

BICAMS:

Shedding light on cognition in Multiple Sclerosis

Multiple Sclerosis (MS) is a disease that attacks the central nervous system, leading to a variety of symptoms, across the physical and psychological domains. For many people with MS, symptoms can include difficulties with memory and thinking, which impacts on the quality of many aspects of their life. Dawn Langdon, Professor of Neuropsychology at Royal Holloway, University of London, has led an international project to develop BICAMS, an innovative battery of tests to revitalise our understanding of cognition in MS, with the aim that this aspect of the condition will be better understood and managed.

Multiple Sclerosis (MS)¹ affects more than 100,000 people in the UK and millions more worldwide. It usually affects people between the ages of 20 and 50 years, and the average age of onset is approximately 34 years. MS is a neurological autoimmune condition, in which the body's immune system attacks its own nerve cells².

MS attacks the myelin sheaths³ that surround brain and spinal cord cells. Myelin – a fatty substance that covers neurons – speeds up the transmission of electrical signals between cells allowing for efficient brain function. It is essential for normal motor, or movement, control and for other functions, including thinking and planning. In MS, the myelin sheath coating the nerves is damaged, leading to ineffective signalling between brain cells, and eventually cell death.

The majority of patients start experiencing relapsing remitting episodes, meaning that the symptoms of the condition come in waves of new

or worse symptoms⁴, which generally improve before another relapse occurs. This is called relapsing-remitting MS⁵. Most relapsing-remitting patients enter the secondary progressive phase⁵ sooner or later, when disability accumulates over time. Patients with primary progressive MS⁵ do not have remission or relapse cycles; instead their symptoms gradually worsen over time from the outset.

Some medications are available that reduce relapses and slow disability progression⁶. Researchers are working to identify treatments that will halt the disease.

INVISIBLE SYMPTOMS

MS is most known for its effects on motor control, leading some people to use wheelchairs eventually as the disease progresses. However, due to its widespread impact on the central nervous system, there are a constellation of other symptoms linked to the condition and a high range of variability between patients. Some of the lesser recognised effects of MS – sometimes referred to as the 'invisible symptoms' – can have a profound impact on quality of life. The invisible symptoms include fatigue, depression and pain. MS can also impact cognition.

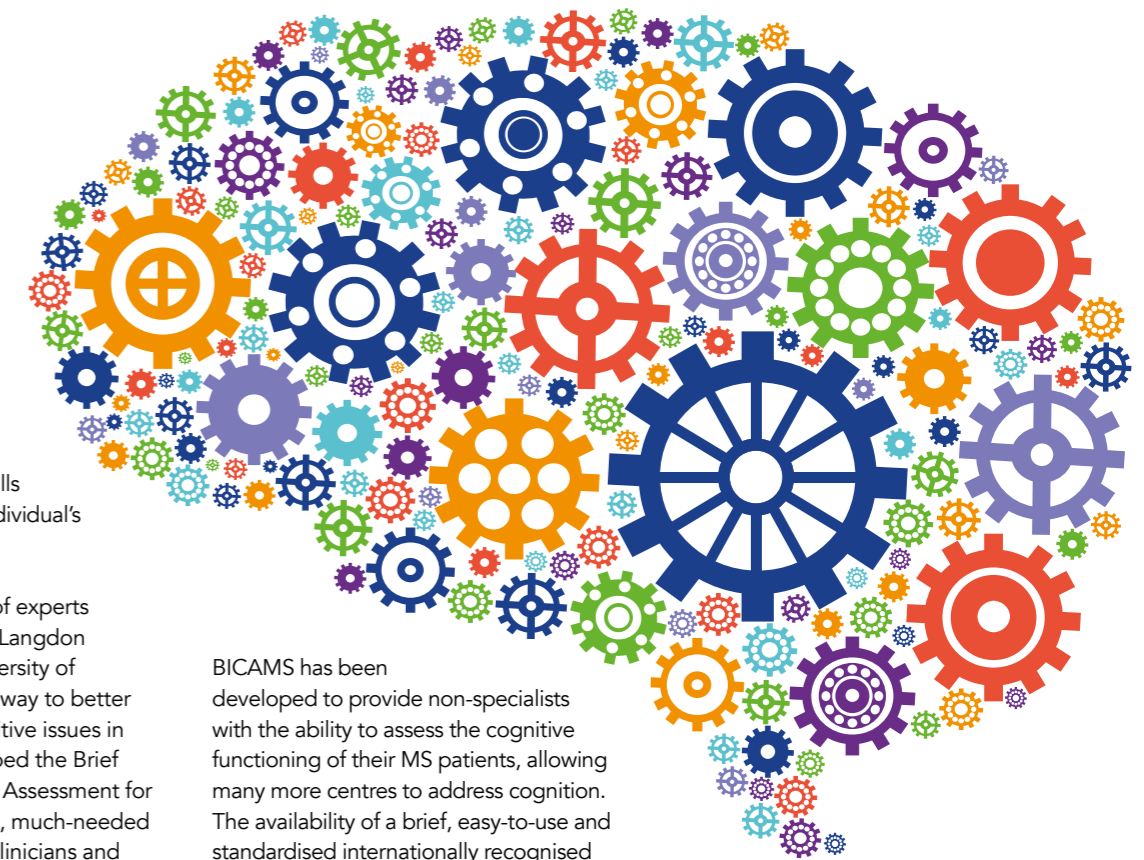
Cognitive problems⁷ – issues with memory, thinking and attention skills – are common in MS, affecting approximately half of patients living with the condition. Problems with thinking in MS are sometimes known as 'cog fog'⁸ as patients describe being unable to think as clearly as they had done previously. Cognitive impairment typically worsens as the disease progresses. As cognitive issues are not well known in MS, family and friends can find them hard to recognise and understand. Impairments in memory and concentration can

affect daily tasks such as keeping up with conversations or managing household bills and can influence an individual's ability to work⁹.

An international team of experts led by Professor Dawn Langdon of Royal Holloway University of London are paving the way to better understanding of cognitive issues in MS. They have developed the Brief International Cognitive Assessment for MS (BICAMS)¹⁰, a short, much-needed tool aimed at helping clinicians and researchers quickly and effectively understand the cognitive difficulties that affect more than half of patients.

DEVELOPING BICAMS

Assessing cognitive impairment traditionally requires a lengthy neuropsychological testing – tests that reveal how brain function and aspects of cognition have been affected by disease or trauma, such as a stroke or accident. Neuropsychological testing is conventionally carried out by trained psychologists using in-depth and lengthy pen and paper assessments. Whilst this approach is comprehensive, it is also restrictive, limiting its use to specialist neuropsychologists, who are trained to use such assessments in scarce, well-resourced centres. As such, many people with MS who have cognitive impairment receive few valid tests of their cognitive function, meaning that their difficulties go misunderstood or even neglected, resulting in mismanagement¹¹.



BICAMS has been developed to provide non-specialists with the ability to assess the cognitive functioning of their MS patients, allowing many more centres to address cognition. The availability of a brief, easy-to-use and standardised internationally recognised testing battery have also made it more likely that pharmaceutical trials are including assessments of cognition as part of their outcome measurements, meaning that cognitive impairment could

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be better treated or managed in future¹². Cognitive impairment can be taken into consideration when potential drugs in the pharmaceutical pipeline are being assessed. Importantly, taking only 15 minutes to complete and requiring only pen and paper, BICAMS allows cognition to be tested inexpensively, maximising its potential use across centres and across countries.

PRINCIPLES OF NEUROPSYCHOLOGICAL TESTING

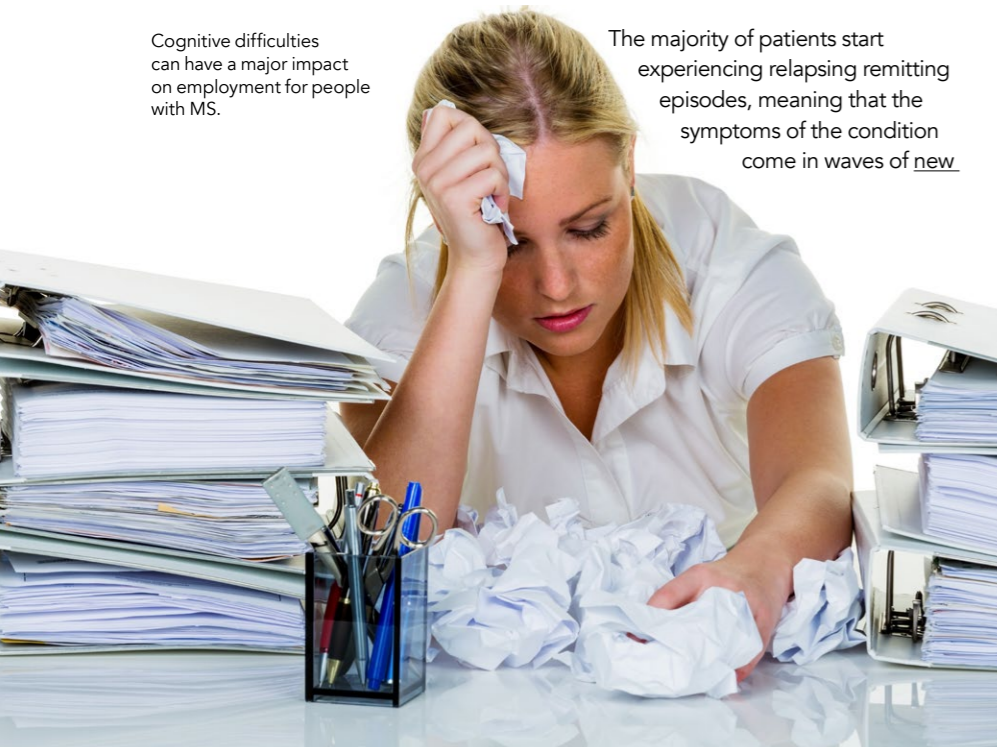
In order to be an effective neuropsychological test, assessments must be shown to fulfil key criteria that measure robustness, including reliability

and validity. Reliability refers to the test's robustness over repeated testing and between raters, whereas validity refers to the ability of the test to assess what it is intended to. A thorough evaluation of BICAMS revealed that it fulfilled all these markers of solid neuropsychological testing, making it a good measure.

Importantly, the battery has also been shown to be repeatable without marked learning effects, where participants do better on tests purely because they have done them previously.

The BICAMS development process has had an international outlook¹³ from the outset, ensuring that the tests would be available to as many people as possible. This validation process has been carried out in eleven languages and in 16 different locations and cultures, again maximising its use across the world, which is key for its usefulness in clinical trials, which are increasingly carried out in multiple sites worldwide.

Cognitive difficulties can have a major impact on employment for people with MS.



Q&A

Professor Dawn Langdon is Co-Chair of the BICAMS initiative and has led on the development of the iPad version of the cognitive assessment. She is passionate about raising awareness of the cognitive impact of MS and using international collaboration to create meaningful progress. We spoke to her about her motivations, the success of the BICAMS initiative and the reach she hopes it will have globally.

What inspired your work in this area?

I was working in a clinical job at the National Hospital for Neurology and Neurosurgery in London, on a rehabilitation unit where half of the people had multiple sclerosis (MS). It was very clear that many of them were struggling with cognitive

difficulties, but this aspect of the disease was not recognised or well managed by their families, friends, or even health professionals outside of specialist centres. I wanted to try to understand these difficulties better and improve health care services.

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Why do you think the cognitive impact of MS has been almost overlooked in the past in favour of physical symptoms?

Partly I think it is because physical symptoms are immediately apparent to other people, for example using a walking stick or wheelchair. Also, cognitive difficulties can be hard to admit to and to talk about. The pattern of cognitive difficulties in multiple sclerosis is not clear in conversation or even clinic consultations. This is because information processing speed is often the most affected ability, which can be thought of as band width. It is a bit like your own personal internet slowing and freezing. This can make

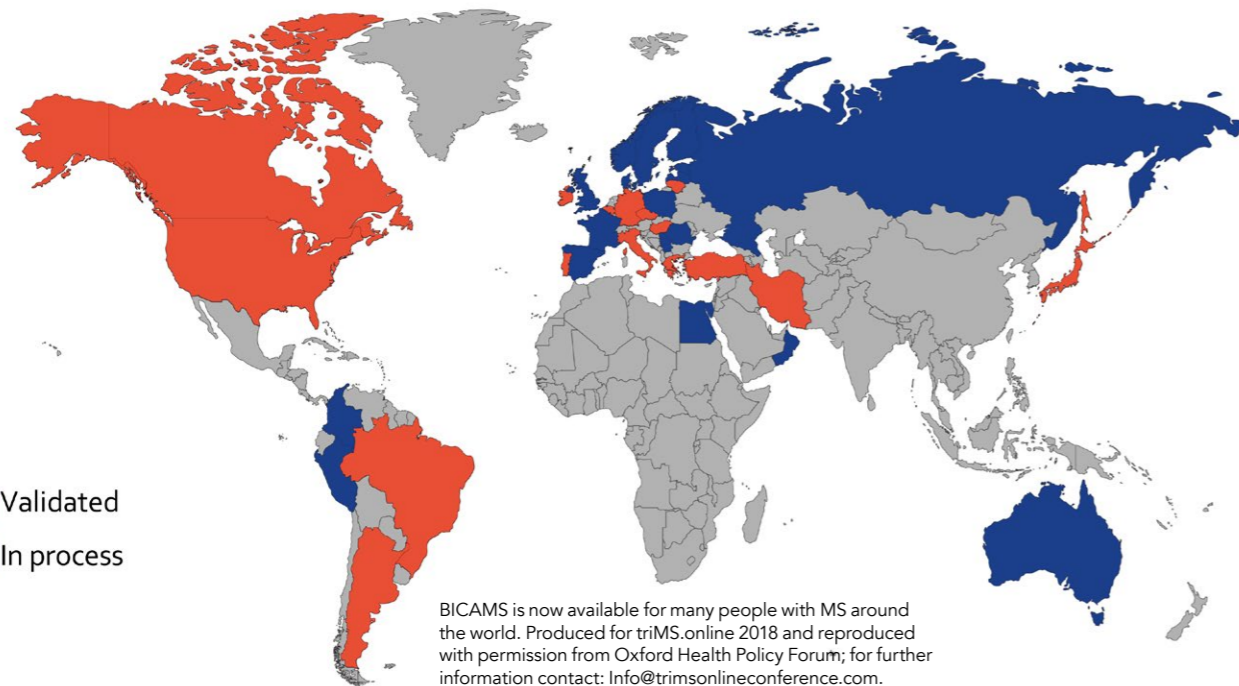
it hard to follow fast speech or pick up information against a distracting background. Memory is also often affected. However, everyday language functions are often pretty much OK. This means in casual conversations, nothing seems wrong. Because MS cognitive difficulties are not on the surface, they tend to get overlooked.

How do you get an international community working together in such a successful manner?

I convened an international committee of 12 neurologists and neuropsychologists, who were all experts on MS cognition and represented all of the major language groups, and countries on both sides of the Atlantic.

BICAMS is a truly international initiative with input from researchers across the globe and from all major language groups.

Myself and my Co-Chair, Professor Ralph Benedict did our homework and worked to obtain a consensus. We published two consensus papers. In fact, from there the international MS community pretty much adopted BICAMS and set out to validate it in a proactive and committed way. I did the usual academic things, writing papers and speaking at scientific conferences, but colleagues picked up the BICAMS torch and ran with it. I was always ready to accept invitations to speak about BICAMS and do training sessions, but these were small contributions. I think that first, cognition was acknowledged to be an under recognised and poorly managed aspect of MS, which made life difficult for people with MS and their families. Secondly, committed health care workers realised that a brief, feasible and psychometrically sound cognitive measure would be very useful in their practice. Unexpectedly, BICAMS has been utilised in many scientific papers about MS cognition, which was not part of our original planning and goals.



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COMPONENTS OF BICAMS

In deciding which items should be included in BICAMS, Professor Langdon and her team selected tests that would tap into the cognitive areas – or domains – already known to be affected in some people with MS. The tests included in BICAMS focus on how quickly people can process information, their ability to remember a verbal word list and their memory of abstract shapes shortly after they have seen them. The battery utilises the most relevant components of existing tests, including sections of the California Verbal Learning Test-II, the Brief Visuospatial Memory Test-Revised and the Symbol Digits Modalities Test.

FINDINGS USING BICAMS

Since the BICAMS was introduced it has been cited in a number of peer-reviewed publications, going some way to filling the knowledge gap surrounding cognition in MS. A recent [meta-analysis](#)¹⁴ by Professor Langdon has shown that BICAMS testing has highlighted significantly reduced cognitive functioning compared to people living without MS across all of the domains tested, namely, information processing speed, immediate recall memory and immediate visual recall memory, in 14 countries.

Excitingly, the BICAMS has also been used in intervention studies, including one that demonstrated that six weeks of [cognitive rehabilitation](#)¹⁵ taking place on a computer at home can lead to improvements on some, but not all, aspects of cognition. The improvements were mirrored by a change in the activation of some areas

of the brain, assessed by functional MRI studies. Whilst it is not known how this change impacts on the quality of life of patients, it is a positive indication that some aspects of cognition can be rescued with the right management.

FUTURE STEPS

Already the BICAMS has made great inroads into understanding the cognitive impairment that so affects the lives of those living with MS. It has recently been adopted and recommended by the American Academy of Neurology, further cementing its place as the go-to testing battery for this condition. An iPad version of the BICAMS is currently undergoing validation studies and, if successful, is only set to increase the amount it is used. Computerised testing reduces raters' variability, making the measurement even more precise, and facilitates data collection to databases on servers. Feasible, effective and inexpensive means of assessing cognition are absolutely crucial to patient management, disease monitoring and assessing the effects of interventions. The development of BICAMS has started a small but powerful revolution in bringing cognition to the forefront of MS management, shedding light on its effect on quality of life. People living with MS are only set to benefit from its increasing uptake by both clinicians and researchers.

BICAMS



What advice would you give others about to embark on a similar project i.e. one that brings together an international community?

I think a broadly based, expert consensus group to back and author the project is essential. Encouraging engagement and offering support to centres as and how they need it is essential, so everyone can be involved at the level, and as independently, as they choose to be. Although everyone involved is a serious scientist and/or clinician, I have tried to foster a sense of being in the BICAMS family. I think a shared purpose and understanding across nationalities creates bonds, trust and energy.

BICAMS has received funding from multiple sources. Does this bring any unique challenges and/or benefits?

I am very proud of the "patchwork" model of funding that BICAMS has created. We were very lucky to have funding for our committee's work and meetings from Bayer at the outset. Subsequently, validation and scientific

This range of funders means that BICAMS doesn't belong to a single organisation or entity. It is truly owned by the international MS community, which is an enormous benefit.

studies across the world using BICAMS have been funded by national pharma, neurology associations, national MS charities, or sometimes by colleagues who had a master's student who needed a project. Novartis have kindly funded a UK first implementer study. Several international pharma are using BICAMS in major international drug trials. This range of funders means that BICAMS doesn't belong to a single organisation or entity. It is truly owned by the international MS community, which is an enormous benefit.

What are the next stages for rolling out BICAMS worldwide? What are your hopes for this tool?

We are currently working to identify clinics around the world who are

using BICAMS for routine clinical assessment. So far we know about 10,000 patients a year are being routinely assessed on BICAMS. We want to support and extend BICAMS' use for routine clinical assessment. The AAN endorsement helps and we are involved in other groups producing guidelines for MS clinical assessment. We are validating an iPad BICAMS which we hope will make BICAMS even more feasible. Our vision is that every MS patient in the world will have access to routine cognitive assessment. There is a very widely used measure of mainly physical disability in MS, the Expanded Disability Status Scale, or EDSS. It would be wonderful if BICAMS could become the cognitive EDSS. Already there are studies that compare and combine the two measures, so this may not be a far-fetched idea.

This tool could make a difference for people with MS around the world. How does it feel to be involved in work with such widespread impact?

I feel very humble as Co-Chair of BICAMS as I work alongside so many expert clinical researchers putting their time and effort into successfully developing the BICAMS story, and also seeing the data coming in from so many thousands of people with MS who have consented to participate in these studies. It is all about teamwork and each study has only succeeded because of the commitment and partnership of health professionals and people with MS. I am very proud that the international MS community has come together in such an effective and influential way, to address and manage the cognitive aspects of MS.



Behind the Research

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Research Objectives

The Brief International Cognitive Assessment for MS (BICAMS), is a short, much-needed tool to assess cognitive function for people with Multiple Sclerosis.



Detail

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Bio

Having trained at St Hilda's College, Oxford and King's College London, Dawn Langdon worked at Queen Square for 16 years as a clinical neuropsychologist, obtaining a PhD from the Institute of Neurology, London. She is now Professor of Neuropsychology at Royal Holloway, University of London, FBPS and BICAMS Co-Chair. She is a Trustee of the UK MS Trust.

Funding

DL has participated in speaker bureau for Bayer, Merck, Almirall, Execemed, TEVA, Roche, Novartis, Biogen, Sanofi; has had consultancy from Novartis, Bayer, Merck, Biogen, TEVA, Sanofi; has had research grants from Bayer, Merck, Novartis, Biogen. All are paid into DL's institution.

Collaborators

- Prof Ralph Benedict, Co-chair BICAMS, University of Buffalo, New York, USA
- Prof Maria Pia Amato, University of Florence, Italy
- Dr Jan Boringa, Meander Medisch Centrum, Amersfoort, Netherlands
- Prof Bruno Brochet, Université Bordeaux-Segalen, France

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Personal Response

How could findings from BICAMS influence how clinicians manage the care of people living with MS?

// Cognitive assessment offers a range of benefits. It is known that cognitive status at diagnosis predicts how fast the disease will progress and so clinics can monitor patients more closely. Positive lifestyle choices and regular mentally stretching activities can protect against cognitive decline and cognitive assessment can form the basis of coaching people with MS to adopt these helpful behaviours. People with MS who have cognitive impairment are less likely to manage their disease well, including medication, and once alerted to cognitive impairment, clinics can present information in a way that is easy to assimilate and monitor disease management. Cognitive impairment makes problems at work and unemployment more likely and clinics can refer for appropriate help. Cognitive impairment increases risks of falling and driving accidents, and clinics can act to reduce these risks. //