed for us to accommodate further questions, discussions, reflections and role-plays to practice administration and scoring. Additionally, HCPs were interested in BICAMS and wanted to acquire skills to assess MS cognition in their clinic, whereas physician assistants were recruited from 65 neurological centres to be participants in a research study (Penner et al., 2021).

Notably, agreement between scorers was numerically lowest for the BVMT-R, and this was reflected in the HCP qualitative survey. Four HCPs shared that BVMT-R scoring was “difficult”, with one HCP describing this subtest as “the hardest one to score” since it has the “most variability”. Several HCPs expressed that they were “overgenerous” and had “given a bit of leeway” with the BVMT-R. This is highlighted in the mean HCP raw score for the BVMT-R (20), which was higher than the mean TCP raw score (18.67). Similarly, the study assessing level of agreement between two independent psychologists observed the highest frequency of raw score differences on the BVMT-R, compared to the other sub-tests (Renner et al., 2020). Whilst agreement on scoring was compared between two psychologists, it reinforces the variability of scoring on BVMT-R and suggests that training and feedback should aim to focus more on the BVMT-R.

Exploratory research question

The study explored whether MS HCPs' perception of MS patients' cognitive function changed following completing, scoring, and feeding back on BICAMS. Changes in HCP perception of MS patients' cognitive function was measured using the MSNQ-I interspersed with BICAMS completion, scoring and feedback. The findings showed no significant changes in accuracy of HCPs perception of patients' cognitive status (versus BICAMS objective scores) across the three time points. The non-significant findings do not supplement existing knowledge on meta-cognition, specifically, how new evidence can lead to PwMS and HCPs re-evaluating PwMS' cognition and adjusting their internal model of PwMS' cognitive abilities. The lack of significance could be explained by several reasons. Firstly, the MNSQ-I is a validated measure of informant perception of cognitive performance in PwMS, however this measure is typically used with relatives/carers (Benedict et al., 2003), which may also explain the insignificant findings. There is also the question of how sensitive the MSNQ-I is to change, which has not been clearly determined.

Though, importantly, all six HCPs acknowledged, on the HCP qualitative surveys, that BICAMS had impacted on their perceptions of cognitive impairment. Specifically, it had increased their awareness of cognitive difficulties and how patients are impacted by cognitive impairment. One HCP expressed they have "picked up on issues that were not necessarily apparent in everyday interactions", highlighting the invisibility of cognitive impairment reported in the literature (Lakin et al., 2021). This reinforces the need for objective, accurate cognitive assessment to tackle the invisibility of cognition in clinical practice (Bakirtzis et al., 2018; Kalb et al., 2018; Morrow et al., 2022). Thus, the lack of statistical significance could relate to issues with the scale psychometrics or too few participants for power.

Qualitative surveys from MS HCPs

The present study sought to explore HCPs experiences of administering, scoring and feeding back on BICAMS as well as impact on perceptions of cognitive impairment. This information would inform

guidance offered to MS HCPs regarding preparation before assessment and feedback. All six HCPs completed the qualitative survey after feeding back to each patient (with a total n of 18). There was a general consensus across HCPs that administration and scoring felt easier the more experience they had with BICAMS. There was also an acknowledgement of the benefits to receiving feedback on scoring as this placed confidence in HCPs to deliver feedback on cognitive test performance to PwMS. All reported that BICAMS had changed their perceptions of cognitive impairment and had increased their aware of submit cognitive changes in MS. BICAMS had also improved their knowledge and understanding of confounders of self-reported cognitive complaints, including fatigue. Overall, HCPs were receptive to BICAMS, and this was clear from the training sessions where HCPs showed an enthusiasm to use BICAMS in their everyday clinical practice.

Strengths

There are some strengths of the present study which should be acknowledged. First, to ensure a diversity of viewpoints and to maximise the generalisability of results, MS HCPs and patients were recruited from a range of services (district general hospital, community service and registered charity), across different locations in the South East of the UK (Sussex, Dartford, and Guildford). Data from various services provided a broader service representation, including underserved populations. Secondly, MS HCPs involved in the study included a mixture of professions (nurses and physiotherapists) to provide a representative sample of HCPs and accommodate membership of MS support teams. Thirdly, the inclusion of study-specific qualitative surveys enabled HCPs to speak about their experiences of administering and scoring BICAMS, giving feedback, and whether these experiences had changed their perceptions of MS cognition. These surveys provided rich, phenomenological data, allowing HCPs to elaborate on information that would otherwise not be possible using quantitative measures. Thematic analysis allowed us to capture emerging themes, providing a deeper understanding of the topic of interest.

Limitations

There were also some noteworthy methodological limitations to the study. First and foremost, the study comprised 18 PwMS and thus may lack generalisability given the small sample. The power analysis was performed solely for the purposes of the primary objective, to assess level of agreement between scorers. Therefore, it may have been possible that we had too few participants for the exploratory analyses to generate statistically significant findings. Furthermore, a study-specific, non-validated survey was designed to explore HCPs' experiences of BICAMS and impact on patient cognition. Thus, there exists a level of researcher imposition, whereby, the researcher makes their own assumptions about what is considered important or not when developing the survey. Further, the measures of mood, disability and fatigue relied on self-report. The drawbacks of self- report measures in research have been widely discussed in the literature (e.g., Demetriou, Ozer and Essau, 2015). For example, these responses can be influenced by patients' honesty, understanding of the questions, assumptions or hypotheses regarding the expected or target response, and social desirability bias. Importantly, the current clinical classification of MS phenotypes used in this sample is currently under scrutiny in light of advancements to the understanding of factors contributing to disability accumulation (Granziera et al., 2023; Tur et al., 2023). It should also be noted that BICAMS does not take into account premorbid abilities. PwMS with high premorbid cognitive functioning may notice cognitive difficulties in their daily life whilst falling within the normal range on cognitive testing (Stein et al., 2023). Indeed, this can be problematic in ascertaining whether cognitive functioning has declined relative to a patient's premorbid abilities. BICAMS was designed to be used globally by HCPs who acquire no formal psychometric training. Thus, this compromise was judged necessary when developing BICAMS. This makes it more likely to give a false negative which a sophisticated assessment strategy with highly trained personnel could avoid.

BICAMS critique

It is also important to acknowledge the shortcomings of BICAMS as a cognitive assessment. Firstly, BICAMS only assesses information processing speed, visual and verbal memory. It can therefore be criticised for not including a measures of executive functioning, such as those included in MACFIMS (Gromisch et al., 2018). In devising BICAMS, there was a consensus that assessments of executive functioning were too long and too challenging to find culturally equivalent versions of executive functioning tests across different countries (Langdon et al., 2012). Secondly, BICAMS originates from a western psychometric context and the committee comprises white Europeans and North Americans. Thus, BICAMS is grounded in a white Western milieu and does not adequately represent non-western cultural, racial, ethnic, socio-economic, and educational profiles. This suggests that the international application of BICAMS should consider national differences and continue to collect national norms (Smerbeck et al., 2017). Thirdly, neuropsychological test performance can be confounded by a range of factors, such as concurrent medication, fatigue, and MS physical symptoms (Langdon et al., 2012). For example, severe motor impairment may impact performance on the BVMT-R (Sumowski et al., 2018) and one validation study excluded patients who had a severe hand disability for this reason (Niino et al., 2017). Finally, there is limited evidence that BICAMS has ecological validity, however, in one BICAMS validation study, all three subtests emerged as significantly correlated with employment (Dusankova et al., 2012). Further, a handful of studies have shown that the SDMT can significantly predict employment status in PwMS (e.g., Campbell et al., 2017; Strober et al., 2014).

Clinical implications and future directions

BICAMS was designed to be used globally by MS HCPs who acquire no formal psychometric training. While there is mounting evidence on the validity and feasibility of BICAMS administered by doctors and psychologists internationally (Potticary & Langdon, 2023), there is little on how BICAMS is used by HCPs specifically. Our primary findings demonstrate that HCPs are accurate at scoring BICAMS, thus supporting its use by a range of professionals within the MS multidisciplinary team including nurses and physiotherapists. Prior to our study, the three participating centres were not

routinely assessing cognition yet all HCPs recognised the importance of embedding cognitive testing in their clinical practice. HCPs are therefore encouraged to receive training in BICAMS administration, scoring and feedback to support the routine assessment and monitoring of cognition in PwMS as per recommendations from NICE (2022) and AAN (2014). Routinely assessing cognition can cultivate an awareness of MS cognition, shed light on invisible symptoms (Lakin et al., 2021), legitimise patient experiences and prompt appropriate management (Jarrett, 2022; Longley, 2022). Further, using BICAMS as a brief screening tool can prompt referral for further targeted assessment including more comprehensive neuropsychological batteries to capture a detailed picture of cognitive impairment in PwMS.

In relation to the exploratory analysis, the study did not show any significant changes in HCPs' perceptions of patient cognitive impairment. Future research should aim to acquire a larger sample size to evaluate further the effects of completing BICAMS and receiving feedback. It will also be important to perform an appropriate power analysis for this, to ensure statistically relevant findings.

Conclusion

Cognitive impairment negatively impacts quality of life, yet it remains an overlooked and under-diagnosed symptom in PwMS. Assessment of cognition should therefore form part of MS routine consultation to facilitate further targeted assessment and treatment, including cognitive rehabilitation and lifestyle adjustments. The primary aim of the study was to examine the accuracy of BICAMS when scored by UK MS HCPs and the impact on MS HCPs' and MS patients' perception of cognitive impairment. The findings demonstrated excellent reliability between scorers on BICAMS and demonstrates that HCPs are accurate at completing and scoring BICAMS. BICAMS was designed to be completed by HCPs who may not acquire specific training in cognitive assessments, allowing more clinics to address cognition. Thus, these findings encourage HCPs to implement BICAMS in their

clinical practice. However, difference scores between BICAMS and MSNQ-Is did not change significantly after BICAMS completion or knowledge of BICAMS objective test scores. Future studies should endeavor to explore potential changes in perceptions of cognitive impairment, possibly involving more targeted training and education.

Chapter 3: A Systematic Review and Meta-analysis of the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) International Validations

Abstract

Cognitive impairment is a prevalent and debilitating symptom of MS, yet it is often overlooked by health professionals. There is an increasing need to include formal cognitive assessment into routine clinical practice for PwMS. BICAMS was developed in 2012 as part of an international endeavour to regularly screen and monitor cognition in MS patients. Against this backdrop, this systematic review and meta-analysis aimed to identify, synthesise, and critically appraise current literature on the international validations of BICAMS.

The literature search was conducted using the PubMed, PsycINFO and Web of Science electronic databases in August 2022. Quantitative, peer-reviewed adult studies, which followed the BICAMS international validation protocol and were published in English, were included.

The search identified a total of 203 studies, of which 26 were considered eligible for inclusion. A pooled sample of 2,833 adults with MS and 2,382 healthy controls (HC) were included in this review. The meta-analysis showed that BICAMS identified impaired cognitive functioning in adults with MS compared to HC. This was the case for all three subtests: information processing speed ($g = 0.854$, 95% CI = 0.765, 0.944, $p < 0.001$), immediate verbal recall memory ($g = 0.566$, 95% CI = 0.459, 0.673, $p < 0.001$) and immediate visual recall memory ($g = 0.566$, 95% CI = 0.487, 0.645, $p < 0.001$).

BICAMS has been validated in 26 countries to date. BICAMS is shown to be a valid and feasible international MS cognitive assessment. Relapsing-remitting MS was over-represented, possibly

leading to an underestimate of MS cognitive decline. Research sites, being largely specialist centres, and selective recruitment strategies may also limit the generalisability of results. BICAMS is a valid and feasible international MS cognitive assessment.

Keywords: Multiple sclerosis, Brief International Cognitive Assessment for Multiple Sclerosis, BICAMS, Cognition, Systematic review, Meta-analysis

Introduction

Overview

Despite its ubiquitous negative impact on the lives of PwMS, cognition in MS is often not prioritised by healthcare professionals. The assessment of cognitive functioning is undervalued and poorly managed in routine MS clinical practice (Kalb et al., 2018). BICAMS attempts to meet this challenge by delivering a brief and viable, psychometrically sound, international measure designed to routinely screen cognition in clinical settings (Langdon et al., 2012). The aim of the present systematic review is to integrate findings from BICAMS' international validations to date and evaluate its feasibility and psychometric properties in different cultures.

MS neurology

MS is a chronic autoimmune-mediated disease of the central nervous system, involving inflammatory and degenerative processes (Dobson & Giovannoni, 2018). This can manifest a constellation of symptoms in the physical, sensory, psychological, and cognitive domains. MS affects over 2.8 million people worldwide (Walton et al., 2020) and is typically diagnosed in adults aged 20 to 30 years (McGinley et al., 2021). The course of the disease is highly variable and has been categorised into different clinical phenotypes, with RRMS being the most frequent. In RRMS, clinical symptomatic relapses lasting 24 hours or more, are followed by periods of remission.

RRMS may later develop into SPMS which involves a gradual accumulation of disability with or without periods of remission. PPMS is experienced by a small proportion of patients and involves progressive disease from onset, independent of relapses. When patients experience an initial, single clinical episode of clinical demyelination but are yet to fulfil criteria for a diagnosis of MS, this is known as CIS. Treatment for MS involves DMDs, symptom management, psychological support, and lifestyle adaptations (McGinley et al., 2021).

MS cognition

Cognitive impairment is a prevalent and debilitating symptom of MS, affecting between 40-65% of patients (Benedict et al., 2020). It can be observed in all phenotypes, including CIS (Brochet & Ruet, 2019), but severe cognitive impairment predominates in the progressive forms of the disease (Ruano et al., 2016). There are often marked deficits in information processing speed, attention, working memory and executive functioning (Podda et al., 2021; Sumowski et al., 2018). It has a profound negative impact on quality of life (Benedict et al., 2020), including activities of daily living (Gil-González et al., 2020), employment (Clemens & Langdon, 2018; Kavaliunas et al., 2022), disease management (Bruce et al., 2018; Gomes et al., 2022), personality (Roy et al., 2018) and driving safety (Krasniuk et al., 2021). Given the significant adverse consequences of cognitive difficulties, early identification of cognitive status is needed to facilitate optimal management and preserve quality of life in PwMS (Langdon & Young, 2023; Oset et al., 2020). With reference to treatment of MS cognition, there is growing evidence that DMTs are helpful in reducing cognitive decline (Landmeyer et al., 2020; Langdon et al., 2021) as well as cognitive rehabilitation (Brochet, 2021; Chen et al., 2021) and lifestyle interventions (Brandstadter et al., 2019).

MS cognition is overlooked

Cognitive impairment remains a neglected and under-diagnosed symptom of MS. The "invisibility" of cognitive difficulties has meant it is often overlooked by family members,

colleagues, and healthcare professionals since there is no obvious external disability (Walker et al., 2019). PwMS may find certain "invisible" symptoms difficult to discuss with their healthcare professional, which can delay assessment and treatment of cognition (Lakin et al., 2021). As a result, patients feel they are not understood and continue to live with hidden needs (Parker et al., 2021). At routine consultation, neurologists are poor at identifying MS-related cognitive impairment (Romero et al., 2015) and instead, prioritise physical needs such as ambulation issues, imbalance, falls and urinary incontinence. Conversely, patients consider non-physical symptoms such as cognitive and memory problems to be more significant (Marin et al., 2021). This disparity is also evident in treatment goals, as patients report goals around maintaining memory and cognitive ability whilst, for healthcare professionals, goals around physical health take precedence (Col et al., 2018). Similarly, disability outcome measures used in MS clinical trials place emphasis on physical disability with minimal attention given to cognition (Pardo et al., 2022; Uitdehaag, 2018). Many of these trials are not powered for cognitive outcomes, which reflects the lack of awareness and provision to target cognitive impairment in MS. MS patients also recognise the importance of cognition and feel it should receive equal attention to physical symptoms with respect to research, treatment, and support throughout the disease course (Mortensen et al., 2020).

Routine cognitive testing is needed

There is a growing consensus, across MS patients and professionals, that routine cognitive testing should form part of clinical practice to inform management (Elwick et al., 2021). Despite this, objective cognitive testing is rarely delivered in routine clinical practice (Kalb et al., 2018; Klein et al., 2018). NICE (2022) and AAN (2014) recommend an annual cognitive assessment for MS. Regularly monitoring cognition in MS patients can prompt appropriate treatment planning as well as targeted specialist referrals for follow-up expert cognitive assessment and management (Meca-Lallana et al., 2021; Thrue et al., 2021). Once cognitive impairment is identified, healthcare professionals can modify their interaction style with patients and monitor increased risks associated

with cognitive impairment such as driving accidents, risk of falls, unemployment, and poor disease management (Langdon & Young, 2023). Awareness of cognitive impairment also allows the clinic to triage between cognition, fatigue, and depression so they can put appropriate management strategies in place. Healthcare professionals can complete a cognition audit of exacerbating and protective factors and potentially identify breakthrough disease which can instigate other investigations and treatment escalation. They can educate the patient and their carer about cognition in MS as well as brain health, explaining lifestyle choices that can protect cognition.

Self-report measures for MS cognition

A handful of reliable and validated self-report measures are available to assess cognition in MS. The MSNQ (Benedict et al., 2003) is a 15-item measure of neuropsychological competence during activities of daily living and is validated for patient self-report (MSNQ-P) and informant-report (MSNQ-I). Another self-report tool is the Perceived Deficits Questionnaire (PDQ; Sullivan et al., 1990), a 20-item measure of cognitive dysfunction in MS which forms part of the Multiple Sclerosis Quality of Life Inventory (MSQLI; Fischer et al., 1999). These screening tools only offer a rudimentary estimate of cognitive functioning and cannot replace a full neuropsychological assessment.

Confounders of self-reported cognition

Relying on patient self-disclosure of cognitive difficulties can hinder accurate identification of cognitive impairment because self-report, alone, is not an accurate means of assessing objective cognitive status (McNicholas et al., 2020; Walker et al., 2019). Self-perceived cognition can be confounded by depression (Portaccio, 2016), anxiety (Vissicchio et al., 2019), perceived stress (Beier et al., 2015), sleep problems (Hughes et al., 2017), and self-efficacy (Hughes et al., 2015). Patient self-report of cognitive impairment on the MSNQ-P, for example, have been significantly correlated with depressive symptoms but poorly correlated with objective cognitive performance

(Benedict et al., 2004; Nauta et al., 2019). Similar findings have been observed with the PDQ (Henneghan et al., 2017; Lovera et al., 2006). Confounders can reduce the clinical utility of self-report measures (Strober et al., 2016), warranting objective cognitive assessments to discriminate between cognitive deficits and psychosocial factors (Oreja-Guevara et al., 2019; Ruet & Brochet, 2020).

Neuropsychological batteries for MS cognition

Over the last 30 years, there has been a surge in the development of neuropsychological batteries to assess MS cognition. The BRB-N (Rao et al., 1990) comprises the Selective Reminding Test (SRT; to assess verbal memory), the Symbol Digit Modalities Test (SDMT; to assess information processing speed), the Paced Auditory Serial Addition Test (PASAT; to assess information processing speed), the 10/36 Spatial Recall Test (SPART; to assess visuospatial memory), and the Word List Generation Test (WLG; to assess semantic verbal fluency). This battery takes 45 minutes to complete. There is also a short, modified version of the BRB-N called the Brief Battery of Portaccio which consists of the SRT, SDMT and PASAT (Portaccio et al., 2009).

MACFIMS (Benedict et al., 2002) was proposed by an expert panel of psychologists and neuropsychologists in 2001 in an effort to develop a more comprehensive battery to assess MS cognition. This battery takes 90 minutes to complete and consists of the PASAT and SDMT (to assess information processing speed), in addition to the CVLT-II (to assess verbal memory), the BVMT-R (to assess visual memory), the Delis–Kaplan Executive Function System Sorting Test (D-KEFS; to assess executive functioning), the WLG and the Judgment of Line Orientation (JLO; to assess visuospatial skills).

Towards the development of a brief screening tool

Assessing cognitive impairment traditionally requires extensive neuropsychological testing, which is costly, time-consuming and is not routinely available outside specialist centres. It has required specialist expertise in test selection, administration, and interpretation, yet there is limited availability of neuropsychologists in most MS centres (Meca-Lallana et al., 2021). Thus, these batteries are not viable for routine clinical assessment. These constraints warranted the need for a brief, feasible, well-validated measure that could be used clinically by a range of health professionals to capture cognitive impairment in MS patients.

The development of BICAMS

In 2012, an international consensus committee of 12 leading international MS experts convened to develop a review process to select scales that could be combined to produce a feasible, valid, and international MS cognitive assessment. The committee examined the available cognition scales from the literature, as well as their psychometric qualities and clinical applicability. This approach took account of both the psychometric standards (reliability, validity, and sensitivity) and the pragmatic standards (international applicability, ease of administration, patient acceptability, and contextual feasibility). The committee agreed that the assessment tool should assess information processing speed, verbal memory, and visual memory (immediate recall) and prompted the selection of the following subtests: the SDMT (oral form), the first five learning trials of the CVLT-II, and the first three learning trials of the BVMT-R (Langdon et al., 2012). These three subtests are highly reliable and sensitive to MS cognitive impairment.

BICAMS scales

The SDMT (Smith, 1982) is a measure of information processing speed comprising a key of single numbers, each paired with an abstract symbol. The patient is presented with rows of symbols that are arranged pseudo-randomly. They are required to say the correct number for each of the symbols as fast and as accurately as they can in 90 seconds, using the key provided.

In the CVLT-II (Delis et al., 2000), a measure of verbal memory, only the first five learning trials are administered. The patient is read a 16-item word list at a slightly slower rate than one item per second. The list is read aloud five times and the patient is instructed to recall as many of the items as possible, in any order, across the five learning trials.

In the BVMT-R (Benedict, 1997), a measure of visual memory, only the first three learning trials are administered. This test involves presenting to patients a 2x3 stimulus array of abstract geometric figures across three learning trials, each 10 seconds in length. The array is then removed from the patients view, and they are instructed to draw the geometric figures in the correct position from memory. The components of BICAMS can be compared with the BRB-N and MACFIMS in Table 12. The SDMT shows high sensitivity for MS-related cognitive dysfunction and is now widely acknowledged as the gold standard for a quick cognitive screening (Portaccio & Amato, 2022).

Table 12

Components of BRB-N, MACFIMS and BICAMS

	BRB-N	MACFIMS	BICAMS
Information processing speed	SDMT	SDMT	SDMT
Working memory	PASAT	PASAT	
Verbal memory	SRT	CVLT-II	CVLT-II (first 5 trials)
Visuospatial memory	SPART (10/36)	BVMT-R	BVMT-R (first 3 trials)
Executive functioning		D-KEFS Sorting Test	
Verbal fluency	WLG	WLG	

Visuospatial perception	JLO

Note.
BRB-N= Brief Repeatable Battery of Neuropsychological Test; MACFIMS= Minimal Assessment of Cognitive Function in MS; BICAMS= Brief Cognitive Assessment for Multiple Sclerosis; PASAT= Paced Auditory Serial Addition Test; SRT= Selective Reminding Test; SPART= 10/36 Spatial Recall Test; SDMT= Symbol Digit Modalities Test; CVLT-II= California Verbal Learning Test; BVMT-R= Brief Visuospatial Memory Test-Revised; D-KEFS= Delis–Kaplan Executive Function System; WLG= Word List Generation; JLO= Judgment of Line Orientation

Recommendations for routine clinical use

BICAMS has been recommended as a 15-minute international measure to routinely screen and monitor cognition in MS patients (Langdon et al., 2012). It was designed for healthcare professionals who may not acquire specific training in cognitive assessments, allowing more clinics to address cognition. This brief assessment tool does not require any special equipment beyond a pen, paper, and stopwatch and therefore allows cognition to be tested inexpensively. BICAMS can be easily implemented into routine clinical practice across centres and countries internationally (Langdon et al., 2012). The committee have also published an international validation protocol, to guide national validation studies.

International validity of BICAMS

BICAMS has been validated in 26 countries to date, including Argentina, Belgium, Turkey, and Japan (e.g., Corfield & Langdon, 2018). These national studies have investigated the validity and reliability of BICAMS in different cultures and language groups, and that its sensitivity to cognitive impairment, in comparison with lengthy and expensive “gold standard” batteries (Dusankova et al., 2012). The world leader in setting standards for clinical care, AAN, has recommended BICAMS in their Quality Measurement Sets for MS in both 2014 and 2020 (AAN, 2014). The Canadian Guidelines for MS Treatment endorsed BICAMS in 2020 (Freedman et al., 2020) and over 20 peer

review papers in international clinical neurology journals, arbiters of clinical practice, also recommend BICAMS for routine cognitive assessment in MS clinics (e.g., Artemiadis et al., 2021).

How BICAMS can improve clinical practice

Traditional assessments of MS cognition require extensive materials and expertise to administer; they are time-consuming and are not routinely available outside specialist centres. BICAMS, however, reduces the cost, time and training required to assess cognition in PwMS, compared to the BRB-N and MACFIMS (Table 13). BICAMS has increased both the skills of healthcare professionals and the awareness of cognition among healthcare services, leading to better management. It is available for international use and can be easily performed in a clinical setting to routinely screen and monitor cognitive status in MS patients. Embedding BICAMS into routine clinical practice facilitates measuring, understanding, and addressing cognitive status in MS (Bakirtzis et al., 2018).

Table 13

Comparison of BRB-N, MACFIMS and BICAMS

	BRB-N	MACFIMS	BICAMS
Administration time required	45 minutes	90 minutes	15 minutes
Neuropsychologist expertise required	Yes	Yes	No
Extensive test materials required	Yes	Yes	No

Note.
BRB-N= Brief Repeatable Battery of Neuropsychological Test; MACFIMS= Minimal Assessment of Cognitive Function in MS; BICAMS= Brief Cognitive Assessment for Multiple Sclerosis

The international adoption of BICAMS

BICAMS has been adopted by the international MS community. For example, the Arabic version of BICAMS represents the most used cognitive battery for assessing MS cognition in the Arab world (Paul et al., 2019). It has an international reach, with 11,000 patients routinely assessed every year. There has been a systematic review of the first 16 national validation studies on BICAMS (Corfield & Langdon, 2018). However, there have since been additional national validation studies, warranting an updated systematic review of the validation literature and international findings.

The aim of the present systematic review and meta-analysis was to identify, synthesise and critically evaluate current literature on the progress of BICAMS in meeting the objectives of global collaboration and a credible international validation protocol.

Method

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed as a guide for standardised conduct and reporting of the current systematic review and meta-analysis (Moher et al., 2009). Studies were identified using three databases – PubMed, PsycINFO and Web of Science. Boolean search terms were developed and used to identify studies examining the validity of BICAMS in August 2022, with the advice and guidance from Deborah Phillips at RHUL Library Services (Table 14). Search terms were informed by initial searches and developed further during the process of the review, to ensure that all relevant articles were identified.

Table 14

Search Terms for Systematic Review

Search Terms
"Multiple Sclerosis" OR "MS" OR "Clinically Isolated Syndrome" OR "CIS"
AND
"Brief International Cognitive Assessment for Multiple Sclerosis" OR "BICAMS"
AND
"Validation" OR "International Validation" OR "Validity" OR "Sensitivity"

Eligibility criteria

To refine the studies which were included as part of the international validation of the BICAMS protocol, only the following eligibility criteria were applied. The inclusion criteria for the studies in the present review were as follows: (a) studies which were undertaken as part of the international validation of the BICAMS protocol (b) quantitative studies (c) peer-reviewed studies with no date restriction which are written in the English language and (d) samples including adults with any clinical subtypes of MS and CIS. The exclusion criteria were studies which included BICAMS but were not part of the international validation of the BICAMS protocol.

The additional criteria for inclusion in the meta-analysis were as follows: (a) studies including an HC comparison group and (b) studies reporting standard quantitative information based on the SDMT, CVLT-II and BVMT-R subscales (mean, standard deviation, and sample size), or appropriate substitute scales, of the MS and/or CIS, and HC comparison groups.

Data extraction

One reviewer (HP) extracted data from the studies directly into tables made specifically for the current review and this was examined and verified by a second reviewer (DL). Data on study characteristics, sample demographics and patient disease information were extracted from the 26 short-listed studies.

Study characteristics included the name of the first author, year of publication, and country. Sample demographic information about the MS and HC sample included number of participants, age, gender, education, and employment. Finally, patient disease information included MS phenotype, disease duration, and Expanded Disability Status Scale (EDSS; Kurtzke, 1983) score. Data on correlations between BICAMS scores on each subtest and patient variables (specifically age, disease duration, EDSS score, education, and employment) were also extracted for the purposes of the review.
For the meta-analysis, the standard quantitative information based on the subtests of SDMT, CVLT-II and BVMT-R (mean, standard deviation, and sample size) of the MS cases and HC comparison group were extracted for baseline assessments of BICAMS. Data on the percentage of those who emerged as impaired on cognitive functioning on atleast one subtest were also extracted, along with the sensitivity and specificity of BICAMS (where reported).

Quality assessment

Two reviewers (HP and KM) independently assessed the quality of the retrieved articles using the Effective Public Health Practice Project (EPHPP), and any disagreements were discussed and resolved. This quality assessment tool assigns ratings to quantitative studies in 6 categories: study design, withdrawals and dropouts, data collection, selection bias, blinding for controlled trials and confounders. Each category is assigned a mark ranging from ‘strong’, ‘moderate’ and ‘weak’. A final quality rating is derived from the individual ratings of the categories.

Statistical analysis

The meta-analysis was conducted using the Comprehensive Meta-Analysis (CMA; Version 3) software (Borenstein, 2005). Three individual analyses were performed based on the average scores of the SDMT, CVLT-II and BVMT-R subtests for both groups (MS and HC). Effect sizes were calculated as standardised mean differences with Hedges *g* using the following interpretation: 0.2 = small; 0.5 = medium; 0.8 = large (Cohen, 1988). Hedges *g* was used to measure the effect size for

the difference between means as opposed to Cohen's *d* because it offers the same interpretation whilst correcting any biased estimates of effect sizes that occur from small sample sizes. Thus, it is recommended to use Hedges *g* to calculate effect size when two sample sizes are not equal (Cumming, 2013).

The meta-analysis employed a random-effects model because it estimates the mean of a distribution of effects as opposed to one true effect (Borenstein et al., 2009; Riley et al., 2011) and the number of studies are large enough i.e., more than five studies. Compared to a fixed-effect model, this model yields a wider confidence interval (CI) when there is notable statistical heterogeneity among the effect sizes (Tufanaru et al., 2015). Heterogeneity was assessed using the Cochran's Q test and the magnitude of heterogeneity was evaluated using the I^2 statistic. The I^2 statistic assesses the percentage of variation across studies that are due to heterogeneity rather than chance and can be interpreted as a small (25%), moderate (50%) or high (75%) level of heterogeneity (Higgins, 2003).

Forest plots were created for each subtest to visually summarise the amount of heterogeneity as well as the estimated effect sizes (Hedges *g*) and 95% CIs. Funnel plots were also generated as a graphical tool for investigating publication bias and other bias (assessed by the Egger's test), which, if found, may lead to funnel plot asymmetry (Sterne & Harbord, 2004). If asymmetry was shown, the Duval and Tweedie trim and fill analysis would model the data as if it were symmetrically distributed by adjusting for missing studies (Duval & Tweedie, 2000).

Results

Search results

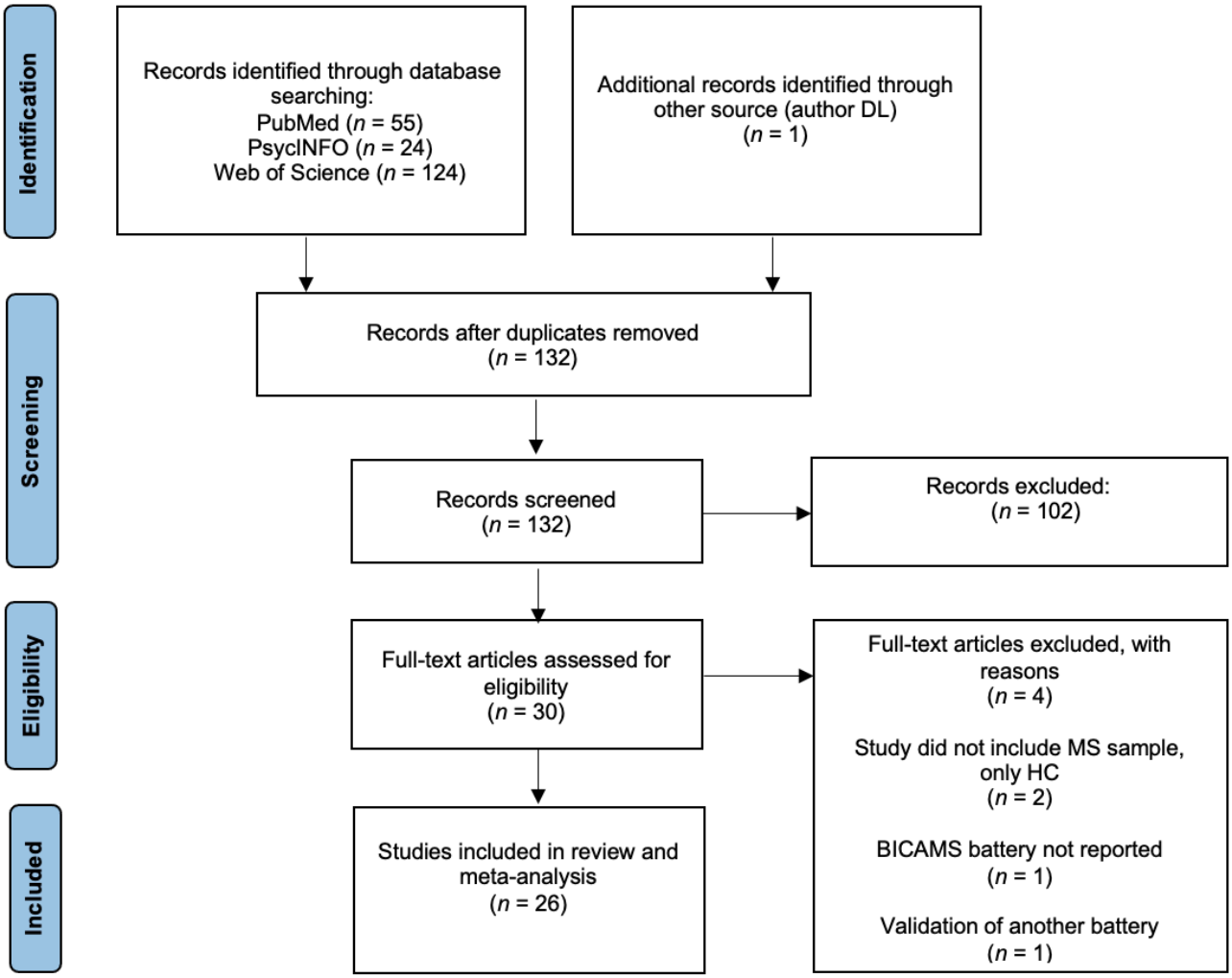
Using the pre-specified eligibility criteria, 55 results were generated from PubMed, 24 from PsycINFO and 124 from Web of Science. First, 132 duplicate studies across databases were

removed (Figure 3). To assess for eligibility, all titles and abstracts were initially screened independently by two reviewers (HP and DL). The 30 full-text articles that met the eligibility criteria were re-evaluated to determine their final inclusion or exclusion. Following this, four studies were removed from the final review according to the exclusion criteria, including 2 articles that were BICAMS validation studies but only used a HC sample (Alboudi et al., 2020; Goretti et al., 2014). A total of 26 studies met criteria for final inclusion in the systematic review.

Studies were organised according to whether they met criteria for the systematic review, meta-analysis, or both. All 26 studies met the criteria for the meta-analysis from those included in the systematic review. All relevant data for the current review and meta-analysis were obtained from numerical information in texts, tables, figures, and statistical analysis.

Figure 3

PRISMA Flowchart for Selection Process of Studies in Systematic Review and Meta-analysis



Study characteristics

Data on study characteristics, sample demographics and patient disease information are shown in Table 15. The 26 validation studies were published between the years of 2012 and 2022.

Sample demographics

Adults with MS were recruited from a variety of settings including medical centres, university hospitals, specialist clinics and tertiary referral centres. HC were either recruited from the community, an established normative sample or among relatives, friends, or carers of PwMS. The studies included a total of 2,833 adults with MS and 2,382 healthy controls. Sample size of both groups differed greatly between studies; in PwMS, the samples ranged from 40 to 500 participants

whilst for HC, this ranged from 20 to 276. Age of PwMS ranged from 20-61 years with an average age of 39.9, whilst the age of HC ranged from 22-51 years, with a similar average age of 38.9. The percentage of females in the MS and HC sample disproportionately favoured females and ranged from 47-82% in the MS sample and 33-86% in the HC. Eight studies used the same number of males and females. Years of education averaged 14.13 years in the MS sample and 14.58 years in HC. Higher rates of employment were seen in the HC in comparison to the MS sample (39-98% compared to 20-89%, respectively).

Patient disease information

Six studies recruited a RRMS sample, whilst the remaining studies also included a mixture of the other phenotypes (e.g., SPMS, PPMS, PRMS and CIS). RRMS was the most represented phenotype (33-100%), followed by SPMS (0-38%). Three studies included participants with CIS in their sample. The revised McDonald criteria for MS was the most commonly used diagnostic criterion (Thompson et al., 2018). The average disease duration was 9.16 years and ranged from 1.08 to 14.67 years. The average EDSS score was 2.75, indicating that on average, the participants were in the mild disability range and could walk unaided.

Correlations between BICAMS and sample variables

Correlations between BICAMS subtest scores and sample variables (age, disease duration, EDSS score, education, and employment) were extracted (Table 17). Correlations between age and BICAMS scores were the most frequently reported, followed by EDSS score. Only two studies reported correlations with employment (Dusankova et al., 2012; Filser et al., 2018). In the study by Dusankova and others, all three subtests emerged as significantly correlated with employment ($p < .05$) and in the study by Filser and others, only the SDMT was significantly correlated with employment ($p < .001$).

Table 15

Study Characteristics, Sample Demographic and Patient Disease Information

Study (first author, year)	Country	Number of participants	Age in years Mean (SD), {median}, [range]	Gender (female %)	Education in years Mean (SD), {median}, [range]	Employment (employed %)	MS phenotype (CIS/RR/SP/ PP/PR) %	Disease duration in years Mean (SD), {median}, [range]	EDSS Mean (SD), {median}, [range]
Alarcón et al (2020)									
MS	Columbia	50	41.44 (10.99)	64%	14.76 (2.61)	Nr	0/100/0/0/0	7.66 (5.61)	1.33 (1.54)
HC		100	37.75 (12.63)	48%	14.73 (3.57)	Nr	-	-	-
Betscher et al (2021)									
MS	Poland	61	{39}	74%	{13}	84%	0/74/20/6/0	RR = {5} SP = {19.5} PP = {7.5}	RR = {3} SP = {4.75} PP = {4.5}
HC		61	{37}	75%	{13}	98%	-	-	-
Botchorishvili et al (2021)									
MS	Georgia	68	39.2 (9.9)	71%	14.3 (2.1)	57%	0/76/18/6/0	7.0 (5.7)	3.3 (1.6)
HC		68	38.5 (9.9)	68%	14.5 (1.9)	84%	-	-	-
Costers et al (2017)									
MS	Belgium	97	45.42 (9.24)	68%	14.28 (1.86)	Nr	0/84/12/4/0	12.97 (7.16)	3.50 (2.50)
HC		97	43.52 (12.69)	75%	14.69 (1.61)	Nr	-	-	-
Darwish et al (2022)									
MS	Lebanon	43	36.06 (12.37)	81.4%	14.63 (3.17)	48.84%	0/81/14/5/0	8.61 (7.36)	1.89 (1.7)
HC		180	45.01 (19.36)	60%	15.13 (3)	56.11%	-	-	-
Drulović et al (2022)									
MS	Serbia	500	39.9 (9.4)	70.2%	14.0 (2.9)	Nr	0/100/0/0/0	9.2 (6.7)	{2.0}
HC		69	40.3 (11.5)	63.77%	14.1 (3.4)	Nr	-	-	-
Dusankova et al (2012)									
MS	Czech Republic	367	34 (10)	68%	14 (3)	40%	0/68/26/3/3	8 (7)	3 (1.5)
HC		134	34 (9)	71%	14 (2.5)	73%	-	-	-
Estiasari et al (2019)									
MS	Indonesia	40	{31}, [20-61]	82.5%	>12yrs = 75%	Nr	0/78/22/0/0	{4}, [0.1-15]	{3}, [1-7.5]
HC		66	{29}, [22-51]	72.7%	>12yrs = 89.4%	Nr	-	-	-
Evdoshenko et al (2022)									
MS	Russia	98	38.44 (11.47)	70.4%	15.12 (2.79)	Nr	0/86/14/0/0	9.5 (7.44)	{3.0}

HC		86	38.17 (13.29)	63.95%	16.26 (3.02)	Nr	-	-	-
Farghaly et al (2021)									
MS	Egypt	90	30.8 (6.7)	77.78%	14.5 (2.6)	Nr	0/86/12/2/0	6.2 (5.8)	2.8 (1.8)
HC		85	30.5 (7.9)	70.59%	14.3 (3.3)	Nr	-	-	-
Filser et al (2018)									
MS	Germany	172	43.33 (11.64)	68%	10.74 (1.56)	76.4%	0/87/9/4/0	Nr	Nr
HC		100	43.04 (15.59)	71%	10.77 (1.58)	92%	-	-	-
Giedraitienė et al (2015)									
MS	Lithuania	50	38.8 (10.2)	47%	15.9 (2.8)	54%	4/88/6/2/0	11.7 (9.2)	3.3 (1.3)
HC		20	36.7 (16.4)	33%	17.5 (3.5)	75%	-	-	-
Hämäläinen et al (2021)									
MS	Finland	65	50.9 (8.8)	71%	13.8 (9.8)	20%	0/62/38/0/0	15.9 (9.8)	4.8 (2.0)
HC		45	49.4 (12.6)	71%	14.0 (2.1)	86.7%	-	-	-
Marstrand et al (2020)									
MS	Denmark	65	37.2 (8.8)	63%	15.2 (2.4)	Nr	0/100/0/0/0	3.9 (2.7)	1.8 (1.2)
HC		65	36.8 (9.6)	63%	15.9 (2.1)	Nr	-	-	-
Maubeuge et al (2021)									
MS	France	123	49.69 (9.41)	63.4%	14–16 yrs = 30.1%	44.7%	0/33/33/34/0	14.67 (9.09)	{4.0}, [0-8]
HC		276	43.84 (12.42)	57.3%	14–16 yrs = 38%	Nr	-	-	-
Niino et al (2017)									
MS	Japan	156	41.4 (9.3)	69%	14.1 (1.9)	Nr	0/88/11/1/0	10.3 (7.2)	2.4 (2.0)
HC		126	39.3 (11.9)	72%	14.3 (1.6)	Nr	-	-	-
O'Connell et al (2015)									
MS	Ireland	67	42.7 (12.8)	68%	14.1 (3.1)	41.8%	0/70/28/2/0	10.2 (8.4)	1.8 (0.9)
HC		66	43.9 (12.1)	73%	13.6 (2.7)	80.3%	-	-	-
Ozakbas et al (2017)									
MS	Turkey	173	37.5 (10.7)	71%	13.9 (7.3)	23.7%	0/87/10/3/0	9.2 (6.1)	2.4 (1.7)
HC		153	36.9 (8.9)	71%	15.4 (8.8)	39.1%	-	-	-
Polychroniadou et al (2016)									
MS	Greece	44	40.2 (9.9)	61%	13.9 (4.2)	Nr	7/77/9/7/0	9.1 (4.1)	{3.5}, [1.0–6.0]
HC		79	36.2 (10.6)	60%	15.6 (5.5)	Nr	-	-	-
Sandi et al (2015)									
MS	Hungary	65	41.9 (8.9)	75%	>12yrs = 52.3%	Nr	0/100/0/0/0	11.1 (7.6)	2.5 (1.8)
HC		65	40.9 (11.8)	75%	>12yrs = 52.3%	Nr	-	-	-
Skorve et al (2019)									
MS	Norway	65	37.02 (0.40)	64.6%	14–16 yrs = 37%	89.2%	0/100/0/0/0	1.08 (0.74)	1.28 (0.88)

HC		68	38.13 (11.40)	66.2%	14–16 yrs = 46%	97.0%	-	-	-
Souissi et al (2022)									
MS	Tunisia	104	33.3 (9.8)	75%	14–16 yrs = 14.42%	Nr	0/88/8/4/0	7 (6.4)	2.65 (2.06)
HC		104	33.3 (9.4)	75%	14–16 yrs = 14.42%	Nr	-	-	-
Sousa et al (2018)									
MS	Portugal	105	38.26 (11.03)	66.7%	13.55 (3.71)	58.1%	4/92/4/0/0	6.52 (5.95)	{1.5}, [0–6]
HC		60	36.17 (12.01)	58.3%	14.62 (3.47)	94.9%	-	-	-
Spedo et al (2015)									
MS	Brazil	58	41.2 (12.2)	69%	12.7 (5.2)	Nr	0/100/0/0/0	8.3 (6.6)	4.2 (2)
HC		58	40.3 (11.9)	55%	12.5 (3.6)	Nr	-	-	-
Vanotti et al (2016)									
MS	Argentina	50	43.4 (10.2)	74%	14.9 (2.8)	Nr	0/78/18/4/0	13.1 (9.1)	3.29 (2.55)
HC		100	42.4 (10.1)	75%	14.9 (2.5)	Nr	-	-	-
Walker et al (2016)									
MS	Canada	57	45.4 (9.9)	80%	15.44 (2.7)	Nr	0/77/16/7/0	10.11 (7.72)	2.7 (1.85)
HC		51	41.9 (10.8)	86%	16.31 (2.1)	Nr	-	-	-

Note.
MS= Multiple sclerosis; HC= Healthy control; CIS= Clinically Isolated Syndrome; RR= Relapsing-Remitting MS; SP= Secondary Progressive MS; PP= Primary Progressive MS; PR= Progressive-Relapsing MS; EDSS= Expanded Disability Status Scale; Nr= Not reported; SD= Standard deviation

Table 16

BICAMS Psychometrics

Study (first author, year)	SDMT Mean (SD)	CVLT-II Mean (SD)	BVMT-R Mean (SD)	Impaired cognition on at least one subtest (%)	Sensitivity (%)	Specificity (%)
Alarcón et al (2020)						
MS	46.47 (14.24)	45.34 (10.14)[a]	21.64 (6.91)	50%	Nr	Nr
HC	54.11 (12.19)	48.78 (8.45)[a]	25.67 (6.81)	-	-	-
Betscher et al (2021)						
MS	48.8 (12.1)	51.7 (10.9)	24 (7.7)	34%	Nr	Nr
HC	57.2 (9.7)	56.1 (9.2)	27.1 (5.7)	Nr	-	-
Botchorishvili et al (2021)						
MS	35.5 (12.7)	51.0 (11.8)	22.0 (8.0)	43%	Nr	Nr
HC	46.0 (11.8)	58.5 (8.2)	25.6 (6.8)	14%	-	-
Costers et al (2017)						
MS	52.1 (13.1)	60.1 (12.9)	25.4 (29)	Nr	Nr	Nr
HC	61 (10.2)	61.3 (9.7)	28.2 (5.1)	Nr	-	-
Darwish et al (2022)						
MS	47.2 (17.98)	56.9 (10.04)[b]	22 (9.79)	61%	Nr	Nr
HC	59.22 (12.27)	54.10 (8.71)[b]	24.23 (6.66)	Nr	-	-
Drulović et al (2022)						
MS	45.9 (16.7)	50.0 (11.7)	18.8 (7.4)	62.9%	Nr	Nr
HC	56.3 (12.9)	52.7 (9.6)	22.6 (5.8)	18.6%	-	-
Dusankova et al (2012)						
MS	50 (13)	52 (11)	23 (7)	58%	94%	86%
HC	65 (9)	60 (8)	29 (4)	0.7%	-	-
Estiasari et al (2019)						
MS	40.9 (14.8)	52.0 (12.8)	22.2 (7.7)	40%	Nr	Nr
HC	64.8 (16.2)	61.5 (9.7)	29.3 (5.6)	Nr	-	-
Evdoshenko et al (2022)						
MS	49.16 (13.42)	{61.5}	{26.5}	34.69%	Nr	Nr
HC	58.34 (11.52)	{65.5}	{28}	16.28%	-	-
Farghaly et al (2021)						
MS	39.2 (13.3)	53.7 (10.5)	19.7 (9.2)	SDMT = 31.1% CVLT-II = 19.5% BVMT-R = 23.9%	Nr	Nr

HC	50.9 (10.8)	59.6 (8.5)	25.4 (8.7)	SDMT = 5.8% CVLT-II = 7% BVMT-R = 8.1%	-	-
Filser et al (2018)						
MS	47.43 (11.67)	55.35 (11.43)[c]	24.44 (7.59)	32.6%	Nr	Nr
HC	56.07 (11.64)	55.16 (10.27)[c]	27.37 (5.96)	Nr	-	-
Giedraitienė et al (2015)						
MS	42.7 (13.9)	55.9 (10)	23.1 (7)	Nr	Nr	Nr
HC	57 (11.5)	65.7 (5.9)	29.6 (4.1)	Nr	-	-
Hämäläinen et al (2021)						
MS	41.9 (11.8)	43.0 (11.5)	19.2 (8.0)	60%	Nr	Nr
HC	54.6 (8.3)	51.3 (10.7)	24.7 (6.8)	Nr	-	-
Marstrand et al (2020)						
MS	61.0 (10.0)	65.4 (9.9)	27.4 (5.8)	32.3%	SDMT = 20.0% CVLT-II = 10.8% BVMT-R = 16.9%	SDMT = 95.4% CVLT-II = 89.2% BVMT-R = 93.8%
HC	66.0 (9.6)	68.6 (6.4)	29.6 (3.7)	20%	-	-
Maubeuge et al (2021)						
MS	50.31 (11.12)	49.72 (12.77)[d]	22.89 (7.26)	50.4%	Nr	Nr
HC	58.55 (8.44)	57.78 (8.67)[d]	26.73 (5.67)	19.6%	-	-
Niino et al (2017)						
MS	47.9 (14)	48.6 (12.6)	23.5 (8.4)	Nr	Nr	Nr
HC	61 (9.5)	55.7 (10.5)	28.3 (5.4)	Nr	-	-
O'Connell et al (2015)						
MS	46.0 (12.9)	45.3 (10.2)	17.9 (7.1)	57%	Nr	Nr
HC	56.1 (10.6)	53.6 (9.1)	20.9 (6.5)	17%	-	-
Ozakbas et al (2017)						
MS	43.2 (12.5)	45.7 (11.3)	16.9 (8.5)	45.1%	Nr	Nr
HC	53.5 (9.5)	53.9 (7.7)	22.5 (9.2)	Nr	-	-
Polychroniadou et al (2016)						
MS	45.0 (17.2)	55.5 (12.3)[e]	18.5 (8.3)	47%	Nr	Nr
HC	61.4 (13.1)	60.5 (10.7)[e]	22.1 (6.5)	Nr	-	-
Sandi et al (2015)						
MS	55.6 (15.5)	55.4 (10.7)	22.5 (8.5)	52.3%	Nr	Nr
HC	66.2 (12.4)	59.0 (8.3)	26.7 (5.6)	Nr	-	-
Skorve et al (2019)						
MS	54.65 (10.79)	54.55 (10.86)	26.55 (5.76)	46.2%	Nr	Nr
HC	58.52 (10.53)	60.32 (7.75)	29.03 (4.01)	Nr	-	-

Souissi et al (2022)						
MS	36 (13)	42 (7)[f]	23 (9)	73.1%	SDMT = 74% TVLT = 76%[f] BVMT-R = 75%	SDMT = 56% TVLT = 55%[f] BVMT-R = 53.5%
HC	47 (15)	46 (6)[f]	27 (7)	Nr	-	-
Sousa et al (2018)						
MS	51.77 (11.20)	55.05 (11.84)	21.72 (7.27)	24.8%	Nr	Nr
HC	58.68 (10.02)	60.47 (10.12)	24.68 (5.52)	Nr	-	-
Spedo et al (2015)						
MS	35.9 (16.1)	42.1 (12.4)	19.9 (8.6)	Nr	Nr	Nr
HC	47.5 (13)	53.4 (10.8)	23.8 (7.7)	Nr	-	-
Vanotti et al (2016)						
MS	45.1 (16.1)	50.9 (12.4)	20.7 (7.74)	Nr	Nr	Nr
HC	56.7 (10.9)	60.9 (10.5)	23.4 (5.8)	Nr	-	-
Walker et al (2016)						
MS	49.7 (10.8)	51.6 (10.1)	24.6 (6.5)	57.9%	SDMT = 97.5% CVLT-II = 82.5% BVMT-R = 77.5%	SDMT = 88.2% CVLT-II = 70.6% BVMT-R = 82.4%
HC	59.1 (8.5)	57.7 (7.9)	29.8 (3.6)	Nr	-	-

Note.
MS= Multiple sclerosis; HC= Healthy control; SDMT= Symbol Digit Modalities Test; CVLT-II= California Verbal Learning Test; BVMT-R= Brief Visuospatial Memory Test-Revised; Nr= Not reported; SD= Standard deviation

[a] Alternative verbal memory test used = The Prueba de Aprendizaje y Memoria con Codificación Libre (PAMCL)
[b] Alternative verbal memory test used = The Verbal Memory Arabic Test (VMAT)
[c] Alternative verbal memory test used = The Rey Auditory Verbal Learning Test (RAVLT)
[d] Alternative verbal memory test used = The French Verbal Learning Test (FVLT)
[e] Alternative verbal memory test used = The Greek Verbal Learning Test (GVLT)
[f] Alternative verbal memory test used = The Tunisian Verbal Learning Test (TVLT)

Table 17

Correlations Between BICAMS Scores and Sample Variables

Study (first author, year)	BICAMS scores and sample variables (age, disease duration, EDSS and education)											
	Age and scores *(r)*			Disease duration and scores *(r)*			EDSS and scores *(r)*			Education and scores *(r)*		
	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R
Alarcón et al (2020)												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Betscher et al (2021)												
MS	-.28*	Nr	-.26*	Nr	Nr	Nr	-.58***	-.31*	-.27*	0.36*	0.42***	0.5***
HC	-.35*	Nr	Nr	-	-	-	-	-	-	.44***	.47***	.27*
Botchorishvili et al (2021)												
MS	-.400*	-.112	-.192	-.177	-.106	.125	- .582***	-.403***	-.342***	.243*	.207	.297*
HC	-.457***	-.368***	-.506***	-	-	-	-	-	-	.523***	.439*	.348*
Costers et al (2017)												
MS	-.34***	-.10	-.29**	Nr	Nr	Nr	-.44***	-.35***	-.43***	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Darwish et al (2022)												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Drulović et al (2022)												
MS	-.225*	-.232*	-.271*	-.109*	-.880	-.207*	-.466*	-.320*	-.360*	.339*	.298*	.190*
HC	-.605*	-.430*	-.374*	-	-	-	-	-	-	.521*	.552*	.394*
Dusankova et al (2012)												
MS	Nr	Nr	Nr	.44*	.39*	.41*	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Estiasari et al (2019)												
MS	-.004	-.11	.02	-.23	-.19	-.18	-.5***	-.46*	-.49*	{47}, [15-69]	{54}, [23-72]	{24.5}, [4-32]
HC	-.27*	-.11	-.28*	-	-	-	-	-	-	{63}, [42-110]*	{63}, [36-77]	{31}, [14-36]
Evdoshenko et al (2022)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Farghaly et al (2021)												
MS	−.26[a]*	−.17[a]	−.26 [a]*	−.41[a]***	−.18[a]	−.27[a]*	−.37[a]***	−.31[a]*	−.19[a]	.36[a]***	.27[a]*	.25[a]*

HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Filser et al (2018)												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Giedraitienė et al (2015)												
MS	Nr	Nr	Nr	-.3[a]	-.2[a]	-.2[a]	-5.9[a]***	-3.7[a]***	-2.3[a]***	2.4[a]*	2.4[a]*	1.0[a]*
HC	Nr	Nr	Nr	-	-	-	-	-	-	2.0 [a]*	1.2 [a]*	0.9 [a]*
Hämäläinen et al (2021)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Marstrand et al (2020)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Maubeuge et al (2021)												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Niino et al (2017)												
MS	–.37***	–.25*	–.30***	–.30***	–.12	–.27***	–.56***	–.29***	-.46***	.07	.13	.001
HC	–.44***	–.23*	–.25*	-	-	-	-	-	-	.24*	.25*	.05
O'Connell et al (2015)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Ozakbas et al (2017)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	−.46*	−.40*	−.24	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Polychroniadou et al (2016)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Sandi et al (2015)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	Nr	Nr	Nr	Nr
Skorve et al (2019)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Souissi et al (2022)												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Sousa et al (2018)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	−.497***	−.334***	−.275*	Nr	Nr	Nr

HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Spedo et al (2015)												
MS	−.30*	−.30*	−.29*	Nr	Nr	Nr	Nr	Nr	Nr	.29*	.18*	.27*
HC	−.49*	-	−.34*	-	-	-	-	-	-	.49*	.37*	-
Vanotti et al (2016)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Walker et al (2016)												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	-	.20*	-
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr

Note.
MS= Multiple sclerosis; HC= Healthy control; SDMT= Symbol Digit Modalities Test; CVLT-II= California Verbal Learning Test; BVMT-R= Brief Visuospatial Memory Test-Revised; EDSS= Expanded Disability Status Scale; Nr= Not reported

[a] Regression coefficient reported; Correlation coefficients (r) are presented with significance marks: * $p < .05$, ** $p < .01$, *** $p < .001$

Quality rating

The quality rating of the retrieved articles, using the EPHPP, was carried out jointly between two reviewers (HP and KM) and any disagreements were discussed and resolved. The overall quality of the studies ranged from 'moderate' to 'weak' on the EPHPP template (Table 18). No studies were removed from this review following the quality assessment. Several studies were rated 'strongly' on categories such as confounders, selection bias and data collection. The data collection method, for example, refers to the validity of the primary tool used in the study, which in this case, is BICAMS. Most studies were assigned a rating of 'strong' in this dimension because BICAMS was demonstrated to be both valid (at discriminating between cognitive impairment in MS and HC) and reliable (in showing similar results at re-test). Studies assigned a 'moderate' rating showed that BICAMS was valid but was either not reliable or reliability was not described. Interestingly, the study by Darwish et al (2022) used a culturally adapted verbal memory test as an alternative to the CVLT-II, called the Verbal Memory Arabic Test (VMAT). In this study, the SDMT and BVMT-R significantly discriminated between the MS and HC samples but not the VMAT, therefore partial validity was given. Reviewers decided to assign a 'strong' rating for the data collection method, given that the SDMT and BVMT-R, the standard BICAMS subtests, demonstrated validity.

Table 18

Quality Ratings of BICAMS Validation Studies

Study (first author, year)	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Overall quality rating
Alarcón et al (2020)	Strong	Weak	Strong	Moderate	Strong	Moderate	Moderate
Betscher et al (2021)	Strong	Weak	Moderate	Moderate	Strong	Weak	Weak
Botchorishvili et al (2021)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Costers et al (2017)	Strong	Weak	Strong	Moderate	Moderate	Weak	Weak
Darwish et al (2022)	Strong	Weak	Moderate	Moderate	Strong	Weak	Weak

Drulović et al (2022)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Dusankova et al (2012)	Strong	Weak	Strong	Moderate	Moderate	Weak	Weak
Estiasari et al (2019)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Evdoshenko et al (2022)	Strong	Weak	Weak	Moderate	Strong	Weak	Weak
Farghaly et al (2021)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Filser et al (2018)	Weak	Weak	Strong	Moderate	Strong	Strong	Weak
Giedraitienė et al (2015)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Hämäläinen et al (2021)	Weak	Weak	Moderate	Moderate	Strong	Strong	Weak
Marstrand et al (2020)	Moderate	Weak	Strong	Moderate	Strong	Strong	Moderate
Maubeuge et al (2021)	Weak	Weak	Weak	Moderate	Strong	Weak	Weak
Niino et al (2017)	Strong	Weak	Strong	Moderate	Strong	Strong	Moderate
O'Connell et al (2015)	Strong	Weak	Strong	Moderate	Moderate	Weak	Weak
Ozakbas et al (2017)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Polychroniadou et al (2016)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Sandi et al (2015)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Skorve et al (2019)	Moderate	Weak	Moderate	Moderate	Strong	Weak	Weak
Souissi et al (2022)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Sousa et al (2018)	Strong	Weak	Moderate	Moderate	Strong	Weak	Weak
Spedo et al (2015)	Moderate	Weak	Strong	Moderate	Strong	Strong	Moderate
Vanotti et al (2016)	Strong	Weak	Strong	Moderate	Strong	Weak	Weak
Walker et al (2016)	Strong	Weak	Strong	Moderate	Moderate	Weak	Weak

Note.
Overall quality rating: Strong= no weak ratings; Moderate= one weak rating; Weak= two or more weak ratings

Meta-analysis of BICAMS validation studies

Data on the standard quantitative information based on the subtests of the SDMT, CVLT-II and BVMT-R (mean, standard deviation, and sample size) of the MS groups and HC comparison group were extracted for baseline assessments of BICAMS (Table 16). The percentage of people in both groups identified with likely cognitive impairment on at least one subtest was also extracted, along with the sensitivity and specificity of BICAMS. The results from all three subtests showed that adults with MS performed significantly worse than HC. BICAMS identified likely impaired cognition, on at least one subtest, in 25-73% in the MS sample which was significantly higher than HC (1-20%).

SDMT

The forest plot (Figure 4) shows the effect size for each study using the SDMT. Overall, information processing speed was significantly lower in the MS sample compared to HC with a large effect size (g = 0.854, 95% CI = 0.765, 0.944, $p < 0.001$). There was no evidence of outliers, however moderate heterogeneity (Q = 51.9, $p = 0.001$) was indicated ($I^2 = 51.8$). There was no evidence of publication bias (Egger's test: $p > 0.05$, two-tailed). The funnel plot (Figure 5) indicates that the effect sizes were symmetrical. Duval and Tweedie's trim and fill analysis estimated that there were no studies missing from the analysis.

Figure 4

Forest Plot for SDMT

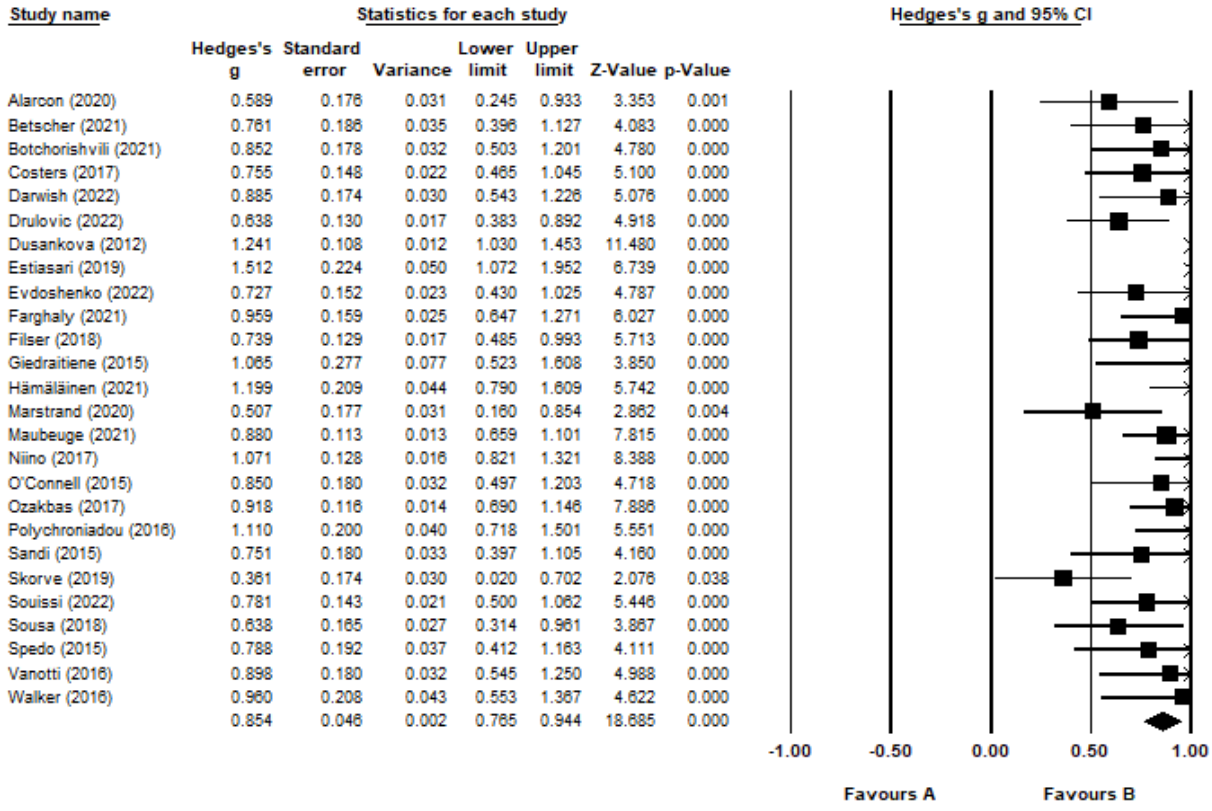
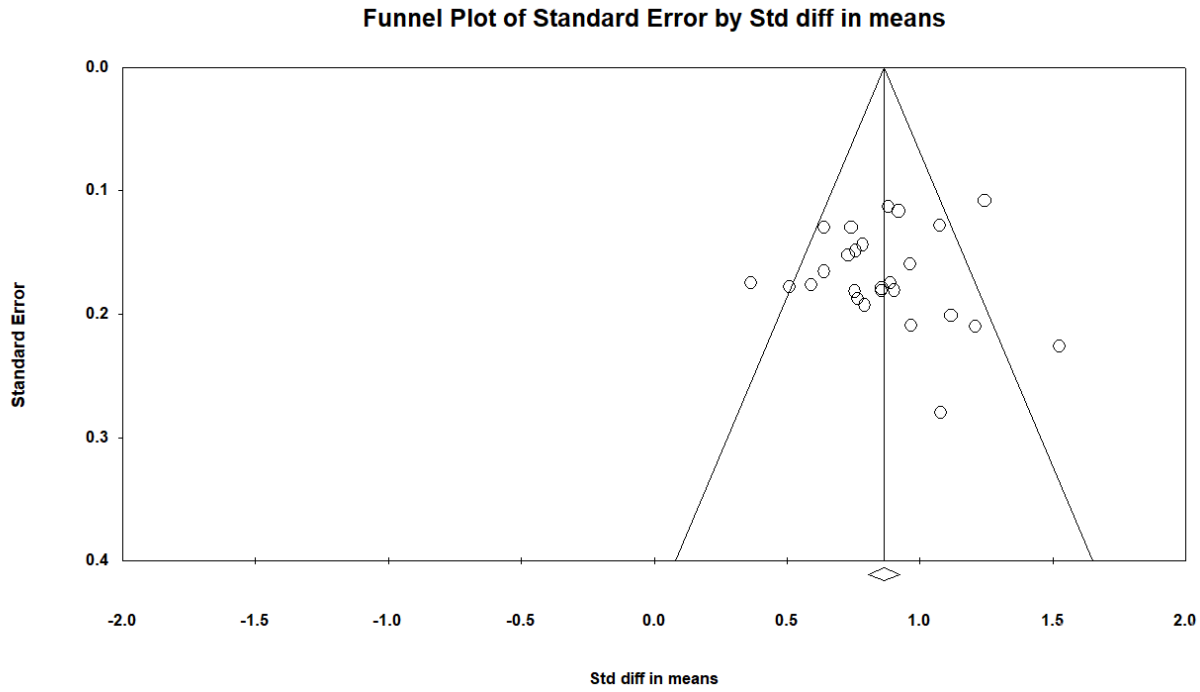


Figure 5

Funnel Plot for SDMT



CVLT-II

A translated version of the CVLT-II was used in 18 validation studies. For 2 studies, the CVLT-II was not translated as the validation studies were conducted in English speaking countries with existing validations (O'Connell et al., 2015; Walker et al., 2016). Importantly, 6 of the studies used an alternative verbal memory test to substitute the conventional CVLT-II (Table 17). The average mean and standard deviation scores of these alternative tests were included in the meta-analysis. Notably, the study with the smallest effect size, with a Hedge's *g* value of 0.017, used a substituted verbal memory test (Filser et al., 2018; Figure 6). The study with the highest effect size, with a Hedge's *g* value of 1.072, used a translated version of the CVLT-II (Giedraitienė et al**.,** 2015; Figure 6).

The forest plot (Figure 6) shows the effect size for each study using the CVLT-II. Overall, immediate verbal recall memory was significantly lower in the MS sample compared to

HC with a medium effect size (g = 0.566, 95% CI = 0.459, 0.673, p < 0.001). There was no evidence of outliers, however a high level of heterogeneity (Q = 77.9, p < 0.001) was indicated (I^2 = 67.9). Duval and Tweedie's trim and fill analysis estimated that 3 studies would need to fall to the left of the mean effect size to make the plot symmetrical (Figure 7). Assuming a random-effects model, the adjusted mean effect size remained medium (p = 0.528, 95% CI = 0.420, 0.635). There was no evidence of publication bias as the Egger's test remained non-significant (Egger's test: p > 0.05, two-tailed).

Figure 6

Forest Plot for CVLT-II

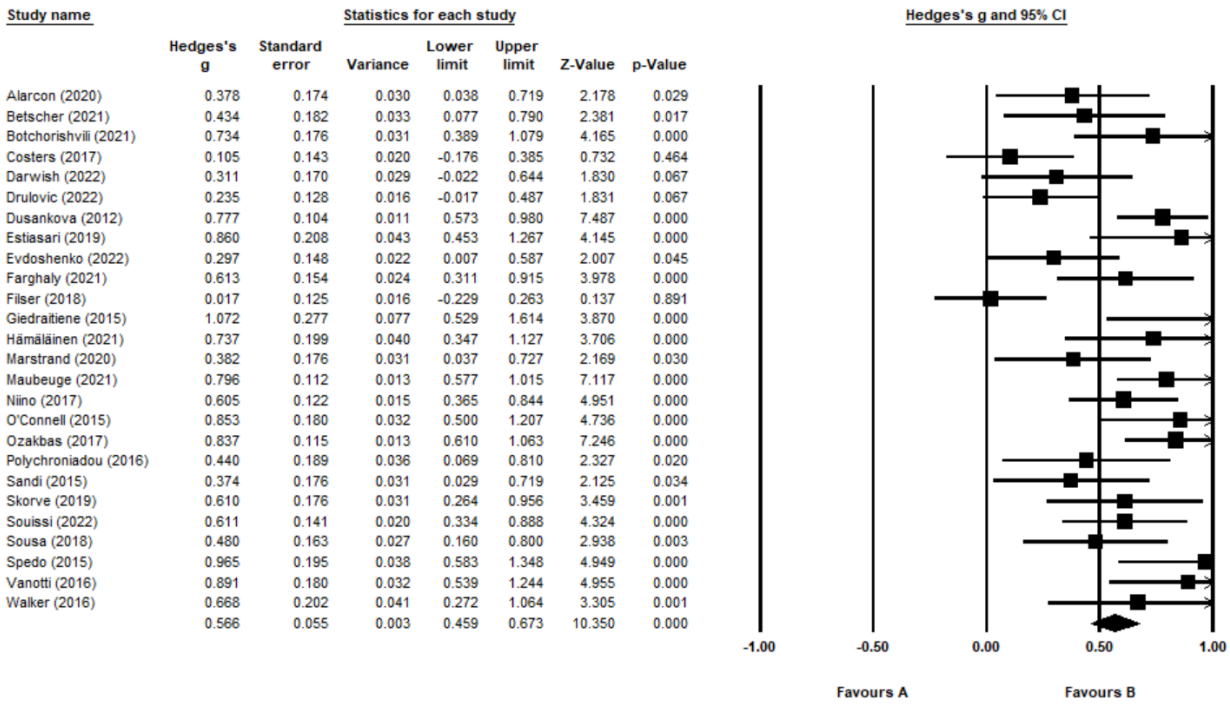
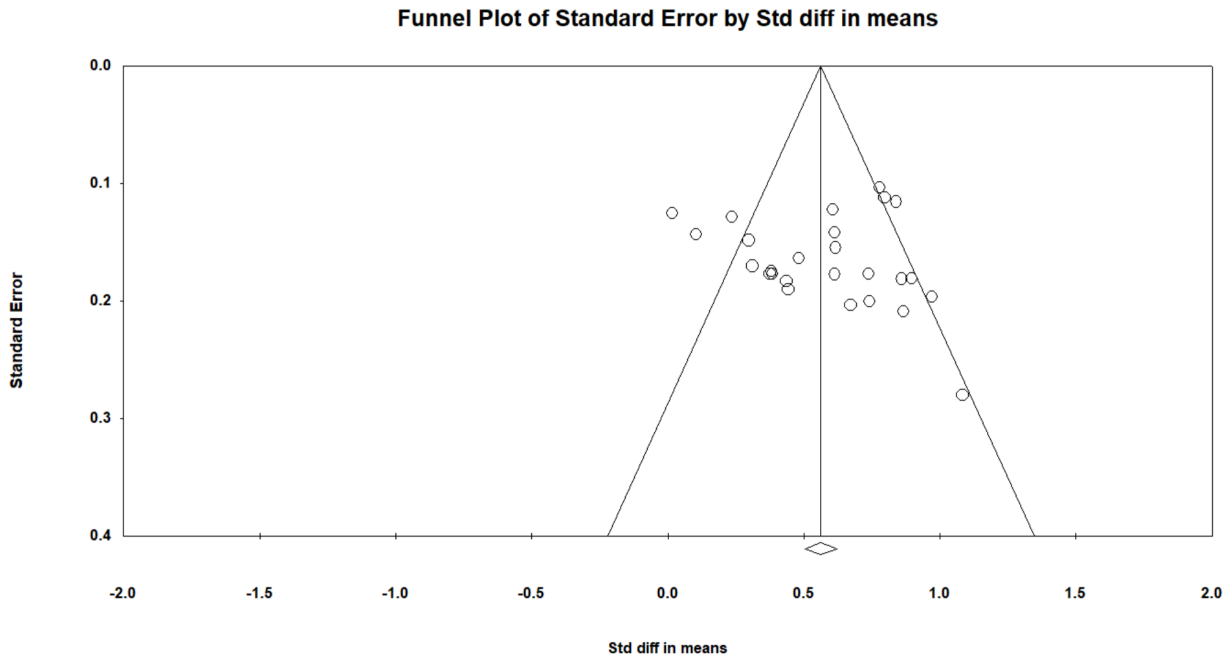


Figure 7

Funnel Plot for CVLT-II



BVMT-R

The forest plot (Figure 8) shows the effect size for each study using the BVMT-R. Overall, immediate visual recall memory was significantly lower in the MS sample compared to HC with a medium effect size ($g = 0.566$, 95% CI = 0.487, 0.645, $p < 0.001$). There was no evidence of outliers, however moderate heterogeneity ($Q = 42.6$, $p < 0.05$) was indicated ($I^2 = 41.4$). There was no evidence of publication bias (Egger's test: $p > 0.05$, two-tailed). The funnel plot (Figure 9) indicates that the effect sizes were symmetrical. Duval and Tweedie's trim and fill analysis estimated that there were no studies missing from the analysis.

Figure 8

Forest Plot for BVMT-R

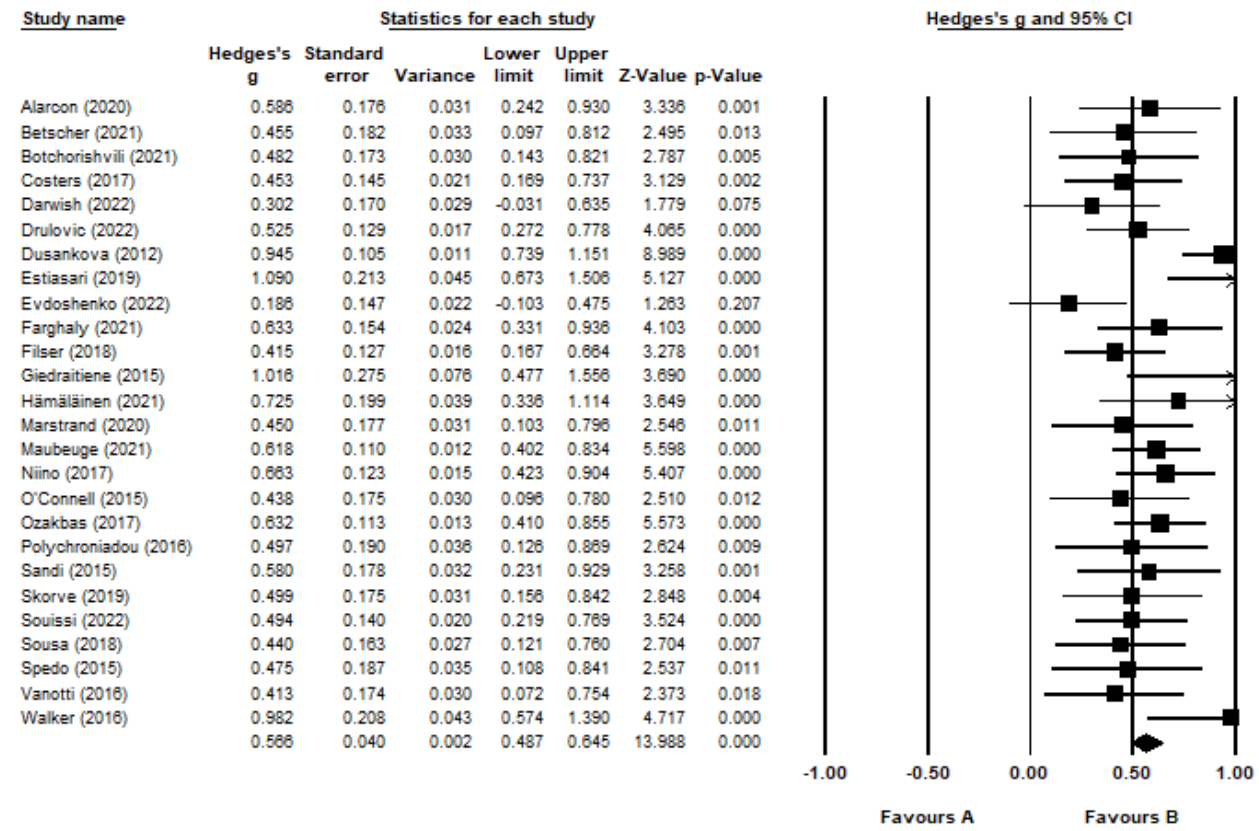
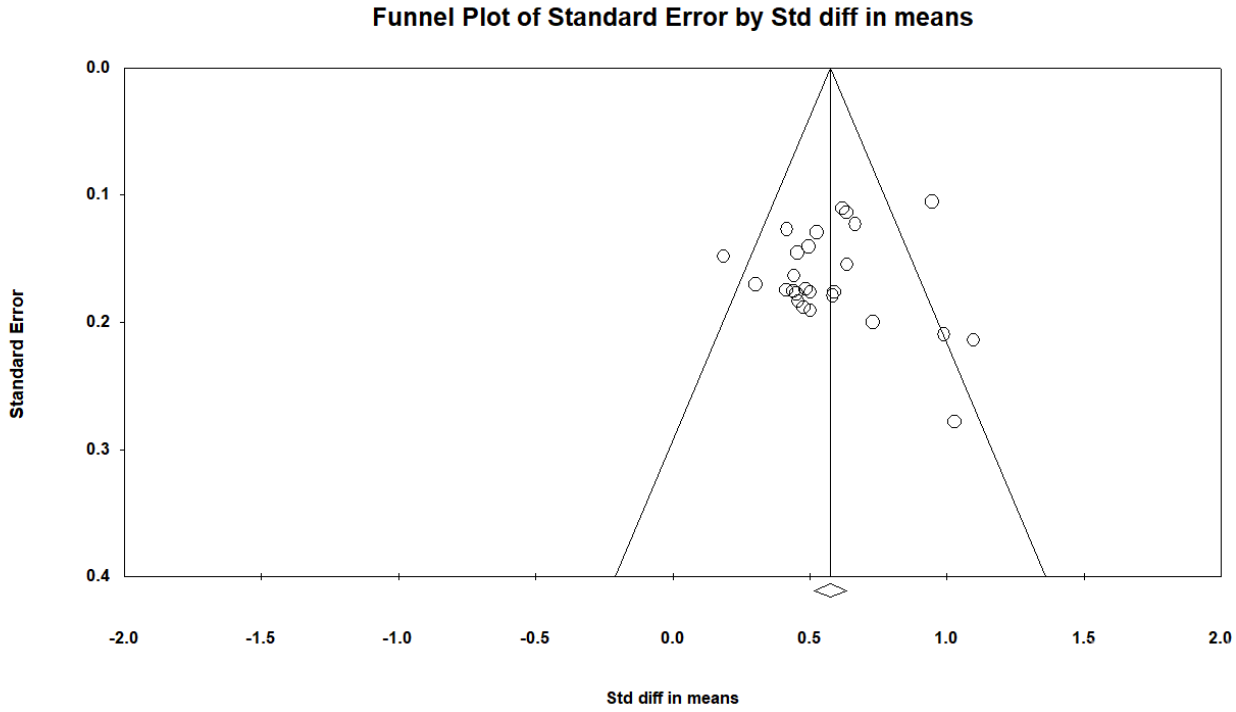


Figure 9

Funnel Plot for BVMT-R



Sensitivity and specificity

Only four studies reported the sensitivity and specificity of BICAMS. Of these four studies, one reported on the sensitivity and specificity of BICAMS overall (94% and 86%, respectively), whilst the remaining three reported on the sensitivity and specificity of the individual subtests (see Table 16). Notably, in the large Czech Republic sample, BICAMS demonstrated the same sensitivity to cognitive impairment as the "gold standard" MACFIMS (Dusankova et al., 2012).

Discussion

Summary of findings

The current review identified, synthesised, and appraised the current literature on the international validation of BICAMS to date. A total of 26 studies were included in both the systematic review and meta-analysis. The results from the systematic review showed that BICAMS has been embraced in many countries worldwide and with a range of clinical samples, including different MS phenotypes (RRMS, SPMS, PPMS, PRMS and CIS), and consequently disease durations and severity. Most studies had included a HC sample with a similar age and educational background. Although BICAMS has been designed to be administered by a range of health professionals, it appeared that, in the studies, BICAMS was primarily completed by a neuropsychologist; however, this information was not routinely reported. Finally, in most studies, the gender ratio in both samples disproportionately favoured females. It is important to consider that this female recruitment bias is a reflection of how common MS is in females compared to males, with a female to male sex ratio of approximately 3:1 (McGinley et al., 2021).

In the majority of validation studies, all three subtests on BICAMS were significantly correlated with higher EDSS scores – a finding which supports previous evidence that higher physical disability is often associated with increased cognitive impairment (Al-Falaki et al., 2021; Elshebawy et al., 2021). Several studies reported significant correlations between BICAMS and age, disease duration, and education; such findings are comparable with other recently published studies (e.g., Costers et al., 2017; Sousa et al., 2018).

The meta-analysis showed that adults with MS performed significantly worse than HC on the three BICAMS subtests – information processing speed and immediate verbal and visual recall. Cognitive functioning was most impaired on the SDMT (a measure of information processing speed). These findings are in line with existing literature proposing that information processing speed is markedly reduced in MS (Costa et al., 2017) and constitutes the most common cognitive limitation in PwMS (Chiaravalloti & DeLuca, 2008). It is important to stress that BICAMS should be administered in its entirety, given that multiple aspects of daily life can be affected by cognitive impairment in addition to processing speed e.g., visuospatial learning as assessed by the BVMT-R (Chiaravalloti et al., 2022).

It is important to note that the BICAMS committee included experts from Europe and America and may lack diversity and inclusivity in development and cross-cultural appropriateness (Al-Jawahiri & Nielsen, 2021; Sousa & Rojjanasrirat, 2011). The CVLT-II scores were more heterogeneous compared to the other subtests, which is possibly a reflection of the additional linguistic and cultural demands of translating the verbal recall list and six studies using alternative verbal memory tests. For example, several validation

studies (e.g., Costers et al., 2017; Drulović et al., 2022) reported difficulties with translating the CVLT-II and described similar scores on the CVLT-II between the MS sample and HC. The CVLT-II is also the most culturally adapted of the three subtests and required more extensive work to accomplish a valid translation (Spedo et al., 2015). Semantic categories for the word list were sometimes adapted to be more applicable for that population e.g., by swapping different types of sports for cooking utensils in Egypt (Farghaly et al., 2021).

Strengths

There are several strengths to this review. Firstly, the search strategy was designed and validated using a combination of three databases – PubMed, PsycINFO and Web of Science to cover a breadth of available and relevant literature. Secondly, strict inclusion and exclusion criteria were employed to ensure appropriate studies were generated. Thirdly, this review identified and synthesised international validation studies reporting objective scores of cognitive abilities in PwMS compared to matched HC in a standardised manner. The findings of this review support previous findings (Corfield & Langdon, 2018) that all three BICAMS' subtests could detect cognitive impairment in an MS sample, compared to HC. Finally, this review captures the advances in validating BICAMS, internationally, since the previous review (Corfield & Langdon, 2018). Across the validation studies, there was a varied spread of cultures, languages and countries involved in the initiative. The countries which participated in the international validation protocol reported that BICAMS could be feasibly administered in approximately 15 minutes, with minimal materials, and was recommended for routine clinical cognitive assessment as a standard of MS care.

Limitations

It is important to acknowledge the potential shortcomings of BICAMS. Firstly, BICAMS only assesses information processing speed, visual and verbal memory. It can therefore be criticised for the exclusion of executive functioning and other cognitive domains, such as those included in MACFIMS (Gromisch et al., 2018). In devising BICAMS, there was a consensus that assessments of executive functioning were too long and too challenging to administer and standardise across different countries (Langdon et al., 2012). Further, the need for remote cognitive assessments have become increasingly urgent following the COVID-19 pandemic. While remote use of BICAMS is yet to be developed, it is supported (Rogers et al., 2022). Of note, further research is needed to overcome the obstacle of manual responses from the BVMT-R (Barcellos et al., 2021) such as the implementation of a tablet-based or motor-free visuospatial task (Sumowski et al., 2018). It is important to note that BICAMS originates from a western psychometric context and the committee comprises white Europeans and North Americans. Therefore, the racial, ethnic, socio-economic, and educational profiles of the populations within this context have been considered disproportionately and BICAMS does not adequately represent non-western cultures. While BICAMS has been validated in many countries (e.g., Japan and Indonesia), normative limitations should be carefully considered. Nationality has been shown to significantly predict performance on BICAMS, with the term 'nationality' encompassing a range of cultural, linguistic, educational, and political differences. For example, an American sample demonstrated higher scores on BICAMS compared to an Italian sample (Goretti et al., 2014). This suggests that the international application of BICAMS should consider national differences and continue to collect national norms (Smerbeck et al., 2017). Finally, neuropsychological test performance can be confounded by a multitude of factors, such as concurrent medication, fatigue, and MS physical

symptoms (Langdon et al., 2012). For example, patients with severe motor impairment may impact performance on the BVMT-R (Sumowski et al., 2018) and one validation study excluded patients who had a severe hand disability for this reason (Niino et al., 2017). It is also worth addressing that six validation studies used alternative verbal memory tests to substitute the CVLT-II (e.g., the VMAT in Lebanon and the RAVLT in Germany). The international expert consensus committee has outlined recommendations for the SDMT, CVLT-II and BVMT-R specifically, and these three subtests have been contemporaneously validated. The international validation protocol outlines that it is possible to use an alternative auditory word-list learning test in some countries to replace the CVLT-II, with the caveat that the procedure remains in the common format (Benedict et al., 2012). The scores from these substituted tests were included in the meta-analysis which may have explained the high level of heterogeneity within the CVLT scores.

There are some notable limitations to the review methodology. First, English language publication was a requirement for inclusion in the review, so it is important to recognise that this may have limited the inclusion of validation studies published in other languages. Secondly, only the terms “Multiple Sclerosis”, “MS”. “Clinically Isolated Syndrome” or “CIS” were used in the database search. This may have restricted the number of studies identified through the database search as there are additional ways to describe MS (e.g., as an autoimmune or neurodegenerative disease). Thirdly, as part of the pre-defined criteria, only peer-reviewed studies were considered eligible for inclusion in this review which meant that possible grey literature (e.g., thesis publications) that were not commercially published would not have been included. Fourthly, there are likely to be international disparities across studies in relation to healthcare systems, accessibility, economic status, and access to general MS support facilities (Dobson et al., 2022; Reilly

et al., 2017). MS healthcare in countries with developing economies may be constrained by limited access to high-efficacy DMTs or diagnostic technology such as magnetic resonance imaging (MRI; Rivera, 2018). Developed countries have significantly higher prevalence and incidence rates of MS compared to developing countries which may reflect better access to diagnostic facilities and subsequent earlier diagnosis, and treatment (Moghaddam et al., 2021; Rivera, 2018). These variations in access and quality of MS healthcare may have made comparisons of disease profiles, such as years since diagnosis and physical disability, less valid. Most of the studies included in this review were conducted in leading centres and university hospitals, which attract a certain sociodemographic population and, therefore, may not be entirely representative of all MS populations. Another limitation to the review lies in the quality of studies as they were rated relatively poorly according to the EPHPP. Notably, high-quality validation studies were rated as 'weak' or 'moderate' on several dimensions (e.g., study design and blinding for randomised controlled trials; RCTs), because the requirements for stringent international validation do not correspond with the parameters typically applied to RCTs. For this reason, sensitivity for assessing the quality of validation studies using this tool is likely to be unsatisfactory. Finally, there was a great deal of heterogeneity between studies – namely in terms of sample size, age, MS phenotypes and disease duration. RRMS was overrepresented compared to other MS phenotypes. It is possible that this may have biased the size of effect found since cognitive impairment is more common in the progressive forms of the disease (Brochet & Ruet, 2019; Ruano et al., 2016). With progressive forms of MS being underrepresented in this review, cognitive impairment may also have been underrepresented in the identified studies compared to the general MS population (Sousa et al., 2022). Also, this review only included adults with MS;

paediatric patients with MS have been shown to perform better on cognitive screens compared to adults with MS (Krupp et al., 2022).

Future directions

The adoption of an international validation protocol and a global collaboration have served to promote BICAMS to an international currency for MS cognition. This is reflected in the number of international validations published, the report of BICAMS data in 150 published studies of MS cognition and its use in many large national and international trials. This initiative could serve as a model for other conditions, improving awareness, understanding, assessment and management of cognitive impairment. It is hoped that further research investigating the feasibility of BICAMS in clinical practice will maximise its use in routine consultation to evaluate cognitive status in MS. This systematic review also prompts future studies to investigate the sensitivity and specificity of the scale in different forms of multiple sclerosis or in groups with different degrees of disability.

Conclusion

BICAMS has been translated and culturally adapted in 26 countries to date. It has shown to be a valid measure of cognitive functioning in MS at a global level. It can detect cognitive impairment in individuals with MS compared to healthy controls across a range of cultures, languages, and countries. This review sheds light on the work of the international MS community at validating BICAMS utilising an international validation protocol. This represents progress in increasing awareness of MS cognition as well as

maximising the implementation of BICAMS into routine clinical practice, to assess and instigate appropriate management of MS cognition across different countries.

Chapter 4: Integration, Impact, and Dissemination

Integration

In this section, I reflect on the process of integrating the different chapters in the thesis and the extent to which I was able to achieve synergy between these. My aim was to contribute to the evidence base which would help support delivery of routine cognitive assessment for PwMS.

First, a systematic review and meta-analysis of BICAMS international validations was performed to identify, synthesise, and critically appraise existing literature on BICAMS international validation studies. The systematic review and meta-analysis provided a conceptual basis for the empirical study, detailing the psychometric strength of BICAMS. The systematic review and meta-analysis identified international validations in 26 countries and showed that BICAMS can detect cognitive impairment in PwMS compared to HC across a range of cultures, languages, and countries. The paper contributes to an ongoing understanding of cognitive deficits in MS and demonstrates an international commitment to pursue and support an agenda to measure MS cognition.

The systematic review and meta-analysis was an updated review of the BICAMS international validations following Corfield and Langdon (2018), published by a previous RHUL TCP alongside my supervisor. This publication had 80 citations, so I was aware that this was an area of interest for the MS community. I was impressed at the number of countries who participated in the international validation protocol, and this left me feeling motivated and curious to identify how many more countries had validated BICAMS since

this first review in 2018. I had never written a systematic review or performed a meta-analysis before, so having a review done previously, on the same topic, was helpful for guidance and inspiration.

Although a feasible and psychometrically robust cognitive measure for MS exists, there is relatively little routine use of BICAMS within UK MS clinics by a range of healthcare professionals. Even when BICAMS is used within hospitals for research studies involving staff training and access to materials, it is not subsequently incorporated into routine practice. In an effort to increase uptake, the empirical study sought to investigate the accuracy of BICAMS when scored by MS HCPs and the impact on MS HCPs' and MS patients' perceptions of cognitive impairment. The experiment was designed to gather theoretical and data support for BICAMS adoption. While the chapters of the thesis were fully integrated and combined to form a unified whole, they can also be considered standalone pieces of work as they both offer distinct contributions on BICAMS.

A great deal of literature is appropriately cited in both chapters, indicating that they largely share a common evidence-base and draw on an awareness and understanding of the breadth of studies on BICAMS and cognition in MS. Having an overarching theme of BICAMS and MS cognition across both chapters enabled a clear and succinct narrative to run through the thesis which, I believe, enabled a degree of integration and cohesion. Further, focusing specifically on one cognitive tool also facilitated integration between chapters since research was consistently anchored to findings inherently related to BICAMS. Having a narrowed emphasis on BICAMS meant that I could focus on the current challenges and offer specific recommendations for future research and clinical implications in light of the study's findings.

I sought to supplement and expand upon my knowledge of cognitive deficits in MS through recommended reading, webinars, and talks. For example, I attended an MS-UK webinar for MS patients on cognition and MS. In this webinar, I heard PwMS ask about cognition which provided valuable insight into their concerns and perspectives on cognitive deficits. I also attended a NeuroSIG meeting where my supervisor delivered a talk on MS cognition to clinical psychologists in an online CPD event. This increased my understanding of cognition in MS and provided me with a professional perspective on the challenges of MS cognition. I also read case studies in the book 'Mind, Mood, and Memory: The Neurobehavioural Consequences of Multiple Sclerosis', written by Anthony Feinstein (2022), and reflected on how cognition can impact PwMS. From these collective experiences, I felt confident to reflect on BICAMS and cognition in MS and felt I had built a sound understanding of the research within this field.

I found supervision to be a great source of support throughout the thesis process, particularly with managing synergy between the chapters. For example, my supervisor and I established well-defined research aims and objectives from the beginning and regularly discussed these during supervisions to create clear actionable steps moving forward. I consistently came away from supervisions feeling a sense of clarity about what I was doing and the rationale for why I was doing it. Prior to undertaking the study, I had limited clinical and research experience in MS and cognitive assessments for MS. I reflect on the initial stages of the thesis where I was in the unconscious incompetent stage of my learning, according to the four stages of competence model developed by Noel Burch in the 1970s. I reflect on how containing the supervision space felt during this time in providing direction as I began to develop my understanding of the evidence-base. During this stage, I was able to draw on my supervisor's experience of the research topic and felt her expertise, coupled with her

pragmatism, kept me focused and prevented drift from research aims. Throughout the thesis journey, I reflected on how I progressed through the other stages of competence as my knowledge and experience on the topic grew.

Additionally, interactions with the HCPs through meetings and training sessions also contributed to an awareness of how BICAMS translates clinically as well as the various setbacks clinics face in being able to assess MS cognition. During these meetings and training sessions, the MS HCPs expressed their interest and enthusiasm for using BICAMS to assess cognition in MS, an aspect of clinical practice which they stated was often neglected. These discussions with the HCPs felt motivating as it cemented the importance of applying the study's findings practically to maximise the use of BICAMS clinically.

Impact

In this section, I discuss the potential clinical, academic and real-world implications of the study's findings. I also carefully consider both the significance, originality, and potential reach of the study beyond academia.

The potential beneficiaries of this study include PwMS but also extend to clinical services in which these HCPs work in. BICAMS has been designed to assess and monitor cognition in routine MS clinical practice, by a range of HCPs. There is extensive evidence on the validity and feasibility of BICAMS in many countries, but very little on how well non-psychologists manage the assessment (Penner et al., 2021). In this study, HCPs learnt about MS cognition, how to administer and score BICAMS and feed back to patients. Training HCPs to

administer and score BICAMS will maximise its clinical use and allow routine monitoring of cognition in MS.

I found the MS HCPs' diligence and enthusiasm to be inspiring throughout the study process. This was reflected in how hard they worked to collect data, considering their high clinical workloads and numerous personal and professional setbacks. Many of the HCPs were working additional hours and, still, were keen to be a part of this study. They all demonstrated a passion and willingness to learn more about assessing MS cognition and valued being trained to use BICAMS in their practice. All the centres we approached to participate in the study showed a keenness to get involved and contribute to research in MS cognition. Many of the HCPs reported that their clinic does not routinely assess or monitor cognition but recognised its importance. Therefore, the HCPs were eager to be trained on BICAMS administration and scoring with a view to continue this in their clinic following completion of the study.

Patients with cognitive impairment, physical disabilities and multiple health conditions remain underserved in research according to the National Institute for Health and Care Research (NIHR, 2020). It is recognised that research should include underserved groups and reflect the clinical community who will benefit from the research taking place, as this is fundamental to providing high-quality, evidence-based health care. The NHS Long Term Plan (2019) outlines its commitment to narrowing healthcare inequalities and addressing unwarranted variation in care. The NIHR recently set out an agenda for action to support equity and tackle inequality through greater inclusion in public partnerships (Imison et al., 2022). Inclusive public partnerships, involving marginalised and excluded communities, should be central to delivering high quality research and impact. This study addressed this

concern by collecting data from patients diagnosed with MS, an underrepresented population in the research community. Furthermore, data were collected from district general hospitals, community services and a registered charity. Involving these participating organisations, as opposed to large teaching hospitals, promoted inclusivity in the research.

A service user, diagnosed with MS, was asked to review the study protocol and comment on the study objectives, design, and procedures. The service user's contributions to the planning and design of the study were pivotal in shaping the study, in its initial stages, and influencing its final form. For example, the service user recommended incentivising patient participation, to which we responded with placing all patients in a prize draw with the chance to win a £50 Amazon voucher. EbE involvement ensured that people from underserved communities had the platform and power to influence and inform research. Discussions with a recent panel of interested partners and survey, which included an EbE as a panel member, was reviewed to give a broad framework for the study design and inform study planning (Langdon et al., 2022). Sussex MS HCPs also provided feedback on the study design and procedures, during the BICAMS training session at Brighton General Hospital. Their feedback was valuable in thinking about the practicalities of data collection particularly within the context of limited patient appointments and high clinical workloads. Together, these contributions highlighted the importance of embedding patient and public involvement in research to improve its quality and impact, in line with the NIHR guidance (NIHR, 2021).

This study also included a qualitative survey for HCPs. This allowed HCPs to have an active voice within the final form and express, through their own words, their experiences of using BICAMS and how it may have impacted their perceptions of cognitive impairment. It was refreshing and interesting to read the experiences of the HCPs particularly as there is limited

understanding about the experience of cognitive assessment for HCPs and how this impacts on their perception of patient cognition.

The systematic review and meta-analysis represented an updated review of BICAMS' international validations which have increased by an additional 12 validations since 2018 (Corfield & Langdon, 2018). This surge in BICAMS international validations reflects the ongoing work of the international MS community since the recommendations for BICAMS were first published (Langdon et al., 2012). The demonstrated validity of BICAMS across 26 countries will likely have a significant impact on research in increasing BICAMS' international reach further within the MS community. The meta-analysis showed that PwMS performed significantly worse than HC on the three BICAMS subtests. Information processing speed (as measured by the SDMT) was most impaired in PwMS compared to HC, with the largest effect size. This fits with previous research proposing that information processing speed is markedly reduced in MS (Costa et al., 2017). Thus, these findings contribute to the ongoing understanding of the cognitive processes involved in MS and awareness of a feasible cognitive assessment option for many cultures and linguistic groups.

I have reflected on the process of writing the thesis and the impact it has had on me. I found recruitment to be the biggest challenge and left me, at times, feeling quite despondent about what was achievable within the given timeframe. MS HCPs were initially recruited from Sussex Community NHS Foundation Trust and had consented to take part in the study at the BICAMS training session at Brighton General Hospital in December 2022. The Brighton HCPs were provided with data collection schedules on two separate occasions but were unable to participate in these due to a combination of illness, family bereavements, high workloads and NHS strikes. This impacted on the final sample size obtained and therefore

shifted what was understood to be realistic goals for the study. In response to the delays in data collection, we needed to recruit new MS HCPs and approached 3 other NHS trusts (Dartford and Gravesham NHS Trust, Wye Valley NHS Trust and Cambridgeshire and Peterborough NHS Foundation Trust) as well as The Samson Centre. An IRAS amendment was submitted to outline the new participating organisations involved in the study. Sites where data collection were feasible either had engaged supportive consultant neurologists or charismatic, award winning, nationally leading HCPs.

I have also reflected on the difficulties of collecting data within the NHS specifically e.g., high clinical workloads, time-limited appointments with patients, scarce resources as well as HCP stress and burnout. Many of the HCPs questioned what they would do in the event that patients show cognitive impairment on BICAMS given the limited or complete lack of access to neuropsychology. These questions were understandable given that they did not want to expose patients to potential worry about their cognition if there was nothing they could do in terms of signposting or providing additional support. They were reassured that progression is slow and difficulties are mild in MS cognition. They were each provided with a free pdf copy of 'Fast Facts: Cognition in Multiple Sclerosis' (Langdon & Young, 2023) which they could use and share with patients. This book contained useful resources that HCPs could signpost patients to e.g., links to MS Brain Health and MS-UK. There were also small logistical details, for example, having no access to a suitable room where test materials could be laid out for the purposes of training the HCPs on BICAMS. This meant using a cramped consulting room at Darent Valley Hospital to train HCPs on BICAMS which had no tables and only a personal laptop for powerpoint projection.

From a professional standpoint, I had limited clinical and research experience of MS prior to completing the thesis, as aforementioned. My learning has vastly grown over the course of the thesis and, fortunately, as part of my clinical training, I completed a placement working in the community with patients with neurological difficulties. On this placement, I administered and scored a range of neuropsychological assessments which helped me to feel more confident about conducting research in this area. Furthermore, I have developed an understanding of communicating clinical research in an appropriate and effective way with multiple partnership groups such as through the MS-UK webinar, service-user input, and training HCPs. I have developed skills in conducting literature searches, critiquing and analysing research, scientific writing, NHS documentation (IRAS, R&D, study documents e.g., slides, HCP and patient packs), training, materials and support tailored to fit with clinical demands. Also, publishing the systematic review and meta-analysis involved liaising with journals, meeting specific manuscript guidelines and responding to peer-reviewed comments in a short timeframe. As a result of these experiences, I feel confident to engage in research and publications in the future.

Dissemination

In this section, I discuss how the thesis has been disseminated thus far and steps that will be taken to disseminate the findings further. The intended audience, and who findings are pertinent to, include people with MS, their families and carers, researchers, services, and MS HCPs.

In January 2023, the systematic review and meta-analysis was published in the Journal of Clinical Medicine – an international, peer-reviewed, scientific journal with an impact factor

of 4.964 (see Appendix 8 for publication). This journal covers topics related to MS and cognition (such as clinical psychology, clinical neurology, and immunology) and therefore felt appropriate for publication of the systematic review and meta-analysis. It also has a broader professional audience than a specialist MS journal (e.g., rehabilitation doctors, general neurologists, doctors in training). Submitting the systematic review to this journal provided me with first-hand experience of engaging with a journal, meeting their submission requirements, as well as taking peer-reviewed comments on board and actioning these within a short time frame. As this journal is open access and published in the English language, it is likely to reach a large audience. Since its publication in January 2023, the paper has been viewed 1,346 times on the publisher's website and has been read 107 times on Research Gate. This indicates a good level of interest in the systematic review.

To further promote the systematic review, the journal shared a 200-word summary of the systematic review on their twitter, titled 'BICAMS – the first 10 years'. RHUL also tweeted that I had published the systematic review on their public twitter account, which received 456 views. My supervisor also tweeted the systematic review on her twitter account, which received four retweets (reaching a total of 5,302 followers), 14 likes and 1,258 direct views. The paper was also shared in the RHUL Psychology Newsletter which was circulated to all RHUL staff and students.

My supervisor shared the systematic review post on LinkedIn. To date, the LinkedIn post has received 37 likes, six reposts and 1,951 impressions. Dr Agne Straukiene, Consultant Neurologist in MS, commented on this post with 'Thank you for sharing this update on BICAMS and the new systematic review of international validations. It's great to see ongoing research efforts in the field of MS and cognition, as this is an important aspect of the disease

that affects many individuals living with MS. I appreciate your efforts to keep the community informed and up to date on the latest developments in MS research.' In response to sharing the systematic review on Twitter and LinkedIn, I reflected on the power of social media at reaching an extensive range of clinicians, researchers and service-users.

MS HCPs involved in the study were offered a summary of the research findings and this presentation was held at the recruitment site. Sharing the findings with the MS HCPs who took part in the study was important to inform how, on a service level, BICAMS can be implemented into MS routine clinical practice. Furthermore, by exploring the feasibility of using BICAMS as part of routine clinical practice, we aimed to understand the experience of assessment from the perspective of PwMS and MS HCPs, which could inform guidance offered to PwMS and MS HCPs. The effect of the experience of BICAMS on perceptions of cognitive status could also inform guidance offered to PwMS and MS HCPs regarding preparation for and feedback after BICAMS.

I also discussed the project with my DClinPsy cohort in a timetabled lecture on 'acquired focal deficits and BICAMS', delivered by my supervisor. I also presented the thesis to other TCP's on the RHUL Doctorate in Clinical Psychology (DClinPsy) programme as part of the third-year research presentations. The research presentation provided the opportunity to promote awareness of MS cognition with soon to be qualified TCPs who may go on to work in services with PwMS. Peers were able to ask questions and provide feedback after the presentation which was valuable for generating further discussions on the topic.

It is an aim to present the findings at an international conference, possibly the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). ECTRIMS hosts

the world's largest annual international conference committed to providing knowledge and scientific advancements in MS. The empirical chapter will also be written up for publication in Multiple Sclerosis and Related Disorders (MSARD) – an international, peer-reviewed journal with an impact factor of 4.808. This journal focuses on research in the field of MS and associated diseases of the central nervous system.

Efforts will be made to share the findings through MS charity webinars, websites, and newsletters. Professional channels will also be used to reach MS nurses such as the UK MS Specialist Nurse Association (UKMSSNA) which is a professional organisation for clinical nurse specialists and other practitioners in MS. Disseminating the research findings to this audience provides an opportunity to influence the development of MS services and increase awareness of BICAMS and its feasibility in assessing MS cognition on both a national and international level.

A summary of the findings will also be shared on the MS Trust professional website. The MS Trust is a well-established, national organisation which is highly recognised in the MS community and serves to provide information and support for PwMS. Last year, I witnessed a recently qualified clinical psychologist present the findings of her thesis at a webinar hosted by MS-UK for PwMS. This highlighted how important it is to deliver information to those who take part in the research.

To conclude, the findings of this research have reached a variety of channels and audiences. There are plans to continue to disseminate the findings further, and this will have valuable implications for clinical practice as well as ongoing research in the field of MS cognition.

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Appendices

Appendix 1: Patient information sheet

SUMMARY SHEET – PATIENT

Study title: Accuracy of Brief International Cognitive Assessment for MS when scored by MS HCPs and impact on MS HCPs' and MS patients' perception of cognitive impairment.

Name of researcher: Hannah Potticary

Sponsor organisation: Royal Holloway, University of London

In this research study we will use information from you and your medical records. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study.

Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules.

At the end of the study, we will save some of the data in case we need to check it. We will make sure no-one can work out who you are from the reports we write.

The information pack (attached below) tells you more about this.

PARTICIPANT INFORMATION SHEET – PATIENT

Why have I been invited?

We, the sponsor, would like to invite you to take part in our research study. You have been invited to take part because you have a diagnosis of multiple sclerosis (MS). Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information sheet and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please contact us (details can be found at the end of this information sheet).

What is the purpose of the study?

MS is a lifelong condition that can affect the brain and spinal cord. Among a range of symptoms, including problems with vision, balance and mood, people with MS may also experience problems with their cognition. Cognition describes mental processes such as thinking, understanding, learning, and remembering information. The Brief International Cognitive Assessment for MS (BICAMS) is a short tool used to assess problems with cognition in people with MS. It has been designed to be completed with various healthcare professionals, such as HCPs, but there is little research about how feasible this is. Currently, BICAMS is not routinely available in your MS clinic. We are evaluating this novel assessment and the possibility of it being included in routine clinical practice. However, we need to know how feasible it is for HCPs, to support routine cognitive assessment in MS clinics, which would facilitate cognition being addressed and managed. The purpose of this study is to assess the accuracy of MS HCPs' scores by comparing them with scores of a trainee clinical psychologist (TCP). We will also explore the MS HCPs' and patients' experiences of completing BICAMS and how this impacts their understanding of cognition.

What would taking part involve?

Taking part in the study will involve completing five brief questionnaires relating to mood, disability, fatigue, and your everyday memory. You will complete BICAMS with a HCP, which takes fifteen minutes and involves remembering patterns and words. You will then receive feedback on your performance approximately two weeks later. At the end of the study, you will complete a brief survey on your experiences of completing and receiving feedback on BICAMS. Completing these measures with your HCP is likely to take place as part of your normal routine clinical appointment. However, there may be instances where extra clinical visits are required if there is no time during your usual appointment. You will be offered a choice between completing these measures during a home visit or in clinic.

This survey should be answered honestly. Your MS HCP will not see or be made aware of your responses, as your responses will be sealed in an envelope which will state your study number and will be shared only with the researchers involved in this study. The questionnaires and BICAMS will be administered by your regular MS HCP and not the University researcher of this study.

Do I have to take part?

No, taking part is entirely voluntary. If you decide to take part but change your mind during your participation in the study, you can withdraw without giving a reason and this will not affect your clinical care.

How long am I expected to take part for?

We aim for approximately two weeks from your assessment to the feedback, however, for logistical or clinical reasons it may mean that for some participants, the involvement may be slightly longer.

Are there any possible disadvantages or risks from taking part?

We do not expect any major disadvantages or risks from taking part in the study. However, as the procedures involve reflecting on information concerning cognitive impairment, it is possible that some participants may find this distressing. The HCPs are experienced in managing psychological distress if this occurs. BICAMS has been used extensively in the UK and across the world with tens of thousands of patients and patient distress has not been reported. Furthermore, your participation will involve a time commitment of one hour for the assessment and thirty minutes for the feedback approximately two weeks later.

What are some benefits of taking part?

You will receive information about your cognitive status, as determined by BICAMS. Your MS clinic will also have access to this information and can modify their consultations with you, if appropriate. You will also be placed into a prize draw to win a £50 Amazon voucher if you consent to this. This draw will be held at the end of the study, and you will be notified if you have won and will be compensated accordingly.

How will we use information about you?

We will need to use information from you and your medical records for this research project. This information will include your name, disease and demographic data relating to lifetime history of MS, type of MS, current medications, and other mental health/neurological/medical conditions, and research data relating to the study. People will use this information to do the research or to check your records to make sure that the research is being done properly. Researchers who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

Where can I find out more about how my information is used?

You can find out more about how we use your information through:

- This website www.hra.nhs.uk/information-about-patients/
- This leaflet www.hra.nhs.uk/patientdataandresearch
- Speaking to our data protection officer by emailing dataprotection@rhul.ac.uk
- Asking one of the research team by emailing hannah.potticary.2020@live.rhul.ac.uk

Will my data be kept confidential?

Participants will be allocated a study number in accordance with the BPS Code of Ethics and Conduct. A list of study numbers and patient names will be kept securely and separately from the questionnaire data. Anonymised BICAMS data, with no study number or date, will be stored in a database for further analysis to develop new scoring methods and investigate statistical properties.

How will my data be stored?

Your data will be electronically stored on an encrypted USB stick or computer file which is only accessible to the researchers involved in the study, and a back-up will be stored on the Royal Holloway University of London (RHUL) server. In accordance with research policies at RHUL, data will be stored on RHUL's secure data depository, Figshare, and destroyed after 5 years. The consent form with your name and a list of study numbers and patient names will be stored in a locked cabinet in the Department of Psychology at RHUL and will be destroyed after 2 years.

Who will be informed of my participation?

Your MS HCP must log your involvement in the study in the medical record. The MS HCPs will therefore inform other healthcare professionals via the medical record. Your GP will also be contacted and informed of your participation if you decide to consent.

What will happen to the results of the study?

This study is part of an educational project and will contribute to the fulfilment of a doctoral thesis, which is forms part of the lead researcher's professional qualification to practice as a clinical psychologist in the NHS. The group findings will be presented to other health care professionals and patient groups. We aim to share the findings at an international conference and through MS charity webinars, websites, and newsletters.

How can I find out the results of the study?

If you are interested in receiving a summary of the study once it has been completed, please let your MS HCP know and they will happily circulate that information to you. In the attached consent form, you will be asked to consent to your contact details being used for this purpose. Your contact details will be deleted upon circulating this information to you.

What if there is a problem?

We hope that you will have no cause for concern from your involvement in our study. However, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during this study, you should contact Hannah Potticary by sending an email to hannah.potticary.2020@live.rhul.ac.uk

You can also get in touch with Patient Advice and Liaison Service (PALS) to make a complaint and receive support with this process. PALS investigate all formal complaints so we can learn and improve our services for our patients and service users.

A complaint can be made face to face, by phone, email, online or in a letter to:

Patient Advice and Liaison Service,
Brighton General Hospital,
Elm grove,
Brighton,
BN2 3EW
Telephone: 01273 242292
Email: sc-tr.serviceexperience@nhs.net

Thank you for reading this information.
If you would like to take part in this study, please kindly sign the consent form provided.

Appendix 2: Patient consent form

PARTICIPANT CONSENT FORM – PATIENT

Study Title: Accuracy of Brief International Cognitive Assessment for MS when scored by MS HCPs and impact on MS HCPs' and MS patients' perception of cognitive impairment.

Name of Researcher: Hannah Potticary

If you agree, please initial box

1. I confirm that I have read the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by the researchers, individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. ☐
5. I understand that the information held and maintained by the NHS may be used to help contact me to provide information about my health status. ☐
6. I understand that MS HCPs will log my involvement and data from the study in the medical record and my GP will also be informed of my participation. ☐
7. I understand that anonymous quotes from patients may be used in publications of this study. ☐
8. *(Optional)* I consent to being placed into a prize draw to win a £50 Amazon gift voucher and for my contact details to be used to notify me if I have won. ☐
9. *(Optional)* I give permission for my contact details to be used to send me a summary of the study if I have expressed interest to the MS HCP. These details will be deleted upon circulation of the study summary. ☐
10. I agree to take part in the study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person seeking consent	Date	Signature

Appendix 3: HCP information sheet

SUMMARY SHEET – MS HCP

Study title: Accuracy of Brief International Cognitive Assessment for MS when scored by MS HCPs and impact on MS HCPs' and MS patients' perception of cognitive impairment.

Name of researcher: Hannah Potticary

Sponsor organisation: Royal Holloway, University of London

In this research study we will use information from you. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study.

Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules.

At the end of the study, we will save some of the data in case we need to check it. We will make sure no-one can work out who you are from the reports we write.

The information pack (attached below) tells you more about this.

PARTICIPANT INFORMATION SHEET – MS HCP

Why have I been invited?

We, the sponsor, would like to invite you to take part in our research study. You have been invited to take part because you are a multiple sclerosis (MS) HCP. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information sheet and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please contact us (details can be found at the end of this information sheet).

What is the purpose of the study?

MS is a lifelong condition that can affect the brain and spinal cord. Among a range of symptoms, including problems with vision, balance and mood, people with MS may also experience problems with their cognition. Cognition describes mental processes such as thinking, understanding, learning, and remembering information. The Brief International Cognitive Assessment for MS (BICAMS) is a short tool used to assess problems with cognition in people with MS. It has been designed to be completed by various healthcare professionals, such as HCPs, but there is little research about how feasible this is. Currently, BICAMS is not routinely available in your MS clinic. We are evaluating this novel assessment and the possibility of it being included in routine clinical practice. However, we need to know this to support routine cognitive assessment in MS clinics, which would facilitate cognition being addressed and managed. The purpose of this study is to assess the accuracy of MS HCPs' scores by comparing their scores with the scores of a trainee clinical psychologist (TCP). We will also explore the MS HCPs' and patients' experiences of completing BICAMS and how this impacts their understanding of cognition.

What would taking part involve?

Prior to taking part in the study, you will be invited to attend training on BICAMS which will cover how to administer, score and feed back on this assessment to patients. This training will take place for approximately half a day. Taking part in the study will involve administering brief questionnaires relating to mood, disability, fatigue, and everyday memory to patients. You will also complete an informant version of a measure on patients' cognitive impairment three times across the two-week study timeframe. Taking part will also involve administering, scoring, and feeding back on BICAMS to the patient. At the end of the study, you will complete a brief survey on your experiences of administering, scoring, and feeding back on BICAMS. Completing these measures with the patient is likely to take place as part of their normal routine clinical appointment. However, there may be instances where extra clinical visits are required if there is no time during their usual appointment. The patient will be offered a choice between completing these measures during a home visit or in clinic. Each patient recruited per HCP is likely to require approximately 4

hours of your time. If you wish to be involved in the TCP's thesis papers, we can negotiate this contribution with you.

Do I have to take part?

No, taking part is entirely voluntary. If you decide to take part but change your mind during your participation in the study, you can withdraw without giving a reason. However, we will keep information you have already contributed to the study.

How long am I expected to take part for?

We aim to be collecting data from July 2022 to May 2023.

Are there any possible disadvantages or risks from taking part?

We do not anticipate any major disadvantages or risks from taking part in the study.

What are some benefits of taking part?

You will receive training on how to administer, score and feed back on BICAMS as a result of participating in this study. Knowing whether your patients have cognitive impairment or not will enable you to manage their MS in a more informed way.

How will we use information about you?

We will need to use information from you for this research project. This information will include your name along with research data relating to the study. People will use this information to do the research or to check your records to make sure that the research is being done properly. Researchers who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. Publications will be written in such a way that your scores will not be linked to you in any way or identifiable as your work.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

Where can I find out more about how my information is used?

You can find out more about how we use your information through:

- This website www.hra.nhs.uk/information-about-patients/
- This leaflet www.hra.nhs.uk/patientdataandresearch
- Speaking to our data protection officer by emailing dataprotection@rhul.ac.uk
- Asking one of the research team by emailing hannah.potticary.2020@live.rhul.ac.uk

Will my data be kept confidential?

MS HCPs will be allocated an MS HCP study number in accordance with the BPS Code of Ethics and Conduct. A list of study numbers will be kept securely and separately from the questionnaire data. However, because the study design involves supporting your scoring and patient interactions concerning BICAMS, your identity will be known to the researchers in relation to your study activity, including completed questionnaires. Data relating to your performance on scoring BICAMS and feeding back to patients will remain confidential within the research team. Publications will be written in such a way that your scores will not be linked to you in any way or identifiable as your work.

How will my data be stored?

Your data will be electronically stored on an encrypted USB stick or computer file which is only accessible to the researchers involved in the study, and a back-up will be stored on the Royal Holloway University of London (RHUL) server. In accordance with research policies at RHUL, data will be stored on RHUL's secure data depository, Figshare, and destroyed after 5 years. The consent form with your name and a list of study numbers will be stored in a locked cabinet in the Department of Psychology at RHUL and will be destroyed after 2 years.

What will happen to the results of the study?

This study is part of an educational project and will contribute to the fulfilment of a clinical doctorate thesis, which forms part of the lead researcher's professional qualification to practice as a clinical psychologist in the NHS. The group findings will be presented to other health care professionals and patient groups. We aim to share the findings at an international conference, through MS charity webinars, websites, and newsletters and via peer review journals.

How can I find out the results of the study?

MS HCPs who have participated will receive a presentation of the findings. A written summary will be available on request. You will also be advised of any resulting publications.

What if there is a problem?

We hope that you will have no cause for concern from your involvement in our study. However, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during this study, you should contact Hannah Potticary by sending an email to hannah.potticary.2020@live.rhul.ac.uk

You can also get in touch with Patient Advice and Liaison Service (PALS) to make a complaint and receive support with this process. PALS investigate all formal complaints so we can learn and improve our services for our patients and service users.

A complaint can be made face to face, by phone, email, online or in a letter to:

Patient Advice and Liaison Service,
Brighton General Hospital,
Elm grove,
Brighton,
BN2 3EW
Telephone: 01273 242292
Email: sc-tr.serviceexperience@nhs.net

Thank you for reading this information.
If you would like to take part in this study, please kindly sign the consent form provided.

Appendix 4: HCP consent form

PARTICIPANT CONSENT FORM – MS HCP

Study Title: Accuracy of Brief International Cognitive Assessment for MS when scored by MS HCPs and impact on MS HCPs' and MS patients' perception of cognitive impairment.

Name of Researcher: Hannah Potticary

If you agree, please initial box

1. I confirm that I have read the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ☐
3. I understand that the information collected as part of the study may be used to support other research in the future and may be shared anonymously with other researchers. ☐
4. I consent to administering, scoring, and feeding back on BICAMS to patients as well as administering several other questionnaires to patients. ☐
5. I consent to completing a number of questionnaires for the purpose of this study. ☐
6. I agree to attend BICAMS training which is necessary as part of the study. ☐
7. I understand that anonymous quotes from MS HCPs may be used in publications of this study. ☐
8. I agree to take part in the study. ☐

Name of HCP	Date	Signature
Name of Person seeking consent	Date	Signature

Appendix 5: Ethics approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Hannah Potticary
Trainee Clinical Psychologist
Royal Holloway, University of London
Dept of Psychology
Royal Holloway, University of London
Egham
TW20 0EX

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

26 August 2022

Dear Miss Potticary

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Accuracy of Brief International Cognitive Assessment for MS when scored by MS nurses and impact on MS nurses' and MS patients' perception of cognitive impairment.**
IRAS project ID:	**312888**
Protocol number:	**N/A**
REC reference:	**22/LO/0452**
Sponsor	**Royal Holloway, University of London**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **312888**. Please quote this on all correspondence.

Yours sincerely,
Laura Howe

Approvals Specialist
Email: approvals@hra.nhs.uk

Copy to: *Dr Gary Brown*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Cover Letter [Response to request for further information]	1	25 August 2022
Evidence of Sponsor insurance or indemnity (non-NHS Sponsors only) [Indemnity cover RHUL]	1	28 February 2022
GP/consultant information sheets or letters [GP letter]	1	07 April 2022
IRAS Application Form [IRAS_Form_17052022]		17 May 2022
Non-validated questionnaire [Nurse Survey]	1	09 June 2022
Non-validated questionnaire [Patient Survey]	1	09 June 2022
Non-validated questionnaire [Disease and demographic - patient]	1	09 June 2022
Non-validated questionnaire [Demographic - nurse]	1	17 July 2022
Organisation Information Document		
Other [Study approval by research ethics committee]	1	08 February 2022
Other [Conditional approval responses from RHUL DClinPsy Research Committee]	2	06 February 2022
Other [Checklist of documents required for provisional opinion]	1	26 July 2022
Other [REC responses]	1	26 July 2022
Participant consent form [Nurse consent form]	2	01 July 2022
Participant consent form [Participant Consent Form]	4	03 August 2022
Participant information sheet (PIS) [Nurse information sheet]	3	03 August 2022
Participant information sheet (PIS) [Participant Information Sheet]	4	03 August 2022
Referee's report or other scientific critique report [Conditional response]	1	27 February 2022
Research protocol or project proposal [Ethics protocol]	4	30 June 2022
Schedule of Events or SoECAT [Schedule of events]	1	07 June 2022
Summary CV for Chief Investigator (CI) [CV for chief investigator]	1	04 March 2022
Summary CV for student [CV for student]	1	04 March 2022
Summary CV for supervisor (student research) [CV for supervisor]	1	04 March 2022
Validated questionnaire [MSNQ-P 2]		
Validated questionnaire [MSNQ-P 3]		
Validated questionnaire [BICAMS]		
Validated questionnaire [FSS]		
Validated questionnaire [HADS]		
Validated questionnaire [PDDS]		
Validated questionnaire [MSNQ-I 1]		
Validated questionnaire [MSNQ-I 2]		
Validated questionnaire [MSNQ-I 3]		
Validated questionnaire [MSNQ-P 1]		

IRAS project ID	312888

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is one participating NHS organisation taking part in the study in England. Therefore, there is one site type undertaking the research activities as detailed in the study protocol.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study in accordance with the contracting expectations detailed.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other agreement to be used with participating NHS organisations of this type.	The sponsor has detailed its proposals with respect to whether any study funding will be provided to participating NHS organisations of this type in the relevant Organisation Information Document. This should be read in conjunction with the relevant Schedule of Events/SoECAT which details the cost implications of the study for participating NHS organisations.	In line with HRA/HCRW expectations a Principal Investigator should be appointed at participating NHS organisations of this type.	Where an external individual who does not already hold an NHS employment contract will be conducting any of the research activities that will be undertaken at this site type then they would be expected to hold an Honorary Research Contract. External staff holding pre-existing NHS employment contracts should obtain a Letter of Access. The pre-engagement checks should include an enhanced DBS check (including a check against the DBS 'barred list' for adults) and Occupational Health Clearance.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

NHS
Health Research Authority
London - London Bridge Research Ethics Committee
2 Redman Place |
Stratford
London
E20 1JQ

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

26 August 2022

Miss Hannah Potticary
Trainee Clinical Psychologist
Royal Holloway, University of London
Dept of Psychology
Royal Holloway, University of London
Egham
TW20 0EX

Dear Miss Potticary

Study title:	**Accuracy of Brief International Cognitive Assessment for MS when scored by MS nurses and impact on MS nurses' and MS patients' perception of cognitive impairment.**
REC reference:	**22/LO/0452**
Protocol number:	**N/A**
IRAS project ID:	**312888**

Thank you for your letter responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of

research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as:

- clinical trial of an investigational medicinal product
- clinical investigation or other study of a medical device
- combined trial of an investigational medicinal product and an investigational medical device
- other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by the HRA (for more information on registration and requesting a deferral see: Research registration and research project identifiers).

If you have not already included registration details in your IRAS application form you should notify the REC of the registration details as soon as possible.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit:
https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at:
https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at
https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or

management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Cover Letter [Response to request for further information]	1	25 August 2022
Evidence of Sponsor insurance or indemnity (non-NHS Sponsors only) [Indemnity cover RHUL]	1	28 February 2022
GP/consultant information sheets or letters [GP letter]	1	07 April 2022
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Summary CV for student [CV for student]	1	04 March 2022
Summary CV for supervisor (student research) [CV for supervisor]	1	04 March 2022
Validated questionnaire [BICAMS]		
Validated questionnaire [FSS]		
Validated questionnaire [HADS]		
Validated questionnaire [PDDS]		
Validated questionnaire [MSNQ-I 1]		
Validated questionnaire [MSNQ-I 2]		
Validated questionnaire [MSNQ-I 3]		
Validated questionnaire [MSNQ-P 1]		

Validated questionnaire [MSNQ-P 2]		
Validated questionnaire [MSNQ-P 3]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high-quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 312888 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

Laura Howe
Approvals Specialist

On behalf of

Ms Jane Smith
Chair

Email:londonbridge.rec@hra.nhs.uk

Copy to: Dr Gary Brown

Appendix 6: IRAS amendments

IRAS amendment 1

Amendment Tool

v1.6 06 December 2021

For office use

QC: No

Section 1: Project information

Short project title*:	Accuracy and feasibility of BICAMS when scored by MS nurses.
IRAS project ID* (or REC reference if no IRAS project ID is available):	312888
Sponsor amendment reference number*:	Non-Substantial Amendment 01
Sponsor amendment date* (enter as DD/MM/YY):	31 December 2022
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	A. Our original IRAS permission was for us to recruit MS Nurses as site investigators. Having met with the site team, it emerged that physiotherapists are also working in the MS support team, fulfilling the same community support role as MS Nurses. We would therefore like to recruit physiotherapists from the community support team as well as MS Nurses as site investigators. B. Our original IRAS permission was for the MS patients to meet with the health professional investigators on three occasions: 1 To read information sheet and sign consent 2 To complete majority of questionnaires, including assessment of cognition (memory and concentration) 3 To receive feedback on cognitive assessment and complete final few questionnaires. Patients would complete survey unseen by health professional investigator and place and seal in an envelope, which would be handed to health professional investigator and posted to Royal Holloway researchers. There would be no personal information on the survey, only date and patient study number. Having met with our on-site collaborators, these health professionals feel that the burden on patients and themselves could be reduced if the first and third contact were by phone: 1 To read information sheet and consent form during a phone interview (patients are on email so documents can be sent to them) 2 At least a week later, to review information sheet in person and sign consent form. To complete majority of questionnaires, including assessment of cognition (memory and concentration) 3 Approximately a week later, to receive feedback on cognitive assessment and complete final few questionnaires during a phone interview. Patients would be prompted to complete survey and place and seal in a stamped addressed envelope, which would be posted to Royal Holloway researchers.

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	Yes	No	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		**No**	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		**No**	
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		**No**	
Did the study involve children OR does the amendment introduce this?:	Yes		**No**	
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**		No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes		**No**	
	England	Wales	Scotland	Northern Ireland

Lead nation for the study:	**Yes**	No	No	No
Which nations had participating NHS/HSC organisations prior to this amendment?	**Yes**	No	No	No
Which nations will have participating NHS/HSC organisations after this amendment?	**Yes**	No	No	No
Was this a "single site, self sponsored" study in England or Wales prior to this amendment?	Yes		**No**	

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1				
Area of change (select)*:	Participant Procedures			
Specific change (select - only available when area of change is selected first)*:	Participant procedures - minor change that can be implemented within existing resource at participating organisations - Please specify in the free text below			
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	1. Our original IRAS permission was for us to recruit MS Nurses as site investigators. Having met with the site team, it emerged that physiotherapists are also working in the MS support team, fulfilling the same community support role as MS Nurses. This aligns with the Health Education England Multidisciplinary Team Toolkit (2021) guidance (https://www.hee.nhs.uk/sites/default/files/documents/HEE_MDT_Toolkit_V1.1.pdf). We would therefore like to recruit physiotherapists from the community support team as well as MS Nurses as site investigators.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 2				
Area of change (select)*:	Participant Procedures			
Specific change (select - only available when area of change is selected first)*:	Participant procedures - minor change that can be implemented within existing resource at participating organisations - Please specify in the free text below			
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	2. Contact 1. Our original IRAS permission was for the MS patients to meet with the health professional investigators for an in person visit to read information sheet and sign consent form. Our health professional site investigators feel that this places an unnecessary burden on patients and investigators. We are therefore requesting that the first contact should be a phone interview, when the information sheet and consent form are fully discussed, but the actual signing of the consent form take place at least a week later at the only in person contact (see change 3 below). The health professional site investigators are aware that all patients are on email and so documents can easily be provided. The recruited patients are well known to the health professional investigators, who meet with them regularly for clinical care, typically over a number of years.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 3				
Area of change (select)*:	Study Design			
Specific change (select - only available when area of change is selected first)*:	Other minor change to study design that can be implemented within existing resource in place at participating organisations - Please specify in the free text below			
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	3. Contact 2. Our original IRAS permission was for a second in person contact to complete the majority of questionnaires and a 15-minute cognitive assessment. Contact 2 will now be the only in person meeting. We are requesting that the actual wet ink signing of the consent form will also take place at the start of this meeting, with the information sheet and consent form having been fully discussed at least a week previously in a telephone interview (see change 2 above). The recruited patients are well known to the health professional investigators, who meet with them regularly for clinical care, typically over a number of years.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No

Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**	Some
		Remove all changes below

Change 4	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Other minor change to study design that can be implemented within existing resource in place at participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	4. Contact 3. Our original IRAS permission was for a third contact to be an in person meeting to receive feedback on cognitive assessment and complete final few questionnaires, approximately a week after Contact 2. Having met with our on-site collaborators, these health professionals feel that the burden on patients and themselves could be reduced if the first and third contact were by phone. We are therefore requesting that the third contact will be a telephone interview, rather than in person. The questionnaire to be completed comprises 15 questions about the impact of cognitive difficulties on daily life (e.g. forgetting to take tablets). It is a validated questionnaire with extensive research data, which is summarised in our original IRAS application (Multiple Sclerosis Neuropsychology Questionnaire, Benedict et al., 2003). Our original IRAS permission required that patients would complete a brief survey of their experience unseen by the health professional investigator and place and seal it in an envelope, which would be handed to the health professional investigator and posted to Royal Holloway researchers. We are requesting the change that patients would be prompted in the phone interview to complete the survey and place and seal in a stamped addressed envelope, which the patients would post to Royal Holloway researchers. There is no personal information on the brief survey, only date and patient study number are included on the document. The recruited patients are well known to the health professional investigators, who meet with them regularly for clinical care, typically over a number of years.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	

Add another change

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

*Name [first name and surname]**:	Hannah Potticary
*Email address**:	hannah.potticary.2020@live.rhul.ac.uk

Lock for submission

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IRAS amendment 2

Amendment Tool

For office use
QC: No

Section 1: Project information

Short project title*:	Accuracy and feasibility of BICAMS when scored by MS HCPs.
IRAS project ID* (or REC reference if no IRAS project ID is available):	312888
Sponsor amendment reference number*:	Non-Substantial Amendment
Sponsor amendment date* (enter as DD/MM/YY):	04 May 2023
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	Our original IRAS permission was to collect data between June 2022 and April 2023. However, we have encountered some delays in data collection. Initially, MS HCPs were recruited from Sussex Community NHS Foundation Trust and had consented to take part in the study at the BICAMS training session at Brighton General Hospital in December 2022. The Brighton HCPs were unable to start data collection due to a combination of illness and family bereavements. The disruption caused by the NHS strikes also posed a challenge to recruitment. Since Brighton HCPs were delayed in collecting data, approached 2 other trusts – Dartford and Gravesham NHS Trust and Wye Valley NHS Trust. We are awaiting Research and Development (R&D) approval from both recruitment sites to commence data collection. We therefore request an amendment that the data collection window is extended to 31st December 2023.

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	Yes	No	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		**No**	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		**No**	
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		**No**	
Did the study involve children OR does the amendment introduce this?:	Yes		**No**	
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**		No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes		**No**	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	**Yes**	No	No	No
Which nations had participating NHS/HSC organisations prior to this amendment?	**Yes**	No	No	No
Which nations will have participating NHS/HSC organisations after this amendment?	**Yes**	No	No	No
Was this a "single site, self sponsored" study in England or Wales prior to this amendment?	Yes		**No**	

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Extension to study duration that will not have any additional resource implications for participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	Our original IRAS permission was to collect data between June 2022 and April 2023. However, we have encountered some delays in data collection. Initially, MS HCPs were recruited from Sussex Community NHS Foundation Trust and had consented to take part in the study at the BICAMS training session at Brighton General Hospital in December 2022. The Brighton HCPs were unable to start data collection due to a combination of illness and family bereavements. The disruption caused by the NHS strikes also posed a challenge to recruitment. Since Brighton HCPs were delayed in collecting data, approached 2 other trusts – Dartford and Gravesham NHS Trust and Wye Valley NHS Trust. We are awaiting Research and Development (R&D) approval from both recruitment sites to commence data collection. We therefore request an amendment that the data collection window is extended to 31st December 2023.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	

Add another change

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

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- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name [first name and surname]:*	Hannah Potticary
Email address:*	hannah.potticary.2020@live.rhul.ac.uk

Lock for submission

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Lock for submission

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IRAS amendment 3

Amendment Tool	For office use QC: No

Section 1: Project information

Short project title*:	Accuracy and feasibility of BICAMS when scored by MS HCPs.
IRAS project ID* (or REC reference if no IRAS project ID is available):	312888
Sponsor amendment reference number*:	Non-Substantial Amendment
Sponsor amendment date* (enter as DD/MM/YY):	10 May 2023
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	A. Our original IRAS permission was to collect data from Sussex Community NHS Trust. However, the Brighton HCPs were unable to start data collection within the scheduled time frames due to a combination of illness, family bereavements and NHS strikes. Since Brighton HCPs were delayed in collecting data, we approached 3 other trusts/centres – Dartford and Gravesham NHS Trust, Wye Valley NHS Trust and The Samson Centre. We are therefore requesting an amendment that data is also collected at the 3 other trusts/centres, in addition to Sussex Community NHS Trust. B. Our original IRAS application, our first patient contact, to discuss the information sheet and consent form, was via telephone. Similarly, in our original IRAS application, our third patinet contact, to give feedback and collect final questionnaire data, was also via telephone. Having met with our collaborator at The Samson Centre, it is felt that all 3 contacts could be completed face-to-face since they often see patients for weekly face-to-face appointments. We are therefore requesting that, for The Samson Centre, the first and third contact is either completed face-to-face or via telephone call.

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	Yes	No	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		**No**	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		**No**	
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		**No**	
Did the study involve children OR does the amendment introduce this?:	Yes		**No**	
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**		No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes		**No**	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	**Yes**	No	No	No
Which nations had participating NHS/HSC organisations prior to this amendment?	**Yes**	No	No	No
Which nations will have participating NHS/HSC organisations after this amendment?	**Yes**	No	No	No
Was this a "single site, self sponsored" study in England or Wales prior to this amendment?	Yes		**No**	

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1	
Area of change (select)*:	Participating Organisations
Specific change (select - only available when area of change is selected first)*:	Addition of sites undertaking the same activities as existing sites

Further information (free text - note that this field will adapt to the amount of text entered):	Our original IRAS permission was to collect data from Sussex Community NHS Trust. However, the Brighton HCPs were unable to start data collection within the scheduled timeframes due to a combination of illness, family bereavements and NHS strikes. Since Brighton HCPs were delayed in collecting data, we approached 3 other trusts/centres – Dartford and Gravesham NHS Trust, Wye Valley NHS Trust and The Samson Centre. We are therefore requesting an amendment that data is also collected at the 3 other trusts/centres, in addition to Sussex Community NHS Trust. The Samson Centre for MS (https://samsoncentre.org.uk/) is a charity set up for people with MS, by people with MS. Today the Samson Centre has over 250 users of all ages. It is not an NHS clinic. The staff are keen to participate in our project.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NI HSC/I HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 2	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Other minor change to study design that can be implemented within existing resource in place at participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	Our original IRAS permission was for the first and third patient contact to be via telephone call, with the second being face-to-face, to reduce the burden on patients and HCPs. Having met with our collaborator at The Samson Centre, it is felt that all 3 contacts could be completed via telephone call or face-to-face since they regularly see patients face-to-face. We are therefore requesting that, for The Samson Centre, the first and third contact is either completed face-to-face or via telephone call.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	**Yes**	No	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Add another change	

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

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*Name [first name and surname]**:	Hannah Potticary
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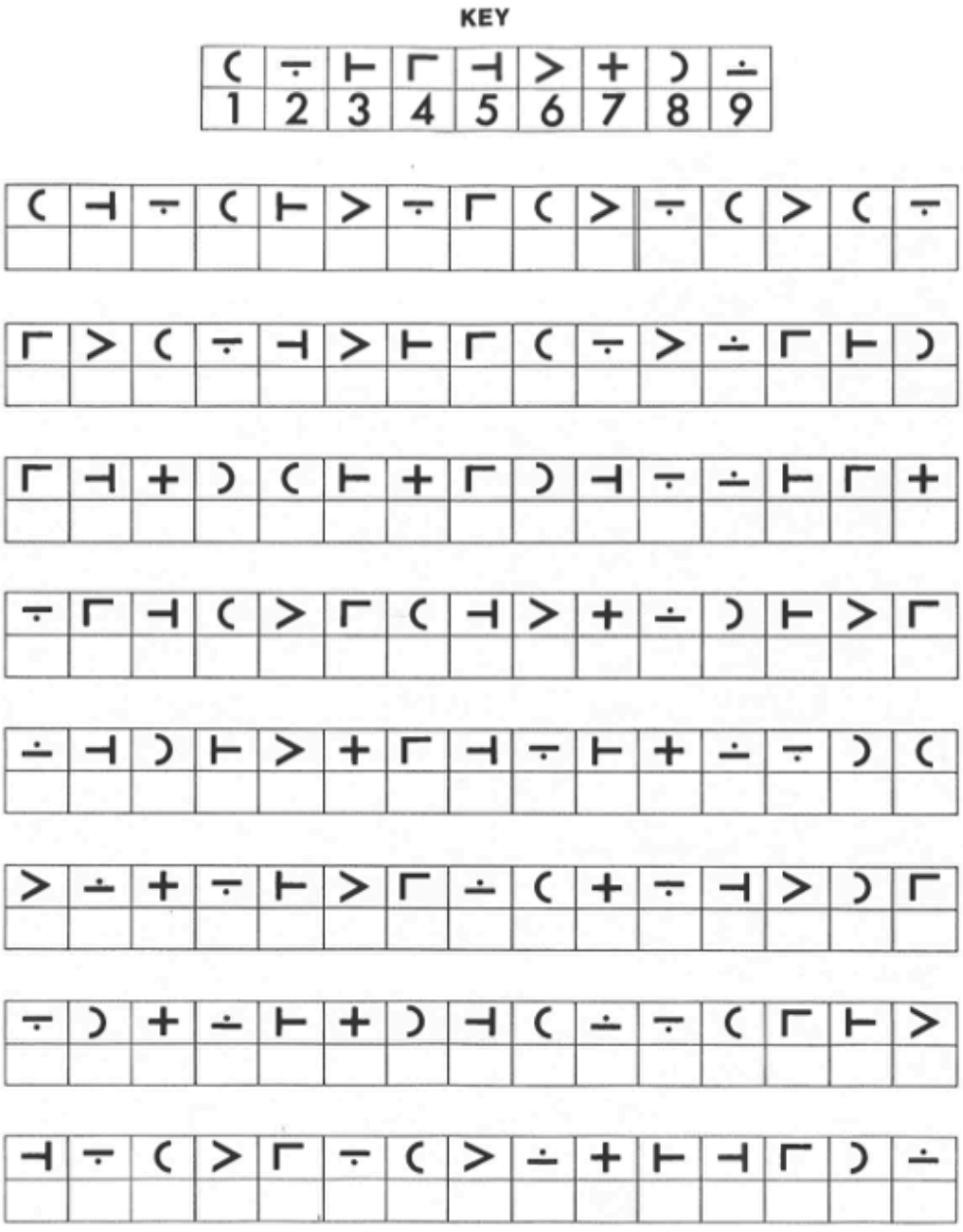
Appendix 7: Measures

BICAMS (SDMT)



BICAMS (CVLT-II)

Trial 1 - Immediate Free Recall
I'm going to read a list of words to you. Listen carefully because when I'm through, I want you to tell me as many of the words as you can. You can say them in any order, just say as many of them as you can. Are you ready?

Trial 2
I'm going to read the same list again. Like before, tell me as many of the words as you can, in any order. Be sure to also say words from the list that you told me the first time.

Trial 3 and 4
I'm going to read the same list again. Like before, tell me as many of the words as you can, in any order, including words from the list you've said before.

Trial 5
I'm going to read the same list one more time. Like before, tell me as many of the words as you can, in any order, including words from the list you've said before.

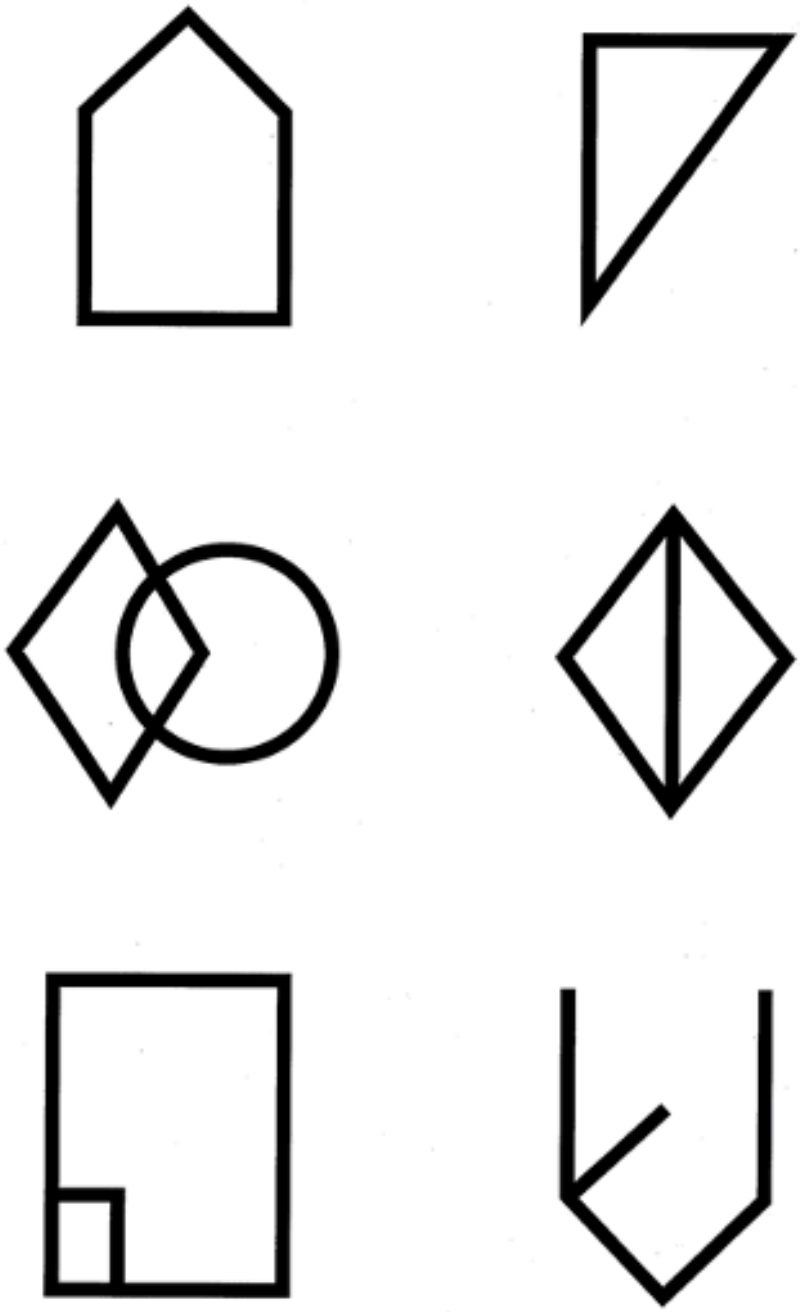
Read list at an even pace, taking slightly longer than one second per word, so the entire list takes 18 to 20 seconds. Then say: **Go ahead.**

Record all responses verbatim, in the order recalled. Prompt only once (e.g., Anything else?) at the end of each free and cued recall trial (i.e., after 15 seconds with no response or when the examinee says he/she cannot remember more words).

List
Truck
Spinach
Giraffe
Bookcase
Onion
Motorcycle
Cabinet
Zebra
Coach
Lamp
Celery
Cow
Desk
Boat
Squirrel
Cabbage

Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
1.	1.	1.	1.	1.
2.	2.	2.	2.	2.
3.	3.	3.	3.	3.
4.	4.	4.	4.	4.
5.	5.	5.	5.	5.
6.	6.	6.	6.	6.
7.	7.	7.	7.	7.
8.	8.	8.	8.	8.
9.	9.	9.	9.	9.
10.	10.	10.	10.	10.
11.	11.	11.	11.	11.
12.	12.	12.	12.	12.
13.	13.	13.	13.	13.
14.	14.	14.	14.	14.
15.	15.	15.	15.	15.
16.	16.	16.	16.	16.
17.	17.	17.	17.	17.
18.	18.	18.	18.	18.
19.	19.	19.	19.	19.
20.	20.	20.	20.	20.
Total correct:	Total correct:	Total correct:	Total correct:	Total correct:

BICAMS (BVMT-R)



MSNQ-I

MS Neuropsychological Screening Questionnaire (MSNQ) – Informant Report

	Very often, very disruptive	Quite often, interferes with life	Occasionally, seldom a problem	Very rarely, no problem	Never, does not occur
Is the Person with Multiple Sclerosis (PwMS) easily distracted?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS lose their thoughts while listening to somebody speak?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Is the PwMS slow when trying to solve problems?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS forget appointments or commitments?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS forget what they read?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS have trouble describing shows or programs recently watched?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS need to have instructions repeated?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS have to be reminded to do tasks?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐

Does the PwMS forget errands that were planned?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS have difficulty answering questions?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS have difficulty keeping track of two things at once?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS miss the point of what someone is trying to say?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS have difficulty controlling impulses?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS laugh or cry with little cause?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐
Does the PwMS talk excessively or focus too much on your own interests?	4 ☐	3 ☐	2 ☐	1 ☐	0 ☐

HCP qualitative survey

A survey exploring HCPs' perceptions of cognitive impairment

1. What was your experience of administering BICAMS?

2. What was your experience of scoring BICAMS?

3. What was your experience of feeding back on BICAMS?

4. Has your experience of BICAMS impacted your perceptions of cognitive impairment?

5. If yes to above, how has BICAMS impacted your perceptions of cognitive impairment?

Patient disease and demographic questionnaire

Disease and demographic questionnaire – patient

Gender	M F Other Prefer not to say
Age	
Ethnicity	White Mixed Asian / Asian British Black / Black British Arab Other (please state)
Years of education	
Employment	Full time Part time Full time education Homemaker Medically retired Unemployed
Living status	Married Living with partner Living with other family (including adults) Living with children Living alone

1. What type of MS do you have?

2. How long has it been since you were diagnosed with MS?

3. What medication are you taking for your MS?

4. Do you have any other neurological conditions?

5. Do you have any other medical conditions?

6. Do you have any mental health conditions?

7. Please tick the following which applies to you on the Hauser Ambulation Index

- ❑ 0 = Asymptomatic; fully active.
- ❑ 1 = Walks normally, but reports fatigue that interferes with athletic or other demanding activities.
- ❑ 2 = Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 25 feet (8 meters) in 10 seconds or less.
- ❑ 3 = Walks independently; able to walk 25 feet in 20 seconds or less.
- ❑ 4 = Requires unilateral support (cane or single crutch) to walk; walks 25 feet in 20 seconds or less.
- ❑ 5 = Requires bilateral support (canes, crutches, or walker) and walks 25 feet in 20 seconds or less; *or* requires unilateral support but needs more than 20 secondsto walk 25 feet.
- ❑ 6 = Requires bilateral support and more than 20 seconds to walk 25 feet; may use wheelchair on occasion.
- ❑ 7 = Walking limited to several steps with bilateral support; unable to walk 25 feet; may use wheelchair* for most activities.
- ❑ 8 = Restricted to wheelchair; able to transfer self independently.
- ❑ 9 = Restricted to wheelchair; unable to transfer self independently.

HCP demographic questionnaire

Demographic questionnaire – MS HCP

Gender	M F Other Prefer not to say
Age	
Ethnicity	White Mixed Asian / Asian British Black / Black British Arab Other (please state)
Years of education	
Years of experience working as an MS HCP	
Living status	Married Living with partner Living with other family (including adults) Living with children Living alone

PDDS

Patient-determined Disease Steps (PDDS)

Please read the choices listed below and choose the one that best describes your own situation.

This scale focuses mainly on how well you walk. You might not find a description that reflects your condition exactly, but please mark the **one** category that describes your situation the closest.

0 – normal
I may have some mild symptoms, mostly sensory due to MS but they do not limit my activity. If I do have an attack, I return to normal when the attack has passed.

1 – mild disability
I have some noticeable symptoms from my MS but they are minor and have only a small effect on my lifestyle.

2 – moderate disability
I don't have any limitations in my walking ability. However, I do have significant problems due to MS that limit daily activities in other ways.

3 – gait disability
MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult than they used to be. I usually don't need a cane or other assistance to walk, but I might need some assistance during an attack.

4 – early cane
I use a cane or a single crutch or some other form of support (such as touching a wall or leaning on someone's arm) for walking all the time or part of the time, especially when walking outside. I think I can walk 25 feet in 20 seconds without a cane or crutch. I always need some assistance (cane or crutch) if I want to walk as far as 3 blocks.

5 – late cane
To be able to walk 25 feet, I have to have a cane, crutch or someone to hold onto. I can get around the house or other buildings by holding onto furniture or touching the walls for support. I may use a scooter or wheelchair if I want to go greater distances.

6 – bilateral support
To be able to walk as far as 25 feet I must have 2 canes or crutches or a walker. I may use a scooter or wheelchair for longer distances.

7 – wheelchair / scooter
My main form of mobility is a wheelchair. I may be able to stand and/or take one or two steps, but I can't walk 25 feet, even with crutches or a walker.

8 – bedridden
Unable to sit in a wheelchair for more than one hour.

HADS

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.

		I feel tense or 'wound up':			**I feel as if I am slowed down:**
		Most of the time			Nearly all the time
		A lot of the time			Very often
		From time to time, occasionally			Sometimes
		Not at all			Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
		Definitely as much			Not at all
		Not quite so much			Occasionally
		Only a little			Quite Often
		Hardly at all			Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
		Very definitely and quite badly			Definitely
		Yes, but not too badly			I don't take as much care as I should
		A little, but it doesn't worry me			I may not take quite as much care
		Not at all			I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
		As much as I always could			Very much indeed
		Not quite so much now			Quite a lot
		Definitely not so much now			Not very much
		Not at all			Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
		A great deal of the time			As much as I ever did
		A lot of the time			Rather less than I used to
		From time to time, but not too often			Definitely less than I used to
		Only occasionally			Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
		Not at all			Very often indeed

		Not often			Quite often
		Sometimes			Not very often
		Most of the time			Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
		Definitely			Often
		Usually			Sometimes
		Not Often			Not often
		Not at all			Very seldom

Please check you have answered all the questions.

FSS

Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is designed to differentiate fatigue from clinical depression, since both share some of the same symptoms. Essentially, the FSS consists of answering a short questionnaire that requires the subject to rate his or her own level of fatigue. The obvious problem with this measure is its subjectivity.

Here is an example FSS questionnaire containing nine statements that attempt to explore severity of fatigue symptoms. The subject is asked to read each statement and circle a number from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement.

FSS Questionnaire

During the past week, I have found that:	**Agreement Score**
1. My motivation is lower when I am fatigued.	1 2 3 4 5 6 7
2. Exercise brings on my fatigue.	1 2 3 4 5 6 7
3. I am easily fatigued.	1 2 3 4 5 6 7
4. Fatigue interferes with my physical functioning.	1 2 3 4 5 6 7
5. Fatigue causes frequent problems for me.	1 2 3 4 5 6 7
6. My fatigue prevents sustained physical functioning.	1 2 3 4 5 6 7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1 2 3 4 5 6 7
8. Fatigue is among my three most disabling symptoms.	1 2 3 4 5 6 7
9. Fatigue interferes with my work, family, or social life.	1 2 3 4 5 6 7

Appendix 8: Publication of 'A Systematic Review and Meta-analysis of the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) International Validations'

Journal of *Clinical Medicine*

MDPI

Systematic Review

A Systematic Review and Meta-Analysis of the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) International Validations

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Abstract: Cognitive impairment is a prevalent and debilitating symptom of multiple sclerosis (MS) but is not routinely addressed in clinical care. The Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) was developed in 2012 to screen and monitor MS patients' cognition. This systematic review and meta-analysis aimed to identify, synthesise, and critically appraise current BICAMS' international validations. The literature search was conducted using PubMed, PsycINFO and Web of Science electronic databases in August 2022. Quantitative, peer-reviewed adult studies, which followed the BICAMS international validation protocol and were published in English, were included. The search identified a total of 203 studies, of which 26 were eligible for inclusion. These reported a total of 2833 adults with MS and 2382 healthy controls (HC). The meta-analysis showed that BICAMS identified impaired cognitive functioning in adults with MS compared to HC for all three subtests: information processing speed ($g = 0.854$, 95% CI = 0.765, 0.944, $p < 0.001$), immediate verbal recall ($g = 0.566$, 95% CI = 0.459, 0.673, $p < 0.001$) and immediate visual recall ($g = 0.566$, 95% CI = 0.487, 0.645, $p < 0.001$). Recruitment sites and strategies limit the generalisability of results. BICAMS is a valid and feasible international MS cognitive assessment.

Keywords: multiple sclerosis; Brief International Cognitive Assessment for Multiple Sclerosis; BICAMS; cognition; systematic review; meta-analysis

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1. Introduction

Cognition is a significant component of most neurodegenerative conditions and yet systematic, internationally valid measurement remains elusive for most. Early recognition of cognitive impairment allows for diagnosis and appropriate treatment, education, psychosocial support and engagement in shared decision-making regarding life planning, health care, involvement in research and financial matters [1]. It has been hard to meet the challenge of psychometrically sound, clinically feasible assessments, with some exceptions [2]. There is increasing recognition that the stimuli should not disadvantage any particular cultures [3]. Harmonisation of data across different national and ethnic communities needs careful consideration of cultural and linguistic variables [4]. The increasingly diverse populations within individual countries require health services to be agile and inclusive [5]. Important steps to advance cognitive measurement technology are global collaboration and a consensus, credible international validation protocol.

Multiple sclerosis (MS) is a chronic autoimmune-mediated disease of the central nervous system, involving inflammatory and degenerative processes [6]. This can produce a constellation of symptoms in the physical, psychiatric and cognitive domains. MS affects over 2.8 million people worldwide [7] and is typically diagnosed in adults aged 20 to 30 years [8]. Cognitive impairment is a prevalent and debilitating symptom of MS, affecting between 40–65% of patients [9]. It can be observed in all subtypes (Relapsing Remitting Multiple Sclerosis, RRMS; Secondary Progressive Multiple Sclerosis, SPMS; Primary Progressive Multiple Sclerosis, PPMS [10]), but severe cognitive impairment predominates

in the progressive forms of the disease [11]. There are often marked deficits in information processing speed, attention, working memory and executive functioning [9]. It has a negative impact on quality of life [9], including activities of daily living [12], employment [13], disease management [14,15], personality [16] and driving safety [17]. Given the significant adverse consequences of cognitive difficulties, early identification of cognitive status is needed to facilitate optimal management and preserve quality of life in people with MS (PwMS [18]).

Cognitive impairment remains a neglected and under-diagnosed symptom of MS. The "invisibility" of cognitive difficulties has meant they are often overlooked by family members, colleagues and healthcare professionals since there is no obvious external disability [19]. At routine consultation, neurologists are poor at identifying MS-related cognitive impairment [20]. There is a growing consensus, across MS patients and professionals, that routine cognitive testing should form part of clinical practice to inform management [21]. Despite this, objective cognitive testing is rarely delivered [22,23]. Both the National Institute for Health and Care Excellence (NICE [24]) and the American Academy of Neurology (AAN [25]) recommend an annual cognitive assessment for MS. Regularly monitoring cognition in MS patients can facilitate appropriate management as well as targeted specialist referrals for follow-up expert cognitive assessment and management [26,27]. Once cognitive impairment is identified, healthcare professionals can modify their interaction style with patients and monitor increased risks associated with cognitive impairment such as driving accidents, risk of falls, unemployment and poor disease management [18].

In 2012, an international consensus committee of 12 European and American MS experts convened to develop a review process to select scales that could be combined to produce a feasible, valid and international MS cognitive assessment. The committee examined the available cognition scales from the literature, as well as their psychometric qualities and clinical applicability. This approach took account of both the psychometric standards (reliability, validity and sensitivity) and the pragmatic standards (international applicability, ease of administration, patient acceptability and contextual feasibility). The committee agreed that the assessment tool should assess information processing speed, verbal memory and visual memory (immediate recall) and prompted the selection of the following subtests: the Symbol Digit Modalities Test (SDMT; spoken response), the first five learning trials of the California Verbal Learning Test (CVLT-II) and the first three learning trials of the Brief Visuospatial Memory Test-Revised (BVMT-R [28]). These three subtests are reliable and sensitive to MS cognitive impairment.

The SDMT [29] is a measure of information processing speed comprising a key of single numbers, each paired with an abstract symbol. The patient is presented with rows of symbols that are arranged pseudo-randomly. They are required to say the correct number for each of the symbols as fast and as accurately as they can in 90 s, using the key provided. The SDMT shows high sensitivity for MS-related cognitive dysfunction and is now widely acknowledged as the gold standard for a quick cognitive screening [30].

In the CVLT-II [31], a measure of verbal memory, only the first five learning trials are administered. The patient is read a 16-item word list at a slightly slower rate than one item per second. The list is read aloud five times, and the patient is instructed to recall as many of the items as possible, in any order, across the five learning trials.

In the BVMT-R [32], a measure of visual memory, only the first three learning trials are administered. This test involves presenting to patients a 2 × 3 stimulus array of abstract geometric figures across three learning trials, each 10 s in length. The array is then removed from the patient's view, and they are instructed to draw the geometric figures in the correct position from memory.

The Brief Cognitive Assessment for Multiple Sclerosis (BICAMS [28]) has been recommended as a 15 min international measure to routinely screen and monitor cognition in MS patients. It was designed for healthcare professionals who may not have specific training in cognitive assessments, allowing more clinics to address cognition. This brief assessment tool does not require any special equipment beyond a pen, paper and stop-

watch and therefore allows cognition to be tested inexpensively. BICAMS can be easily implemented into routine clinical practice across centres and countries internationally [28]. The committee have also published an international validation protocol to guide national validation studies [33].

BICAMS has been validated in 26 countries to date, including Argentina, Belgium, Turkey and Japan (e.g., [34]). These national studies have investigated the validity and reliability of BICAMS in different cultures and language groups and its sensitivity to cognitive impairment in comparison with the "gold-standard" batteries. The AAN has recommended BICAMS in their quality measurement sets for MS in 2014 and 2020. The Canadian Guidelines for MS Treatment endorsed BICAMS in 2020 [35], and over 20 peer review papers in international clinical neurology journals have also recommended BICAMS for routine cognitive assessment in MS clinics (e.g., [36]).

BICAMS has been adopted by the international MS community. For example, the Arabic version of BICAMS represents the most used cognitive battery for assessing MS cognition in the Arab world [37]. It has an international reach, with 11,000 patients routinely assessed every year. There has been a systematic review of the first 16 national validation studies on BICAMS [34]. However, there have since been additional national validation studies, warranting an updated systematic review of the validation literature and international findings. The aim of the present systematic review and meta-analysis was to identify, synthesise and critically evaluate current literature on the progress of BICAMS in meeting the objectives of global collaboration and a credible international validation protocol.

2. Methods

2.1. Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed as a guide for the standardised conduct and reporting of the current systematic review and meta-analysis [38]. Studies were identified using 3 databases—PubMed, PsycINFO and Web of Science. Boolean search terms were developed and used to identify studies examining the validity of BICAMS in August 2022 (Table 1). Search terms were informed by initial searches and developed further during the process of the review to ensure all relevant articles were identified.

Table 1. Search terms for systematic review.

Search Terms
"Multiple Sclerosis" OR "MS" OR "Clinically Isolated Syndrome" OR "CIS"
AND
"Brief International Cognitive Assessment for Multiple Sclerosis" OR "BICAMS"
AND
"Validation" OR "International Validation" OR "Validity" OR "Sensitivity"

2.2. Selection Criteria

The inclusion criteria were: (a) studies that followed the international validation BICAMS protocol, (b) quantitative studies, (c) peer-reviewed studies with no date restriction that are written in the English language and (d) samples including adults with any clinical subtypes of MS and Clinically Isolated Syndrome (CIS), the MS precursor stage.

The additional criteria for inclusion in the meta-analysis were as follows: (a) studies including an HC comparison group and (b) studies reporting standard quantitative information based on the SDMT, CVLT-II and BVMT-R subscales (mean, standard deviation and sample size) or appropriate substitute scales of the MS and/or CIS and HC comparison groups.

2.3. Quality Assessment

One reviewer (HP) extracted data from the studies directly into tables made specifically for the current review, and this was examined and verified by a second reviewer (DL).

Two reviewers independently assessed the quality of the retrieved articles using the Effective Public Health Practice Project (EPHPP), and any disagreements were discussed and resolved. A final quality rating was derived from the individual ratings of the categories.

2.4. Statistical Analysis

The meta-analysis was conducted using the Comprehensive Meta-Analysis (CMA; Version 3) software [39]. Three individual analyses were performed based on the average scores of the SDMT, CVLT-II and BVMT-R subtests for both groups (MS and HC). Effect sizes were calculated as standardised mean differences with Hedges *g* using the following interpretation: 0.2 = small; 0.5 = medium; 0.8 = large [40].

The meta-analysis employed a random-effects model because it estimates the mean of a distribution of effects as opposed to one true effect [41,42], and the number of studies are large enough i.e., more than 5 studies. Heterogeneity was assessed using the Cochran's Q test, and the magnitude of heterogeneity was evaluated using the I^2 statistic. The I^2 statistic assesses the percentage of variation across studies that are due to heterogeneity rather than chance and can be interpreted as a small (25%), moderate (50%) or high (75%) level of heterogeneity [43].

Forest plots were created for each subtest to visually summarise the amount of heterogeneity as well as the estimated effect sizes (Hedges *g*) and 95% CIs. Funnel plots were also generated as a graphical tool for investigating publication bias and other bias (assessed by the Egger's test), which, if found, may lead to funnel plot asymmetry [44]. If asymmetry was shown, the Duval and Tweedie trim and fill analysis would model the data as if it were symmetrically distributed by adjusting for missing studies [45].

3. Results

3.1. Search Results

Using the pre-specified eligibility criteria, 55 results were generated from PubMed, 24 from PsycINFO and 124 from Web of Science. First, 132 duplicate studies across databases were removed (Figure 1). To assess for eligibility, all titles and abstracts were initially screened independently by two reviewers (HP and DL). The 30 full-text articles were re-evaluated to determine their final inclusion or exclusion. Following this, four studies were removed from the final review according to the inclusion criteria. A total of 26 studies met the criteria for final inclusion in the systematic review.

All 26 studies met the criteria for the meta-analysis from those included in the systematic review. All relevant data for the current review and meta-analysis were obtained from numerical information in texts, tables, figures and statistical analysis.

3.2. Study Characteristics and Sample Demographics

Data on study characteristics, sample demographics and patient disease information are shown in Table 2. The 26 validation studies were published between the years 2012 and 2022.

Adults with MS were recruited from a variety of settings including medical centres, university hospitals, specialist clinics and tertiary referral centres. HC were either recruited from the community, an established normative sample or among relatives, friends or carers of PwMS. The studies included a total of 2833 adults with MS and 2382 healthy controls. Sample size of both groups differed greatly between studies; in PwMS, the samples ranged from 40 to 500 participants, whilst for HC, this ranged from 20 to 276. Age of PwMS ranged from 20–61 years with an average age of 39.9, whilst the age of HC ranged from 22–51 years, with a similar average age of 38.9. The percentage of females in the MS and HC sample disproportionately favoured females and ranged from 47–82% in the MS sample and 33–86% in the HC. Eight studies used the same number of males and females. Years of education averaged 14.13 years in the MS sample and 14.58 years in HC. Higher rates of employment were seen in the HC in comparison to the MS samples (39–98% compared to 20–89%, respectively).

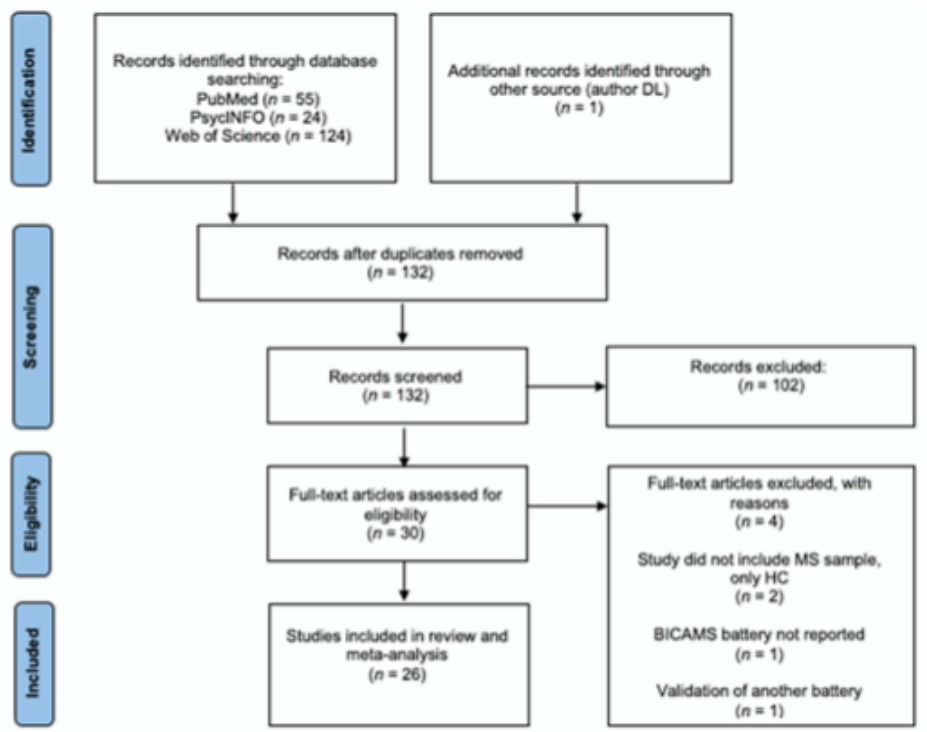

Figure 1. PRISMA flowchart for selection process of studies in systematic review and meta-analysis.

Table 2. Study characteristics and sample demographic and patient disease information.

Study	Country	Number of Participants	Age in Years Mean (SD), [Median], [Range]	Gender (Female %)	Education in Years Mean (SD), [Median], [Range]	Employment (Employed %)	MS Phenotype %(CIS/RR/SP/PP/PR)	Disease Duration in Years Mean (SD), [Median], [Range]	EDSS Mean (SD), [Median], [Range]
Alarcón et al. [46]									
MS	Columbia	50	41.44 (10.99)	64%	14.76 (2.61)	Nr	0/100/0/0/0	7.66 (5.61)	1.33 (1.54)
HC		100	37.75 (12.63)	48%	14.73 (3.57)	Nr	-	-	-
Betscher et al. [47]									
MS	Poland	61	[39]	74%	[13]	84%	0/74/20/6/0	RR = [5] SP = [19.5] PP = [7.5]	RR = [3] SP = [4.75] PP = [4.5]
HC		61	[37]	75%	[13]	98%	-	-	-
Botchorishvili et al. [48]									
MS	Georgia	68	39.2 (9.9)	71%	14.3 (2.1)	57%	0/76/18/6/0	7.0 (5.7)	3.3 (1.6)
HC		68	38.5 (9.9)	68%	14.5 (1.9)	84%	-	-	-
Costers et al. [49]									
MS	Belgium	97	45.42 (9.24)	68%	14.28 (1.86)	Nr	0/84/12/4/0	12.97 (7.16)	3.50 (2.50)
HC		97	43.52 (12.69)	75%	14.69 (1.61)	Nr	-	-	-
Darwish et al. [50]									
MS	Lebanon	43	36.06 (12.37)	81.4%	14.63 (3.17)	48.84%	0/81/14/5/0	8.61 (7.36)	1.89 (1.7)
HC		180	45.01 (19.36)	60%	15.13 (3)	56.11%	-	-	-
Drulović et al. [51]									
MS	Serbia	500	39.9 (9.4)	70.2%	14.0 (2.9)	Nr	0/100/0/0/0	9.2 (6.7)	[2.0]
HC		69	40.3 (11.5)	63.77%	14.1 (3.4)	Nr	-	-	-
Dusankova et al. [52]									
MS	Czech Republic	367	34 (10)	68%	14 (3)	40%	0/68/26/3/3	8 (7)	3 (1.5)
HC		134	34 (9)	71%	14 (2.5)	73%	-	-	-

Table 2. *Cont.*

Study	Country	Number of Participants	Age in Years Mean (SD), (Median), [Range]	Gender (Female %)	Education in Years Mean (SD), (Median), [Range]	Employment (Employed %)	MS Phenotype %(CIS/RR/SP/PP/PR)	Disease Duration in Years Mean (SD), (Median), [Range]	EDSS Mean (SD), (Median), [Range]
Estiasari et al. [53]									
MS	Indonesia	40	[31], [20–61]	82.5%	>12 yrs = 75%	Nr	0/78/22/0/0	(4), [0.1–15]	(3), [1–7.5]
HC		66	[29], [22–51]	72.7%	>12 yrs = 89.4%	Nr	-	-	-
Evdoshenko et al. [54]									
MS	Russia	98	38.44 (11.47)	70.4%	15.12 (2.79)	Nr	0/86/14/0/0	9.5 (7.44)	(3.0)
HC		86	38.17 (13.29)	63.95%	16.26 (3.02)	Nr	-	-	-
Farghaly et al. [55]									
MS	Egypt	90	30.8 (6.7)	77.78%	14.5 (2.6)	Nr	0/86/12/2/0	6.2 (5.8)	2.8 (1.8)
HC		85	30.5 (7.9)	70.59%	14.3 (3.3)	Nr	-	-	-
Filser et al. [56]									
MS	Germany	172	43.33 (11.64)	68%	10.74 (1.56)	76.4%	0/87/9/4/0	Nr	Nr
HC		100	43.04 (15.59)	71%	10.77 (1.58)	92%	-	-	-
Giedraitienė et al. [57])									
MS	Lithuania	50	38.8 (10.2)	47%	15.9 (2.8)	54%	4/88/6/2/0	11.7 (9.2)	3.3 (1.3)
HC		20	36.7 (16.4)	33%	17.5 (3.5)	75%	-	-	-
Hämäläinen et al. [58]									
MS	Finland	65	50.9 (8.8)	71%	13.8 (9.8)	20%	0/62/38/0/0	15.9 (9.8)	4.8 (2.0)
HC		45	49.4 (12.6)	71%	14.0 (2.1)	86.7%	-	-	-
Marstrand et al. [59]									
MS	Denmark	65	37.2 (8.8)	63%	15.2 (2.4)	Nr	0/100/0/0/0	3.9 (2.7)	1.8 (1.2)
HC		65	36.8 (9.6)	63%	15.9 (2.1)	Nr	-	-	-

Table 2. *Cont.*

Study	Country	Number of Participants	Age in Years Mean (SD), [Median], [Range]	Gender (Female %)	Education in Years Mean (SD), [Median], [Range]	Employment (Employed %)	MS Phenotype %(CIS/RR/SP/PP/PR)	Disease Duration in Years Mean (SD), [Median], [Range]	EDSS Mean (SD), [Median], [Range]
Maubeuge et al. [60]									
MS	France	123	49.69 (9.41)	63.4%	14–16 yrs = 30.1%	44.7%	0/33/33/34/0	14.67 (9.09)	[4.0], [0–8]
HC		276	43.84 (12.42)	57.3%	14–16 yrs = 38%	Nr	-	-	-
Niino et al. [61]									
MS	Japan	156	41.4 (9.3)	69%	14.1 (1.9)	Nr	0/88/11/1/0	10.3 (7.2)	2.4 (2.0)
HC		126	39.3 (11.9)	72%	14.3 (1.6)	Nr	-	-	-
O'Connell et al. [62]									
MS	Ireland	67	42.7 (12.8)	68%	14.1 (3.1)	41.8%	0/70/28/2/0	10.2 (8.4)	1.8 (0.9)
HC		66	43.9 (12.1)	73%	13.6 (2.7)	80.3%	-	-	-
Ozakbas et al. [63]									
MS	Turkey	173	37.5 (10.7)	71%	13.9 (7.3)	23.7%	0/87/10/3/0	9.2 (6.1)	2.4 (1.7)
HC		153	36.9 (8.9)	71%	15.4 (8.8)	39.1%	-	-	-
Polychroniadou et al. [64]									
MS	Greece	44	40.2 (9.9)	61%	13.9 (4.2)	Nr	7/77/9/7/0	9.1 (4.1)	[3.5], [1.0–6.0]
HC		79	36.2 (10.6)	60%	15.6 (5.5)	Nr	-	-	-
Sandi et al. [65]									
MS	Hungary	65	41.9 (8.9)	75%	>12 yrs = 52.3%	Nr	0/100/0/0/0	11.1 (7.6)	2.5 (1.8)
HC		65	40.9 (11.8)	75%	>12 yrs = 52.3%	Nr	-	-	-
Skorve et al. [66]									
MS	Norway	65	37.02 (0.40)	64.6%	14–16 yrs = 37%	89.2%	0/100/0/0/0	1.08 (0.74)	1.28 (0.88)
HC		68	38.13 (11.40)	66.2%	14–16 yrs = 46%	97.0%	-	-	-

Table 2. *Cont.*

Study	Country	Number of Participants	Age in Years Mean (SD), [Median], [Range]	Gender (Female %)	Education in Years Mean (SD), [Median], [Range]	Employment (Employed %)	MS Phenotype %(CIS/RR/SP/PP/PR)	Disease Duration in Years Mean (SD), [Median], [Range]	EDSS Mean (SD), [Median], [Range]
Souissi et al. [67]									
MS	Tunisia	104	33.3 (9.8)	75%	14–16 yrs = 14.42%	Nr	0/88/8/4/0	7 (6.4)	2.65 (2.06)
HC		104	33.3 (9.4)	75%	14–16 yrs = 14.42%	Nr	-	-	-
Sousa et al. [68]									
MS	Portugal	105	38.26 (11.03)	66.7%	13.55 (3.71)	58.1%	4/92/4/0/0	6.52 (5.95)	[1.5], [0-6]
HC		60	36.17 (12.01)	58.3%	14.62 (3.47)	94.9%	-	-	-
Spedo et al. [69]									
MS	Brazil	58	41.2 (12.2)	69%	12.7 (5.2)	Nr	0/100/0/0/0	8.3 (6.6)	4.2 (2)
HC		58	40.3 (11.9)	55%	12.5 (3.6)	Nr	-	-	-
Vanotti et al. [70]									
MS	Argentina	50	43.4 (10.2)	74%	14.9 (2.8)	Nr	0/78/18/4/0	13.1 (9.1)	3.29 (2.55)
HC		100	42.4 (10.1)	75%	14.9 (2.5)	Nr	-	-	-
Walker et al. [71]									
MS	Canada	57	45.4 (9.9)	80%	15.44 (2.7)	Nr	0/77/16/7/0	10.11 (7.72)	2.7 (1.85)
HC		51	41.9 (10.8)	86%	16.31 (2.1)	Nr	-	-	-

MS = multiple sclerosis; HC = healthy control; CIS = clinically isolated syndrome; RR = relapsing–remitting MS; SP = secondary progressive MS; PP = primary progressive MS; PR = progressive–relapsing MS; EDSS = expanded disability status scale; Nr = not reported; SD = standard deviation.

3.3. Patient Disease Information

Six studies recruited an exclusively RRMS sample, whilst the remaining studies also included a mixture of other phenotypes (e.g., SPMS or PPMS). RRMS was the most represented phenotype (33–100%), followed by SPMS (0–38%). Three studies included participants with CIS in their sample. The revised McDonald criteria for MS was the most used diagnostic criterion [72]. The average disease duration was 9.16 years and ranged from 1.08 to 14.67 years. The average Expanded Disability Status Scale (EDSS [73]) score was 2.75, indicating that, on average, the participants were in the mild disability range and could walk unaided.

Few studies calculated sensitivity and specificity data (Table 3), and it is noteworthy that, in the large Czech Republic sample, BICAMS demonstrated the same sensitivity to cognitive impairment as the "gold-standard" Minimal Assessment of Cognitive Function in MS (MACFIMS [52]).

Table 3. BICAMS psychometrics.

Study	SDMT Score Mean (SD)	CVLT-II Score Mean (SD)	BVMT-R SCORE Mean (SD)	Impaired Cognition on at Least One Subtest (%)	Sensitivity (%)	Specificity (%)
Alarcón et al. [46]						
MS	46.47 (14.24)	45.34 (10.14) [a]	21.64 (6.91)	50%	Nr	Nr
HC	54.11 (12.19)	48.78 (8.45) [a]	25.67 (6.81)	-	-	-
Betscher et al. [47]						
MS	48.8 (12.1)	51.7 (10.9)	24 (7.7)	34%	Nr	Nr
HC	57.2 (9.7)	56.1 (9.2)	27.1 (5.7)	Nr	-	-
Botchorishvili et al. [48]						
MS	35.5 (12.7)	51.0 (11.8)	22.0 (8.0)	43%	Nr	Nr
HC	46.0 (11.8)	58.5 (8.2)	25.6 (6.8)	14%	-	-
Costers et al. [49]						
MS	52.1 (13.1)	60.1 (12.9)	25.4 (29)	Nr	Nr	Nr
HC	61 (10.2)	61.3 (9.7)	28.2 (5.1)	Nr	-	-
Darwish et al. [50]						
MS	47.2 (17.98)	56.9 (10.04) [b]	22 (9.79)	61%	Nr	Nr
HC	59.22 (12.27)	54.10 (8.71) [b]	24.23 (6.66)	Nr	-	-
Drulović et al. [51]						
MS	45.9 (16.7)	50.0 (11.7)	18.8 (7.4)	62.9%	Nr	Nr
HC	56.3 (12.9)	52.7 (9.6)	22.6 (5.8)	18.6%	-	-
Dusankova et al. [52]						
MS	50 (13)	52 (11)	23 (7)	58%	94%	86%
HC	65 (9)	60 (8)	29 (4)	0.7%	-	-
Estiasari et al. [53]						
MS	40.9 (14.8)	52.0 (12.8)	22.2 (7.7)	40%	Nr	Nr
HC	64.8 (16.2)	61.5 (9.7)	29.3 (5.6)	Nr	-	-
Evdoshenko et al. [54]						
MS	49.16 (13.42)	{61.5}	{26.5}	34.69%	Nr	Nr
HC	58.34 (11.52)	{65.5}	{28}	16.28%	-	-
Farghaly et al. [55]						
MS	39.2 (13.3)	53.7 (10.5)	19.7 (9.2)	SDMT = 31.1% CVLT-II = 19.5% BVMT-R = 23.9%	Nr	Nr
HC	50.9 (10.8)	59.6 (8.5)	25.4 (8.7)	SDMT = 5.8% CVLT-II = 7% BVMT-R = 8.1%	-	-

Table 3. *Cont.*

Study	SDMT Score Mean (SD)	CVLT-II Score Mean (SD)	BVMT-R SCORE Mean (SD)	Impaired Cognition on at Least One Subtest (%)	Sensitivity (%)	Specificity (%)
Filser et al. [56]						
MS	47.43 (11.67)	55.35 (11.43) [c]	24.44 (7.59)	32.6%	Nr	Nr
HC	56.07 (11.64)	55.16 (10.27) [c]	27.37 (5.96)	Nr	-	-
Giedraitienė et al. [57])						
MS	42.7 (13.9)	55.9 (10)	23.1 (7)	Nr	Nr	Nr
HC	57 (11.5)	65.7 (5.9)	29.6 (4.1)	Nr	-	-
Hämäläinen et al. [58]						
MS	41.9 (11.8)	43.0 (11.5)	19.2 (8.0)	60%	Nr	Nr
HC	54.6 (8.3)	51.3 (10.7)	24.7 (6.8)	Nr	-	-
Marstrand et al. [59]						
MS	61.0 (10.0)	65.4 (9.9)	27.4 (5.8)	32.3%	SDMT = 20.0% CVLT-II = 10.8% BVMT-R = 16.9%	SDMT = 95.4% CVLT-II = 89.2% BVMT-R = 93.8%
HC	66.0 (9.6)	68.6 (6.4)	29.6 (3.7)	20%	-	-
Maubeuge et al. [60]						
MS	50.31 (11.12)	49.72 (12.77) [d]	22.89 (7.26)	50.4%	Nr	Nr
HC	58.55 (8.44)	57.78 (8.67) [d]	26.73 (5.67)	19.6%	-	-
Niino et al. [61]						
MS	47.9 (14)	48.6 (12.6)	23.5 (8.4)	Nr	Nr	Nr
HC	61 (9.5)	55.7 (10.5)	28.3 (5.4)	Nr	-	-
O'Connell et al. [62]						
MS	46.0 (12.9)	45.3 (10.2)	17.9 (7.1)	57%	Nr	Nr
HC	56.1 (10.6)	53.6 (9.1)	20.9 (6.5)	17%	-	-
Ozakbas et al. [63]						
MS	43.2 (12.5)	45.7 (11.3)	16.9 (8.5)	45.1%	Nr	Nr
HC	53.5 (9.5)	53.9 (7.7)	22.5 (9.2)	Nr	-	-
Polychroniadou et al. [64]						
MS	45.0 (17.2)	55.5 (12.3) [e]	18.5 (8.3)	47%	Nr	Nr
HC	61.4 (13.1)	60.5 (10.7) [e]	22.1 (6.5)	Nr	-	-
Sandi et al. [65]						
MS	55.6 (15.5)	55.4 (10.7)	22.5 (8.5)	52.3%	Nr	Nr
HC	66.2 (12.4)	59.0 (8.3)	26.7 (5.6)	Nr	-	-
Skorve et al. [66]						
MS	54.65 (10.79)	54.55 (10.86)	26.55 (5.76)	46.2%	Nr	Nr
HC	58.52 (10.53)	60.32 (7.75)	29.03 (4.01)	Nr	-	-
Souissi et al. [67]						
MS	36 (13)	42 (7) [f]	23 (9)	73.1%	SDMT = 74% TVLT = 76% [f] BVMT-R = 75%	SDMT = 56% TVLT = 55% [f] BVMT-R = 53.5%
HC	47 (15)	46 (6) [f]	27 (7)	Nr	-	-
Sousa et al. [68]						
MS	51.77 (11.20)	55.05 (11.84)	21.72 (7.27)	24.8%	Nr	Nr
HC	58.68 (10.02)	60.47 (10.12)	24.68 (5.52)	Nr	-	-
Spedo et al. [69]						
MS	35.9 (16.1)	42.1 (12.4)	19.9 (8.6)	Nr	Nr	Nr
HC	47.5 (13)	53.4 (10.8)	23.8 (7.7)	Nr	-	-

Table 3. *Cont.*

Study	SDMT Score Mean (SD)	CVLT-II Score Mean (SD)	BVMT-R SCORE Mean (SD)	Impaired Cognition on at Least One Subtest (%)	Sensitivity (%)	Specificity (%)
Vanotti et al. [70]						
MS	45.1 (16.1)	50.9 (12.4)	20.7 (7.74)	Nr	Nr	Nr
HC	56.7 (10.9)	60.9 (10.5)	23.4 (5.8)	Nr	-	-
Walker et al. [71]						
MS	49.7 (10.8)	51.6 (10.1)	24.6 (6.5)	57.9%	SDMT = 97.5% CVLT-II = 82.5% BVMT-R = 77.5%	SDMT = 88.2% CVLT-II = 70.6% BVMT-R = 82.4%
HC	59.1 (8.5)	57.7 (7.9)	29.8 (3.6)	Nr	-	-

MS = multiple sclerosis; HC = healthy control; SDMT = symbol digit modalities test; CVLT-II = California verbal learning test; BVMT-R = brief visuospatial memory test-revised; Nr = not reported; SD = standard deviation. [a] Alternative verbal memory test used = The Prueba de Aprendizaje y Memoria con Codificación Libre (PAMCL). [b] Alternative verbal memory test used = The Verbal Memory Arabic Test (VMAT). [c] Alternative verbal memory test used = The Rey Auditory Verbal Learning Test (RAVLT). [d] Alternative verbal memory test used = The French Verbal Learning Test (FVLT). [e] Alternative verbal memory test used = The Greek Verbal Learning Test (GVLT). [f] Alternative verbal memory test used = The Tunisian Verbal Learning Test (TVLT).

3.4. Correlations between BICAMS and Sample Variables

Correlations between BICAMS subtest scores and sample variables (age, disease duration, EDSS score, education, and employment) were extracted (Table 4). Correlations between age and BICAMS scores were the most frequently reported and usually significant; correlations between EDSS scores and BICAMS were occasionally reported and inconsistently significant.

3.5. Quality Ratings

The overall quality of the studies ranged from 'moderate' to 'weak' on the EPHPP template, reflecting the cross-sectional design typical of validation studies. No studies were removed from this review following the quality assessment.

3.6. Meta-Analysis of BICAMS Validation Studies

Data on the standard quantitative information based on the subtests of the SDMT, CVLT-II and BVMT-R of the MS and HC groups were extracted for baseline assessments of BICAMS (Table 3). The percentage of people in both groups identified with likely cognitive impairment on at least one subtest was also extracted, along with the sensitivity and specificity of BICAMS. The results from all three subtests showed that adults with MS performed significantly worse than HC. BICAMS identified likely impaired cognition, on at least one subtest, in 25–73% in the MS sample, which was significantly higher than in HC (1–20%).

The forest plot (Figure 2) shows the effect size for each study using the SDMT. Overall, information processing speed was significantly lower in the MS sample compared to HC with a large effect size ($g = 0.854$, 95% CI = 0.765, 0.944, $p < 0.001$). There was no evidence of outliers; however, moderate heterogeneity ($Q = 51.9$, $p = 0.001$) was indicated ($I^2 = 51.8$). There was no evidence of publication bias (Egger's test: $p > 0.05$, two-tailed). The funnel plot (Figure 3) indicates that the effect sizes were symmetrical. Duval and Tweedie's trim and fill analysis estimated that no studies were missing from the analysis.

Table 4. Correlations between BICAMS scores and MS sample variables.

Study	BICAMS Scores and Sample Variables											
	Age (*r*)			Disease Duration (*r*)			EDSS (*r*)			Education Years (*r*)		
	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R
Alarcón et al. [46]												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Betscher et al. [47]												
MS	−0.28 *	Nr	−0.26 *	Nr	Nr	Nr	−0.58 ***	−0.31 *	−0.27 *	0.36 *	0.42 ***	0.5 ***
HC	−0.35 *	Nr	Nr	-	-	-	-	-	-	0.44 ***	0.47 ***	0.27 *
Botchorishvili et al. [48]												
MS	−0.400*	−0.112	−0.192	−0.177	−0.106	0.125	−0.582 ***	−0.403 ***	−0.342 ***	0.243 *	0.207	0.297 *
HC	−0.457 ***	−0.368 ***	−0.506 ***	-	-	-	-	-	-	0.523 ***	0.439 *	0.348 *
Costers et al. [49]												
MS	−0.34 ***	−0.10	−0.29 **	Nr	Nr	Nr	−0.44 ***	−0.35 ***	−0.43 ***	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Darwish et al. [50]												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Drulović et al. [51]												
MS	−0.225 *	−0.232 *	−0.271 *	−0.109 *	−0.880	−0.207 *	−0.466 *	−0.320 *	−0.360 *	0.339 *	0.298 *	0.190 *
HC	−0.605 *	−0.430 *	−0.374 *	-	-	-	-	-	-	0.521 *	0.552 *	0.394 *
Dusankova et al. [52]												
MS	Nr	Nr	Nr	0.44 *	0.39 *	0.41 *	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Estiasari et al. [53]												
MS	−0.004	−0.11	0.02	−0.23	−0.19	−0.18	−0.5 ***	−0.46 *	−0.49 *	[47], [15–69]	[54], [23–72]	[24.5], [4–32]
HC	−0.27 *	−0.11	−0.28 *	-	-	-	-	-	-	[63], [42–110] *	[63], [36–77]	[31], [14–36]
Evdoshenko et al. [54]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr

Table 4. *Cont.*

Study	BICAMS Scores and Sample Variables											
	Age (*r*)			Disease Duration (*r*)			EDSS (*r*)			Education Years (*r*)		
	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R
Farghaly et al. [55]												
MS	−0.26 [a,*]	−0.17 [a]	−0.26 [a,*]	−0.41 [a,***]	−0.18 [a]	−0.27 [a,*]	−0.37 [a,***]	−0.31 [a,*]	−0.19 [a]	0.36 [a,***]	0.27 [a,*]	0.25 [a,*]
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Filser et al. [56]												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Giedraitienė et al. [57])												
MS	Nr	Nr	Nr	−0.3 [a]	−0.2 [a]	−0.2 [a]	−5.9 [a,***]	−3.7 [a,***]	−2.3 [a,***]	2.4 [a,*]	2.4 [a,*]	1.0 [a,*]
HC	Nr	Nr	Nr	-	-	-	-	-	-	2.0 [a,*]	1.2 [a,*]	0.9 [a,*]
Hämäläinen et al. [58]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Marstrand et al. [59]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Maubeuge et al. [60]												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Niino et al. [61]												
MS	−0.37 ***	−0.25 *	−0.30 ***	−0.30 ***	−0.12	−0.27 ***	−0.56 ***	−0.29 ***	−0.46 ***	0.07	0.13	0.001
HC	−0.44 ***	−0.23 *	−0.25 *	-	-	-	-	-	-	0.24 *	0.25 *	0.05
O'Connell et al. [62]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Ozakbas et al. [63]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	−0.46 *	−0.40 *	−0.24	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr

Table 4. *Cont.*

Study	BICAMS Scores and Sample Variables											
	Age (*r*)			Disease Duration (*r*)			EDSS (*r*)			Education Years (*r*)		
	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R	SDMT	CVLT-II	BVMT-R
Polychroniadou et al. [64]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Sandi et al. [65]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	Nr	Nr	Nr	Nr
Skorve et al. [66]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Souissi et al. [67]												
MS	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr	Nr	-	Nr
HC	Nr	-	Nr	-	-	-	-	-	-	Nr	-	Nr
Sousa et al. [68]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	−0.497 ***	−0.334 ***	−0.275 *	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Spedo et al. [69]												
MS	−0.30 *	−0.30 *	−0.29 *	Nr	Nr	Nr	Nr	Nr	Nr	0.29 *	0.18 *	0.27 *
HC	−0.49 *	-	−0.34 *	-	-	-	-	-	-	0.49 *	0.37 *	-
Vanotti et al. [70]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr
Walker et al. [71]												
MS	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	-	0.20 *	-
HC	Nr	Nr	Nr	-	-	-	-	-	-	Nr	Nr	Nr

MS = multiple sclerosis; HC = healthy control; SDMT = symbol digit modalities test; CVLT-I I= California verbal learning test; BVMT-R = brief visuospatial memory test-revised; EDSS = expanded disability status scale; Nr = not reported. [a] Regression coefficient reported; correlation coefficients (*r*) are presented with significance marks: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

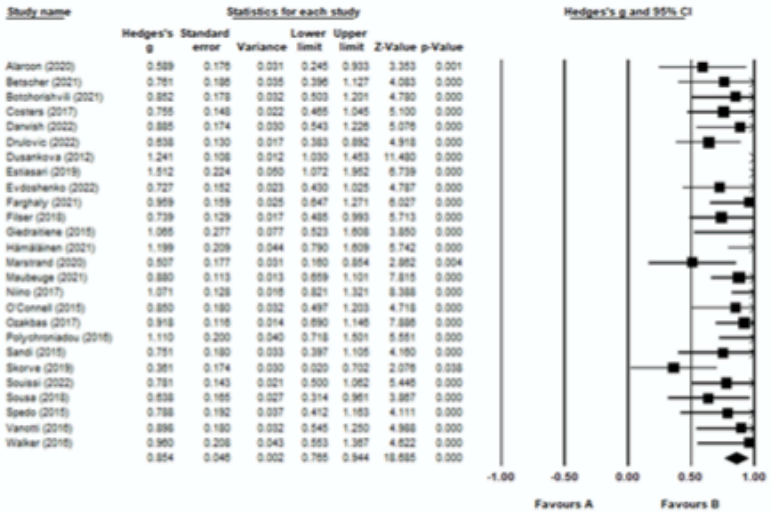

Figure 2. Forest plot for SDMT. Alarcón et al. [46]; Betscher et al. [47]; Botchorishvili et al. [48]; Costers et al. [49]; Darwish et al. [50]; Drulović et al. [51]; Dusankova et al. [52]; Estiasari et al. [53]; Evdoshenko et al. [54]; Farghaly et al. [55]; Filser et al. [56]; Giedraitienė et al. [57]; Hämäläinen et al. [58]; Marstrand et al. [59]; Maubeuge et al. [60]; Niino et al. [61]; O'Connell et al. [62]; Ozakbas et al. [63]; Polychroniadou et al. [64]; Sandi et al. [65]; Skorve et al. [66]; Souissi et al. [67]; Sousa et al. [68]; Spedo et al. [69]; Vanotti et al. [70]; Walker et al. [71].

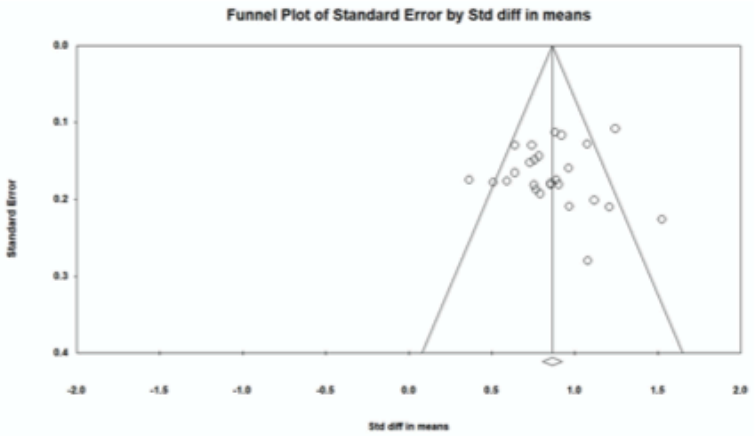

Figure 3. Funnel plot for SDMT.

A translated version of the CVLT-II was used in 18 validation studies. For two studies, the CVLT-II was not translated as the validation studies were conducted in English-speaking countries with existing validations [49,50]. Importantly, six of the studies used an alternative verbal memory test to substitute the conventional CVLT-II (Table 3). The average mean and standard deviation scores of these alternative tests were included in the meta-analysis. Notably, the study with the smallest effect size, with a Hedge's *g* value of 0.017, used a substituted verbal memory test ([51]; Figure 4). The study with the highest effect size, with a Hedge's *g* value of 1.072, used a translated version of the CVLT-II ([52]; Figure 4).

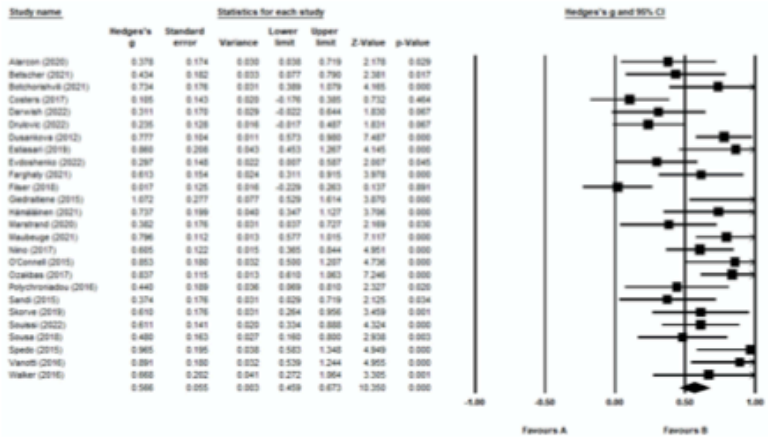

Figure 4. Forest Plot for CVLT-II. Alarcón et al. [46]; Betscher et al. [47]; Botchorishvili et al. [48]; Costers et al. [49]; Darwish et al. [50]; Drulović et al. [51]; Dusankova et al. [52]; Estiasari et al. [53]; Evdoshenko et al. [54]; Farghaly et al. [55]; Filser et al. [56]; Giedraitienė et al. [57]; Hämäläinen et al. [58]; Marstrand et al. [59]; Maubeuge et al. [60]; Niino et al. [61]; O'Connell et al. [62]; Ozakbas et al. [63]; Polychroniadou et al. [64]; Sandi et al. [65]; Skorve et al. [66]; Souissi et al. [67]; Sousa et al. [68]; Spedo et al. [69]; Vanotti et al. [70]; Walker et al. [71].

The forest plot (Figure 4) shows the effect size for each study using the CVLT-II. Overall, immediate verbal recall memory was significantly lower in the MS sample compared to HC with a medium effect size (g = 0.566, 95% CI = 0.459, 0.673, $p < 0.001$). There was no evidence of outliers; however, a high level of heterogeneity (Q = 77.9, $p < 0.001$) was indicated ($I^2 = 67.9$). Duval and Tweedie's trim and fill analysis estimated that three studies would need to fall to the left of the mean effect size to make the plot symmetrical (Figure 5). Assuming a random-effects model, the adjusted mean effect size remained medium ($p = 0.528$, 95% CI = 0.420, 0.635). There was no evidence of publication bias, as the Egger's test remained non-significant (Egger's test: $p > 0.05$, two-tailed).

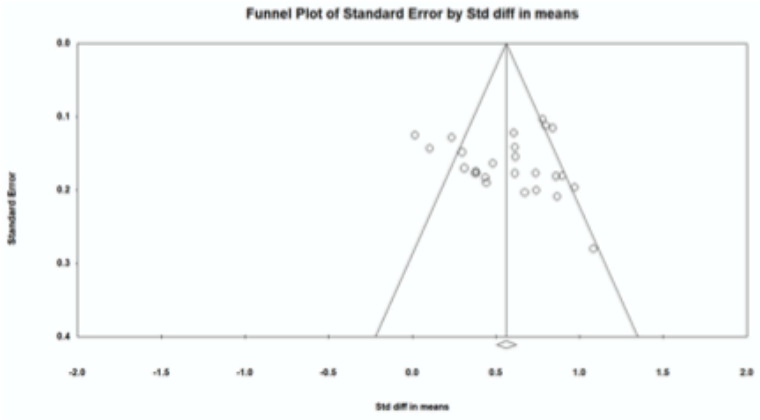

Figure 5. Funnel plot for CVLT-II.

The forest plot (Figure 6) shows the effect size for each study using the BVMT-R. Overall, immediate visual recall memory was significantly lower in the MS sample compared to

HC with a medium effect size (g = 0.566, 95% CI = 0.487, 0.645, $p < 0.001$). There was no evidence of outliers; however, moderate heterogeneity (Q = 42.6, $p < 0.05$) was indicated ($I^2 = 41.4$). There was no evidence of publication bias (Egger's test: $p > 0.05$, two-tailed). The funnel plot (Figure 7) indicates that the effect sizes were symmetrical. Duval and Tweedie's trim and fill analysis estimated that no studies were missing from the analysis.

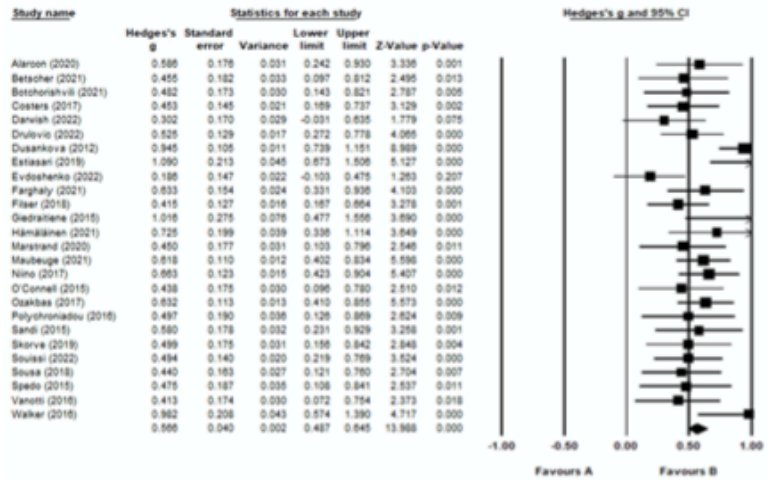

Figure 6. Forest plot for BVMT-R. Alarcón et al. [46]; Betscher et al. [47]; Botchorishvili et al. [48]; Costers et al. [49]; Darwish et al. [50]; Drulović et al. [51]; Dusankova et al. [52]; Estiasari et al. [53]; Evdoshenko et al. [54]; Farghaly et al. [55]; Filser et al. [56]; Giedraitienė et al. [57]; Hämäläinen et al. [58]; Marstrand et al. [59]; Maubeuge et al. [60]; Niino et al. [61]; O'Connell et al. [62]; Ozakbas et al. [63]; Polychroniadou et al. [64]; Sandi et al. [65]; Skorve et al. [66]; Souissi et al. [67]; Sousa et al. [68]; Spedo et al. [69]; Vanotti et al. [70]; Walker et al. [71].

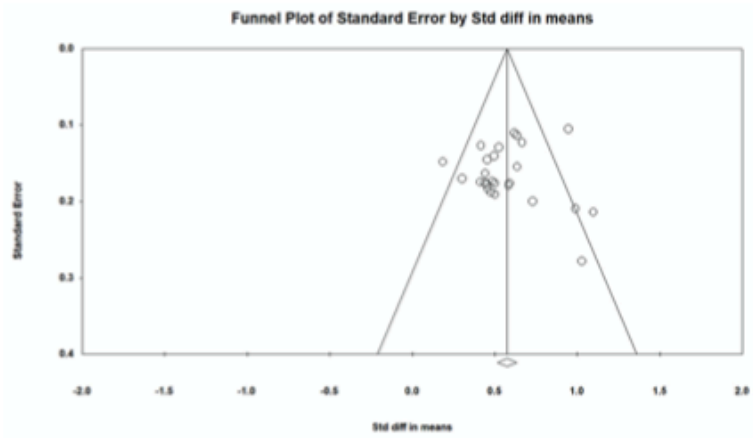

Figure 7. Funnel plot for BVMT-R.

Only four studies reported the sensitivity and specificity of BICAMS. Of these four studies, one reported on the sensitivity and specificity of BICAMS overall (94% and 86%, respectively), whilst the remaining three reported on the sensitivity and specificity of the individual subtests (see Table 3).

4. Discussion

4.1. Summary of Findings

The current review identified, synthesised and appraised the current literature on the international validation of BICAMS to date. A total of 26 studies were included in both the systematic review and meta-analysis. The results from the systematic review showed that BICAMS has been embraced in many countries worldwide and with a range of clinical samples, including different MS phenotypes and consequently, disease durations and severity. Most studies included a HC sample with a similar age and educational background. Although BICAMS was designed to be administered by a range of health professionals, in these validation studies, BICAMS was apparently typically completed by a neuropsychologist or psychology graduate; however, this information was not routinely reported. Finally, in most studies, the gender ratio in both samples disproportionately favoured females. It is important to consider that this female recruitment bias reflects the increased prevalence of MS in females, the female-to-male sex ratio being approximately 3:1 [8].

The meta-analysis showed that adults with MS performed significantly worse than HC on the three BICAMS subtests—information processing speed and immediate verbal and visual recall. Cognitive functioning was most impaired on the SDMT (a measure of information processing speed). These findings are in line with existing literature proposing that information processing speed is markedly reduced in MS [74] and constitutes the most common cognitive limitation in PwMS [75]. It is important to stress that BICAMS should be administered in its entirety, given that multiple aspects of daily life can be affected by cognitive impairment in addition to processing speed, e.g., visuospatial learning as assessed by the BVMT-R [76].

It is important to note that the BICAMS committee included experts from Europe and America and may lack diversity and inclusivity in development and cross-cultural appropriateness [77,78]. The CVLT-II scores were more heterogeneous compared to the other subtests, possibly reflecting the additional linguistic and cultural demands of translating the verbal recall list. Prior to BICAMS, the CVLT-II had separate word lists and validations for the UK and USA. Six BICAMS validation studies used alternative verbal memory tests available in the required language. Several validation studies [49,51] reported difficulties with translating the CVLT-II and described similar scores on the CVLT-II between the MS sample and HC. The CVLT-II is also probably the most culturally sensitive of the three subtests and required more extensive work to accomplish a valid translation of the stimuli [69]. Semantic categories for the word list were sometimes adapted to be more applicable for the population e.g., by swapping different types of sports for cooking utensils in Egypt [55].

4.2. Strengths

There are several strengths to this review. First, the search strategy was designed and validated using a combination of three databases—PubMed, PsycINFO and Web of Science—to cover a breadth of the available and relevant literature. Secondly, strict inclusion criteria were employed to ensure appropriate studies were generated. Furthermore, this review identified and synthesised international validation studies reporting objective scores of cognitive abilities in PwMS compared to matched HC in a standardised manner. This review captures the advances in validating BICAMS internationally since the previous review [34], with further validations in 12 more countries. Across the validation studies, there was a varied spread of cultures, languages and countries involved in the initiative. The countries that participated in the international validation protocol reported that BICAMS could be feasibly administered in approximately 15 min, with minimal materials, and was recommended for routine clinical cognitive assessment as a standard of MS care.

4.3. Limitations

There are also some notable limitations to the review methodology. First, English-language publication was a requirement for inclusion in the review, so it is important to recognise that this may have limited the inclusion of validation studies published in

other languages. Secondly, only the terms "Multiple Sclerosis", "MS". "Clinically Isolated Syndrome" or "CIS" were used in the database search. This may have restricted the number of studies identified through the database search, as there are additional ways to describe MS (e.g., as an autoimmune disease). Thirdly, as part of the pre-defined criteria, only peer-reviewed studies were considered eligible for inclusion in this review, which meant that possible grey literature (e.g., thesis publications) that were not commercially published would not have been included. Fourthly, there are likely to be international disparities across studies in relation to healthcare systems, accessibility, economic status, and access to general MS support facilities [79,80]. MS healthcare in countries with developing economies may be constrained by limited access to high-efficacy disease-modifying therapies (DMTs) or diagnostic technology such as magnetic resonance imaging (MRI [81]). Developed countries have significantly higher prevalence and incidence rates of MS compared to developing countries, which may reflect better access to diagnostic facilities and subsequent earlier diagnosis and treatment [82]. These variations in access and quality of MS healthcare may have made comparisons of disease profiles, such as years since diagnosis and physical disability, less valid. Most of the studies included in this review were conducted in leading centres and university hospitals, which attract a certain sociodemographic population and, therefore, may not be entirely representative of all MS populations. Fifthly, there was a great deal of heterogeneity between studies—namely in terms of sample size, age, MS phenotypes and disease duration. RRMS was overrepresented compared to other MS phenotypes. It is possible that this may have reduced the effect size since cognitive impairment is more common and severe in the progressive forms of the disease [10,11]. With progressive forms of MS being underrepresented in this review, cognitive impairment may also have been underrepresented in the identified studies compared to the general MS population. Finally, the quality assessment tool (EPHPP) used to analyse the methodological quality of the included studies may not have been considered appropriate in this systematic review, since it is not a scale designed for cross-sectional studies. This may explain why the overall quality of the studies ranged from 'moderate' to 'weak' on the EPHPP template. In addition, the possible risk of bias was not studied.

4.4. Future Directions

The adoption of an international validation protocol and a global collaboration have served to promote BICAMS to international currency for MS cognition. This is reflected in the number of international validations published, the report of BICAMS data in 150 published studies of MS cognition and its use in many large national and international trials. This initiative could serve as a model for other conditions, improving the awareness, understanding, assessment and management of cognitive impairment. It is hoped that further research investigating the feasibility of BICAMS in clinical practice will maximise its use in routine consultation to evaluate cognitive status in MS. This systematic review also prompts future studies to investigate the sensitivity and specificity of the scale in different forms of multiple sclerosis or in groups with different degrees of disability.

5. Conclusions

BICAMS has been translated and culturally adapted in 26 countries to date. It has been shown to be a valid measure of cognitive functioning in MS at a global level. It can detect cognitive impairment in individuals with MS compared to healthy controls across a range of cultures, languages, and countries. This review sheds light on the work of the international MS community at validating BICAMS utilising an international validation protocol. This represents progress in the increasing awareness of MS cognition as well as maximising the implementation of BICAMS into routine clinical practice, to assess and instigate the appropriate management of MS cognition across different countries.

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