Mild Behavioral Impairment as a Marker of Cognitive Decline in Cognitively Normal Older Adults

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CONFLICT OF INTEREST

The CogTrack™ System is proprietary to Wesnes Cognition Ltd (www.wesnes.com). Keith Wesnes owns Wesnes Cognition Ltd and consults for various companies involved in clinical trials. Helen Brooker is employed by Wesnes Cognition Ltd. Clive Ballard has received contract grant funding from Lundbeck, Takeda, and Axovant pharmaceutical companies and honoraria from Lundbeck, Lilly, Otusaka, and Orion pharmaceutical companies. Dag Aarsland has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, and GE Health, and serves as a paid consultant for H. Lundbeck and Axovant. Zahinoor Ismail has received research funding from Janssen Pharma and honoraria/consulting fees from Allergan, Avanir, Janssen, Lilly, Lundbeck, Otsuka, Pfizer, and Sunovion.

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ABSTRACT

Objective: Mild Behavioral Impairment (MBI) is a neurobehavioural syndrome characterized by later life emergent neuropsychiatric symptoms (NPS) which represent an at-risk state for incident cognitive decline and dementia in people with Mild Cognitive Impairment. We undertook a study to determine whether MBI was associated with progressive changes in neuropsychological performance in people without significant cognitive impairment.

Methods: 9,931 older adults enrolled in the PROTECT study who did not have MCI or dementia undertook a comprehensive neuropsychological battery measuring attention, reasoning, executive function and working memory at baseline and one year. MBI was ascertained using self-administration of the MBI-C at one year, and participants grouped according to MBI status: no symptoms, intermediate neuropsychiatric symptoms and MBI. All assessments were completed online and data analyzed using MMRM ANOVA.

Results: 949 (10%) people had MBI. These individuals had significantly worse cognitive performance at baseline and significantly greater decline over one year in the four composites cognitive scores measuring attentional intensity ($F(2,8578)=3.97, p=0.019$), sustained attention ($F(2,8578)=18.63$, $p<.0001$), attentional fluctuation ($F(2,8578)=10.13$, $p=<.0001$) and working memory $F(2,9895)=13.1$, $p<.0001$.

Conclusions: Our novel findings show that MBI is associated with faster decline in attention and working memory in this cognitively normal sample. MBI may be an earlier

marker of neurodegenerative disease than MCI, captured at the stage of SCD or before, raising the possibility that MBI represents a novel target for dementia clinical trials or prevention strategies.

OBJECTIVE

Dementia, the most common cause of which is Alzheimer's disease (AD), affects an estimated 45 million people and is a leading cause of morbidity and death; it has devastating impact on people with the disease and those caring for them and costs the world economy around US $818 billion per year (1). Developing new and more effective treatments for AD is an urgent priority however there have been no new licensed pharmacologic therapies for 15 years (2). As such there is an increasing realization of the need for improved markers of early identification of people with pre-clinical AD, and their translation into effective stratification tools and a broader range of treatment targets (3, 4). The identification of a marker which is easily and inexpensively detected in the general population, and whose cognitive correlates could be measured over the short term, would represent a major step change towards reaching this goal. There is an increasing evidence base that later life emergent and persistent neuropsychiatric symptoms (NPS), known as Mild Behavioral Impairment (MBI) (4), may be one such maker.

MBI is a neurobehavioral syndrome characterized by the onset of new and sustained NPS in later life (5). For some individuals, MBI may be an early manifestation of neurodegenerative disease in advance of significant cognitive impairment. MBI consists of five domains: impaired drive and motivation (apathy) (6); emotional dysregulation (mood and anxiety symptoms) (7); impulse dyscontrol/agitation/abnormal reward salience (changes in response inhibition and self-regulation); social inappropriateness (impaired social cognition) (8); and abnormal thoughts/perception (psychosis) (9), assessed individually and collectively for their

impact on cognition. Importantly, MBI explicitly excludes psychiatric illness a priori, and mandates that NPS be emergent in later life, and sustained for 6-months.

Recently, the International Society to Advance Alzheimer's Research and Treatment (ISTAART)-Alzheimer's Association (AA), NPS Professional Interest Area published research diagnostic criteria for MBI, which described explicitly the relationship between MBI and MCI, and generated the five MBI domains for further study (10). Subsequently, the Mild Behavioral Impairment Checklist (MBI-C) was developed to reflect these new criteria and capture these symptoms in preclinical populations with the goal of operationalizing the assessment of the MBI criteria and to serve as a case ascertainment tool (11). It thus provides an inexpensive method for capturing a population at higher risk for cognitive decline and dementia.

There is abundant evidence from longitudinal cohort studies that MBI, or more broadly NPS, in the context of Mild Cognitive Impairment (MCI) is associated with a greater risk of dementia than MCI without NPS (12-16). In addition, MBI is associated with a significantly faster rate of cognitive decline and progression to dementia than late life psychiatric illness (17), emphasizing the importance and utility of this syndrome for detecting this at-risk group. Although not studied using the MBI framework, there is also evidence that some NPS, particularly emergent psychosis, are also associated with a significantly increased risk of incident MCI and dementia over periods up to 5 years in individuals with a mean age over 70 (18-23).

The only study to have examined the detailed neuropsychological profile associated with MBI did so at a single time point (17). Widespread impairments across attention,

memory, and executive function were observed in the MBI group but 25% of the sample had memory impairment, so it likely included some patients with MCI. The profile of neuropsychological impairments associated with MBI in populations with no significant cognitive impairment remains unknown and the question of whether subtle changes in cognitive performance occur over time in these preclinical groups represents an important gap in current understanding.

The aims of this study were to conduct a detailed analysis of the pattern of progressive neuropsychological impairments associated with MBI in a large cohort of 9,931 cognitively normal individuals over the age of 50. We hypothesized that MBI would be present in this group and that, because it represents an at-risk state for dementia, we would observe greater declines in cognition over the course of one year compared to those without MBI.

METHODS

The PROTECT study

The study was conducted through the Platform for Research Online to Investigate Genetics and Cognition in Aging (PROTECT: http://www.protectstudy.org.uk). PROTECT is an innovative UK-based 25-year longitudinal online research study which aims to understand the impact of lifestyle, medical and genetic risk factors of cognitive health and dementia in older adults.

Participants

Participants volunteered to take part in the study by responding to local and national publicity, which included radio, print media, Join Dementia Research and invitations to persons registered for existing research studies at the Institute of Psychiatry, Psychology and Neuroscience at King's College London. Inclusion criteria for PROTECT enrollment are: 1) age 50 or over; 2) regular access to a computer and the internet; and 3) no diagnosis of dementia. There were no exclusion criteria. Volunteers were prospectively recruited from November 2015 through both local and national publicity. PROTECT is an ongoing study and as such a data freeze was implemented in March 2017 with data extracted for volunteers who had completed baseline and 1 year assessments extract. Ethical approval was granted through the London Bridge National Research Ethics Committee (reference: 13/LO/1578) and informed consent obtained for all participants. This study is an analysis of the newly generated baseline and 1 year data from the PRTOECT study.

Procedure

Participants completed a range of online assessments and questionnaires, those pertinent to this paper are demographics, a mental health questionnaire and IQCODE (included as a supplementary measure of subjective cognitive decline) (24) – all completed at baseline - and the MBI-C (completed at 1 year). Core aspects of cognitive function were assessed via two cognitive test batteries; the CogTrack™ System (25, 26) and the PROTECT Cognitive Test System (PCTS) (27, 28). Cognition was assessed at baseline and one year with participants being invited to complete both test systems. The PCTS was mandatory and CogTrack™ was optional. Most participants completed both (Table 1). Participants were instructed to complete up to three test sessions of each system. These repeats had to be completed within seven days with at least 24 hours between each session. This design feature was implemented in order to overcome familiarization effects, which can influence cognitive test data (29, 30).

Assessment of MBI

MBI was rated using the Mild Behavioral Impairment Checklist (MBI-C); a scale developed specifically for functionally independent community dwelling older adults, with language that reflects NPS in this context, as opposed to the dementia-focused language of traditional NPS rating scales used. The MBI-C is a simple and easy to administer NPS rating scale taking ~5-7 minutes to complete (by patient, informant, or clinician), is scalable to large community cohorts, and is free for use in the public domain (available at www.MBItest.org) in several languages (11). The MBI-C comprises 34 questions. Symptoms must be present for at least 6 months

(continuously, or intermittently) and must represent a change from a longstanding pattern of behavior. Each question is answered “Yes” or “No”, and if “Yes” the item is rated according to severity: 1 = mild (noticeable, but not a significant change); 2 = moderate (significant, but not a dramatic change); 3 = severe (very marked or prominent, a dramatic change). The MBI-C allows for the generation of an overall score based on severity responses, thus possible scores range from 0 to 102. MBI diagnosis was operationalized using a cut point on the MBI-C total score of >8, which offers good sensitivity and specificity for clinically diagnosed MBI according to the ISTAART diagnostic criteria in participants with subjective cognitive decline (31). We further excluded anyone with a history of a psychiatric or neurodevelopmental disorder, based on self-report using an online mental health questionnaire to remove confounding of the MBI ratings in accordance with the ISTAART-AA MBI criteria (this resulted in the further exclusion of 151 people). Finally anyone whose cognitive performance was ≥1.5 standard deviations (a level typically associated with MCI) away from the norm on 2 or more cognitive domains were excluded; these criteria were applied to both baseline measures and on decline over the year minimizing the likelihood that there was MCI at baseline and no incident MCI in the sample. To allow for additional sensitivity in our analysis we also split the <8 group in two, creating three groups in total: total MBI-C score of 0, “No symptoms” (NS); 1-8, “Intermediate NPS” (NPS); and >8 “Mild Behavioral Impairment” (MBI).

Assessment of Cognition

The CogTrack™ system

The CogTrack™ System is made up of tasks which have been successfully used for over 30 years in clinical research – they assess a broad range of cognitive domains including information processing, episodic memory, executive control, reasoning and attention (25, 26). Three composite scores measuring Sustained Attention, Attentional Fluctuation and Attentional Intensity were derived from factor analysis of the full CogTrack™ battery. Brief descriptions of these are below with a fuller description contained in the supplementary material.

The Sustained Attention Index reflects the ability to sustain concentration and is comprised of the accuracy scores of the digit vigilance and choice reaction time tasks and the number of false alarms in the digit vigilance task. The cognitive attribute that this factor identifies is not the power of concentration at any particular instance; rather it identifies a separate and independent feature of how well someone is able to keep his/her mind on a single task for a prolonged period.

The Attentional Fluctuation Index is comprised of the coefficient of variance for simple reaction time, digit vigilance and choice reaction time and captures moment to moment fluctuations in attention.

The Attentional Intensity Index is comprised of the speed scores from the simple reaction time, digit vigilance and choice reaction time tasks. In such tasks, speed reflects the intensity of concentration at that particular moment, the faster the response, the more processes that are being brought to bear upon the task. This measures levels of effortful concentration.

PROTECT cognitive test system (PCTS)

The PCTS is comprised of four tasks measuring verbal reasoning, attention and working memory (self-ordered search, paired associates learning, digit span and verbal reasoning) (27). One composite Working Memory score was derived from factor analysis of this battery (comprised of paired associate learning, self-ordered search and digit span). A full description of the PCTS battery is contained in the supplementary material.

IQCODE

The IQCODE scale was included as a supplementary measure of cognitive impairment and was tested for association with MBI-C score. A subset of 6,452 participants whose data was analyzed for this study had a project partner complete the IQCODE scale. Average IQCODE score was calculated and two groups were created (based on a cut-point of 3.3, with higher scores meaning greater cognitive impairment (32)). Self-rated IQCODE (33) was also available for 9,821 participants and was analyzed alongside the informant-rated scale to assess for bias as the inclusion of a project partner was optional. A full description of the IQCODE is included in the supplementary material.

STATISTICAL ANALYSIS

The software package SAS® Version 9.4 was used to analyze the data. As with any cognitive tests, it is well documented that familiarity effects can influence the data.

Thus the first test session at baseline was excluded from analysis, leaving only those people who had completed a minimum of two test sessions at each time point in the analysis. The average performance for the second and third cognitive test session at baseline and first and second session at 1 year have been considered here for all tasks and all participants. A difference score was created by subtracting the baseline scores from the year 1 scores and subjected to a one-way Mixed Effect Model Repeat Measurement (MMRM) ANCOVA. A main effect was fitted using the MBI grouping (3 levels: NS (No Symptoms group, MBI-C=0), NPS (Intermediate NPS group; MBI-C=1-8) and MBI (MBI group >8). Age, gender, education level (six levels: Secondary Education (left school at 16 years); Post-Secondary Education (left school at 18 years); Vocational Qualification; Undergraduate Degree; Post-graduate Degree; Doctorate) , and the number of test sessions performed at baseline and one year were fitted as covariates. In addition to this as some of the participants had access to brain training games on the PROTECT platform the amount of brain training completed was also fitted as a covariate. Mean change adjusted for these covariates is presented as least square means (LSMeans) +/- standard error of the mean (sem). The relationship between IQCODE and MBI grouping was analyzed by chi-square test. Cohen's d effect sizes were also calculated for the difference in score change between MBI groups.

RESULTS

Demographics

CogTrack™ and PCTS were completed by a total of 8,597 and 9,931 participants respectively (Table 1). Mean age (62), gender proportions (around 75% female) and education level were similar for both test packages (as expected given the considerable overlap in people who completed both test packages), see Table 1.

MBI-C Responses

The frequency of MBI (MBI-C >8) in this sample was 10%. Intermediate NPS (MBI-C total score between 1 and 8) were present in 43% of people.

Main Effects of Composite Measures of Sustained Attention, Attentional Intensity, Attentional Fluctuation and Working Memory

At baseline, performance on all four cognitive composite measures was consistently superior for the no symptom group and poorest the MBI group, with the NPS group falling in between (Table 2).

Significant main effects of MBI grouping on decline over one year for the groups were seen for the Attentional Intensity Index $F(2,8578)=3.97, p=0.0189$, the Sustained Attention Index $F(2,8578)=18.63$, $p<.0001$, the Attentional Fluctuation Index

F(2,8578)=10.13, p=<.0001 and the Working Memory Factor F(2,9895)=13.1, p<.0001, see Table 3 and Figure 1. For all four measures, decline in the MBI group was greater than in both the intermediate NPS and no symptoms group. For all measures except the Attentional Intensity Index, decline in the NPS group was also greater than in the no symptom group.

Main Effects of Individual Cognitive Measures

Baseline performance on individual measures broadly mirrored the composite scores, with the MBI group generally performing worse with the exceptions of simple reaction time, digit vigilance accuracy and pattern separation (original stimuli) where there were no differences in performance (Table 2)*.*

Decline over one year on the following 12 measures was significantly associated with MBI: grammatical reasoning accuracy (F(2,8561)=12.14, p<.0001), simple reaction time coefficient of variance (CV) (F(2,8586)=6.52, p=.0015), digit vigilance accuracy (F(2,8585)=9.06, p=.0001), digit vigilance speed (F(2,8585)=12.14, p=.0006), digit vigilance false alarms (F(2,8585)=11.63, p<.0001), digit vigilance CV (F(2,8585)=11.7, p<.0001), choice reaction time accuracy (F(2,8579)=7.55, p=.0005), choice reaction time speed (F(2,8579)=3.43, p=.0324), choice reaction time CV (F(2,8579)=3.53, p<.0295), paired associate learning (F(2,9919)=5.09, p=.0062), self-ordered search (F(2,9895)=18.96, p<0.0001) and verbal reasoning (F(2,9909)=3.62, p=.0269). The seven tests that did not reach statistical significance were grammatical reasoning speed, simple reaction time speed, all four pattern separation tests and digit span (Supplementary table 3).

IQCODE

IQCODE ratings were available for 6,452 participants. A significant relationship was identified between the MBI grouping and the IQCODE grouping (X^2 (2)=116.98, p<.0001), with higher proportions of high IQCODE scores among participants with MBI (Table 4). Self-rated IQCODE showed the same pattern (X^2 (2)=652.97, p<.0001).

CONCLUSIONS

This is the first study to show a clear and measurable pattern of decline in attention and working memory over one year associated with self-reported. It is the largest study of MBI to date by a significant margin and highlights the importance of assessing NPS, in the MBI framework, for testing association with cognitive decline. More importantly, our study provides evidence that MBI identifies a group of people with a mean age of 62 who experienced subtle cognitive decline.

The association found between working memory decline and MBI may be of particular relevance to preclinical AD. Of the three test scores underlying the Working Memory factor, paired associates learning (PAL) and self-ordered search (which reflect visuospatial sketchpad elements of working memory) showed significantly higher declines in the MBI group over one year, perhaps reflecting preclinical AD working memory deficits (34). We also demonstrate a strong association between attentional decline and MBI (as evidenced by the Sustained Attention, Attentional Intensity and Attentional Fluctuation composite measures). While attentional deficits have been noted in early AD, attentional impairments including fluctuating attention are a common feature of dementia with Lewy bodies (35), and further work will be important to determine the predictive value of different MBI symptoms and different neuropsychological profiles for AD and DLB risk.

Neuropsychiatric conditions are associated with cognitive deficits across the lifespan, and we must acknowledge that the etiology of MBI is still unclear (e.g. whether it is prodromal or a risk factor for dementia) and as such this finding may not wholly reflect

an underlying neurodegenerative process. However, given the strong evidence of a relationship between MBI and dementia it is of significance that we have identified a cognitive phenotype which appear to accompany the MBI syndrome in individuals without clinically significant cognitive impairment. There are three other reasons why our data support this relationship. Firstly, in the current study we have removed anyone with a known history of psychiatric illness and evidence of MCI (including incident MCI), decreasing the likelihood of these conditions confounding our results. Secondly, the MBI-C is designed specifically to detect emergent neuropsychiatric disturbances which are relevant to dementia (either as risk factors or as preclinical or prodromal states). Lastly, our analysis of the IQCCODE score showed a very strong relationship between reported memory problems and MBI grouping, suggesting a degree of independently measured memory complaint which is consistent with the results of the cognitive measures we report.

Research must now move on to address whether MBI assessment can provide an additional approach to enrich clinical trial samples for disease modifying therapies (3) and potentially novel opportunities to prevent or delay progressive cognitive decline and dementia. Firstly, deeper phenotyping (including fluid and imaging biomarkers, and longer term follow up) will be critical to establish whether the cognitive decline associated with MBI in this sample translates to MCI or dementia risk. The advantage of the ISTAART-AA MBI criteria and the MBI-C are the generation of domain scores, which were designed and characterized *a priori* specifically for this purpose. Work is underway to first establish the psychometric properties of the MBI-C in this sample which will feed into this work. Only once these questions are answered can research progress to understanding whether MBI may provide an important potential target for

pharmacological and non-pharmacological interventions; establishing whether MBI is a modifiable risk factor or early preclinical/prodromal state will be an important avenue of research here.

While previous studies have mapped NPS ratings on to the ISTAART diagnostic criteria to ascertain MBI (36, 37) our study used the MBI-C, which was designed, *a priori*, for pre-clinical populations. However, we relied upon a self-completed version of the MBI-C which may under-represent the social cognitive domain, resulting in an underestimation of risk. Moreover, the cut-point adopted was derived from an analysis of informant rated MBI-C, showing good sensitivity and specificity for clinically diagnosed MBI in clinical samples but our frequency estimate of 10% is comparable to a 14.2% frequency in a clinical sample of Spanish primary care patients that validated the current cut points (31, 38). This estimate is considerably lower than other recent estimates of around 28% in a community sample (36) and 76.5% in a cognitive neurology clinic sample (37). Both of these studies retrofitted the Neuropsychiatric Inventory items to map onto the ISTAART-AA criteria, and thus required any symptom to be present for only one month to satisfy MBI diagnostic criterion one - a more liberal threshold than the one used in this study. One can speculate that the lower MBI frequency in our study reflects a higher diagnostic specificity, eliminating false positives due to reversible factors and reactive states (11), and identifying a focused group for further assessment and workup, or intervention.

We note the small effect sizes in this study and that the declines observed are not of a level that would be problematic to a given individual. Moreover, very early markers will not by definition manifest as clinically significant declines in cognition. However,

it is important to understand the analysis is of change over one year, in relatively young adults where cognitive changes are generally quite flat. To give context to the effect sizes, the cognitive benefits of the major treatments for AD have an average effect size of 0.28 (39). These subjects have signed up to participate in the study for 25 years and thus the PROTECT study will continue to follow up these MBI groups to assess the progression of the cognitive trajectories. The results demonstrate that the presence of early cognitive deficits can be sensitively detected in concert with the emergence of later life sustained NPS, measured by the MBI-C, an important finding which will engender new hypotheses about the etiology of MBI in the cognitively normal population.

With regard to limitations, while this cognitive battery has provided detailed insight into the neuropsychological profile accompanying MBI and contains measures which are sensitive to AD (e.g. paired associates learning) we acknowledge that there are no measures of verbal episodic memory (e.g. word recall tests) which are also known to be sensitive to age-related cognitive decline. Another limitation of this study is the self-selecting recruitment strategy which led to the overrepresentation of women and those with a higher education level. Although we controlled for these variables in the analysis, some caution should be exercised before generalizing the findings to the wider population.

In conclusion this study provides further evidence that MBI is a feature of cognitive aging in older adults without MCI or dementia. The MBI-C used in the general population could represent a cost effective and easily scalable tool for the early

indication of accelerated cognitive decline prior to the onset of MCI, in those with at most subjective cognitive decline. We found a profile of declines in attention and working memory consistent with those seen in preclinical dementia, providing a strong impetus for future research to establish whether the routine inclusion of subclinical neuropsychiatric and neurobehavioral evaluations into preclinical disease risk modelling and epidemiological studies of cognitive aging is justified.

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