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Publication Date

2022-02-08

DOI

10.1017/S1041610221002878

Peer reviewed

HHS Public Access

Author manuscript

Int Psychogeriatr. Author manuscript; available in PMC 2023 August 08.

Published in final edited form as:

Int Psychogeriatr. ; : 1–10. doi:10.1017/S1041610221002878.

Cognitive profile of people with mild behavioral impairment in Brain Health Registry participants

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Abstract

OBJECTIVES: Dementia assessment includes cognitive and behavioral testing with informant verification. Conventional testing is resource intensive, with uneven access. Online unsupervised assessments could reduce barriers to risk assessment. The aim of this study was to assess the relationship between informant-rated behavioral changes and participant-completed neuropsychological test performance in older adults, both measured remotely via an online unsupervised platform, the Brain Health Registry (BHR).

DESIGN: Observational cohort study.

SETTING: Community dwelling older adults participating in the online BHR. Informant-reports were obtained using the BHR Study Partner portal.

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DESCRIPTION OF AUTHOR ROLES

H. Chen, Z. Ismail, A. McGirr and R. Nosheny designed the study objectives. M. Camacho, S. Mackin, R. Nosheny, M. Weiner and T. Williams supervised the data collection process. H. Chen and Z. Ismail contributed to the statistical design of the study, and H. Chen performed the statistical analysis. H. Chen, Z. Ismail, F. Kassam and A. McGirr wrote the manuscript. Z. Ismail, A. McGirr and M. Weiner advised methodology for the data analysis. All authors contributed to the interpretation of data and revising the manuscript.

Conflict of Interest Declaration

Data used in this study were collected using the BHR, which is funded by the NIH, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, California Department of Public Health, Connie and Kevin Shanahan, The Drew Foundation, General Electric, Global Alzheimer's Platform Foundation, Larry L. Hillbolm Foundation, The Ray and Dagmar Dolby Family Fund, The Rosenberg Alzheimer's Project and Patient-Centered Outcomes Research Institute.

Z. Ismail is funded by the Canadian Institutes of Health Research, and has received consulting fees/honoraria from Otsuka/Lundbeck, outside the submitted work. His institution has received funds from Acadia, Biogen, Roche, and Sunovion, also outside the submitted work. R. Nosheny is a co-investigator for the BHR. S. Mackin has received grant funding from the National Institute of Mental Health and has received research support from Johnson & Johnson. M. Weiner receives support for his work from the following: National Institute of Health, Department of Defense, Patient-Centered Outcomes Research Institute, California Department of Public Health, University of Michigan, Siemens, Biogen, Larry L. Hillbolm Foundation, Alzheimer's Association, The State of California, Johnson & Johnson, Kevin and Connie Shanahan, GE, Vrije Universiteit Medical Center Amsterdam, Australian Catholic University, The Stroke Foundation and the Veterans Administration. He has served on the Advisory Boards for Eli Lilly, Cerecin/Accera, Roche, Alzheon, Inc., and BHR.

PARTICIPANTS: The final sample included 499 participant-informant dyads.

MEASUREMENTS: Participants completed online unsupervised neuropsychological assessment including Forward Memory Span, Reverse Memory Span, Trail Making B, and Go/No-Go tests. Informants completed the Mild Behavioral Impairment Checklist (MBI-C) via the BHR Study Partner portal. Cognitive performance was evaluated in MBI+/− individuals, as was the association between cognitive scores and MBI symptom severity.

RESULTS: Mean age of the 499 participants was 67, of which 308/499 were females (61%). MBI+ status was associated with significantly lower memory and executive function test scores, measured using Forward and Reverse Memory Span, Trail Making Errors and Trail Making Speed. Further, significant associations were found between poorer objectively measured cognitive performance, in the domains of memory and executive function, and MBI symptom severity.

CONCLUSION: These findings support the feasibility of remote, informant-reported behavioral assessment utilizing the MBI-C, supporting its validity by demonstrating a relationship to online unsupervised neuropsychological test performance, using a previously validated platform capable of assessing early dementia risk markers.

Keywords

Mild Behavioral Impairment (MBI); Rating Scales; Neuropsychological Testing; Mild Cognitive Impairment (MCI); Neuropsychiatric Symptoms (NPS)

Introduction

Access to dementia assessments is uneven in North America and across the world (Geddes et al., 2020). This disparity has important clinical repercussions, particularly in regions where specialized resources are limited, and identification is delayed until later manifestations (Kamoga et al., 2019). The development of unsupervised platforms that do not require highly trained administrators may resolve this dual impasse and improve clinical outcomes (Bird and Lim, 2021). Moreover, they may create a low-cost recruitment infrastructure for early intervention trials, where no disease-modifying drug in Alzheimer's disease (AD) has met all primary endpoints (Cummings et al., 2018; Marsden and Mestre-Ferrandiz, 2015) in part due to poor recruitment of individuals without overt impairment or who are in the earliest stages of disease (Gauthier et al., 2016; Mortby et al., 2018). Advances in online services open the possibility of assessment portals in any region with an internet connection, for any individual with access to the internet and a computing device. Moreover, cognitive tests have been computerized and can be delivered without an administrator, and with convergent validity with those administered in tertiary cognitive assessment centers (Brooker et al., 2020; Mackin et al., 2018; Nosheny et al., 2020; Papp et al., 2021; Perin et al., 2020).

The addition of behavioral assessments to online platforms may provide additional relevant information. Neuropsychiatric symptoms (NPS) such as agitation, anxiety, apathy, depression, and psychosis are considered core features of dementia and are associated with poorer patient outcomes (Lanctôt et al., 2017). However, NPS can often precede cognitive symptoms (Shin, 2021), including in 30% of those who develop AD (Wise et

al., 2019). Mild behavioral impairment (MBI) is a pre-dementia neurobehavioral syndrome characterized by the *de novo* emergence and persistence of NPS in older adults representing a change from longstanding patterns of behavior (Ismail et al., 2016). MBI is associated with amyloid, tau, neurodegeneration, and AD risk genes (Andrews et al., 2018; Creese et al., 2021b; Gill et al., 2021; Johansson et al., 2021; Lussier et al., 2020; Matuskova et al., 2021; Miao et al., 2021; Naude et al., 2020; Ruthirakuhan et al., 2022), and a greater risk of incident cognitive decline and dementia (Creese et al., 2019; Gill et al., 2020; Ismail et al., 2021; Matsuoka et al., 2019; Taragano et al., 2018; Tsunoda et al., 2021; Wolfova et al., 2021). Incorporating MBI into screening may provide a complementary approach to early detection (Mortby et al., 2018). However, informant information is often required to validate the syndrome, and structured assessment tools suitable for widespread dissemination through unsupervised platforms have only recently been developed. The Mild Behavioral Impairment Checklist (MBI-C) incorporates informant information and is the validated case ascertainment instrument developed specifically to capture MBI in accordance with the criteria developed by the International Society to Advance Alzheimer's Research and Treatment-Alzheimer's Association (ISTAART-AA)(Creese et al., 2020; Ismail et al., 2017; Mallo et al., 2019; Saari et al., 2021). Translated into over 20 languages, the MBI-C may also allow a broader reach for obtaining online informant reports of behavioral change.

The aim of this study was to investigate informant-based MBI in an online unsupervised platform, the Brain Health Registry (BHR), capable of assessing early dementia risk markers (Weiner et al., 2018). We determined the utility of the BHR for converging assessments of cognitive and behavioral symptoms using neuropsychological testing and informant-reported MBI-C. We hypothesized that participants with MBI+ status would have poorer cognitive performance measured by the Lumos test battery. We further hypothesized that individuals with poorer memory, executive function, processing speed, and inhibitory control would have a higher burden of MBI symptoms.

Methods

Brain Health Registry

The BHR (Weiner et al., 2018) is an internet-based public registry and cohort that recruits participants using a variety of methods including a website, social media, brochures, and online advertising. All participants are required to give informed consent with an online consent form. Upon completion of the consent form, participants may complete questionnaires regarding personal and family medical history, early childhood history, sleep quality, diet, quality of life scales, psychiatric symptomatology, as well as online cognitive testing via Lumosity (Morrison et al., 2015), CogState (Lim et al., 2015), or Memtrax (Ashford et al., 2011) tests. Additionally, study partners of BHR participants can register on the BHR study partner portal, on which informant-rated measures are completed (Nosheny et al., 2018).

Study Participants

Participants were included if: 1) Lumosity cognitive tests were completed; and 2) their informant completed the MBI-C via the BHR study partner portal within a year of the

cognitive tests. Participants were excluded if they reported: 1) developmental or learning disorders; 2) neurological conditions such as movement disorders, multiple sclerosis, traumatic brain injury; 3) current or past psychiatric diagnoses including schizophrenia, major mood or anxiety disorders, or PTSD.

Study Variables

Lumosity online Forward Memory Span—The assessment of Forward Memory Span is based on the Corsi block-tapping tasks (Milner, 1971). The participant is asked to recall the sequence of circles in the same order it was presented. The length of the sequence increases by one every two trials. The session comes to an end when the participant records two incorrect answers at the same span level. This task is used as a measure of visual short-term memory and attention.

Lumosity online Reverse Memory Span—The Reverse Memory Span task is a slightly altered version of the original Corsi block-tapping tasks. It is identical to the forward visual memory span assessment, with the exception that the participant is asked to recall the sequence of circles in the reverse order. This reverse task is used as a measure of visual working memory and attention.

Lumosity online Trail Making Test B—In Trail Making Test (TMT) B, blue circles (numbered 1 to 12) and capital letters (A to L) are arranged in 6 possible layouts with non-overlapping spatial locations. The participant must alternate between numbers and letters for this task, clicking in increasing order. When the blue circle is clicked, it turns orange, and a straight line appears to connect the circles. The timer for the task begins when the participants click the first circle. If the participant records an incorrect click, an X appears on their screen, and they are required to go back to the previous circle. For this study, we included the response time and number of errors as measures of processing speed attention and sequencing ability.

Lumosity online Go/No-Go—In the Go/No-Go assessment, participants are presented with target pictures and distractor stimuli. The target picture is chosen from a set of photos of fruit. Each stimulus appears after a random delay between 1000 and 3000 ms to discourage anticipatory responding. The participant is instructed to respond as quickly as possible within 1500ms. The assessment ends when a participant responds to ten “Go” trials. If the participant submits three incorrect responses (responding to “no-go” or failing to respond to “go”), the participant will restart the task. The participant is given feedback on timing and correctness. This assessment is used to measure response inhibition and speed of information processing.

Mild Behavioral Impairment Checklist—The MBI-C is included in the BHR study partner portal and is therefore completed by an informant. The MBI-C is explicit that symptoms are *de novo* in later life, represent a change from longstanding patterns of behavior, and are persistent for at least six months. The MBI-C consists of questions in the five MBI domains of apathy, mood and anxiety, agitation and impulsivity, impaired social cognition, and psychosis, with items geared towards capturing NPS in community dwelling,

functionally independent, non-demented older adults. The scale takes ~7-8 minutes to complete, consisting of 34 questions; scoring is from 0-3, representing absent, mild, moderate, and severe changes, with a total score range of 0-102 (Ismail et al., 2017).

Statistical Analysis

Continuous demographic variables (age and years of education) were analyzed using independent sample t-tests to compare MBI+ and MBI− groups; sex distribution between the two groups was analyzed using chi-square tests. MBI-C was dichotomized based on a validation in primary care non-demented older adults in which scores of >7 differentiated MBI+ from MBI− with a sensitivity of 0.93, specificity of 0.76 and AUC of 0.93 (Mallo et al., 2018b). As exploratory analyses, cutpoints of >5 and >6 were also analyzed. Univariate Analysis of Covariance (ANCOVA) was used to compare performance on Lumosity cognitive tests between MBI+ and MBI− groups, covarying for age, sex, education, and neuropsychological and neurobehavioral assessment interval. Skewed data were log-transformed; however, the TMT response time variable was analyzed with a negative binomial regression due a skewed distribution with an overrepresentation of zeros. For Go/No-Go errors, ordinal logistic regression was performed because the response variable only had three possible values: 0, 1, and 2.

Additionally, negative binomial regressions were fitted to assess Lumosity task prediction of MBI-C total scores. Negative binomial regression is preferred when the data are skewed, as in this sample where the mode on the MBI-C is zero indicating no emergent and persistent NPS. Lumosity task measures as continuous scores were the independent variables in these models. The covariates included were age, sex, education, and neuropsychological and neurobehavioral assessment interval. The p values for Lumosity task measures were calculated using likelihood ratio tests.

Statistical analyses were performed using SPSS v26 and R 3.6.2.

Results

Participant selection is described in Figure 1. The final sample included 499 participants with a mean age of 67 (SD 10.4), of which 308/499 were females (61%) (Table 1). The number of MBI+ participants was 31 (6.2%) (Figure 1). A significantly greater number of men were classified as MBI+ (64%, p=0.002). MBI+ participants had significantly poorer forward memory span (mean sequence length of 4.68 vs. 5.26, p=0.005; Figure 2a), poorer reverse memory span (3.81 vs. 4.85, p<0.0001; Figure 2b), more TMT errors (4.29 vs. 1.85, p=0.01; Figure 2c), and longer TMT completion time (67.67 vs. 45.08 seconds, p<0.0001; Figure 2d). MBI was not associated with the number of errors (p=0.84) and response time (p=0.16) on the Go/No-Go task (Figures 2e & 2f). The effect sizes for these differences were modest. Of the tests that significantly differed between groups, the largest effect size (Cohen's f) was for reverse memory span (0.20), followed by TMT response time (0.20), memory span (0.13), and TMT accuracy (0.11). See Tables 2a-2c for statistical reporting. Analyses using cutpoints of >5 and >6 for MBI-C show very similar results and are included in supplemental tables (Supplemental tables 1-6).

Negative binomial regressions utilizing Lumosity scores to predict MBI score determined that worse memory span (X^2(1, N=499)=6.6, p=0.01), worse reverse memory span X^2(1, N=498)=5.4, (p= 0.02), more TMT errors (X^2(1, N=499)=5.8, p=0.02) and longer TMT response time (X^2(1, N=499)=9.6, p=0.002) were all associated with higher MBI-C total scores. Go/No-Go errors (X^2(1, N=497)=0.16, p=0.69) and Go/No-Go response time (X^2(1, N=497)=0.97, p=0.33) were not associated with MBI-C score (Table 3).

Discussion

In a sample of 499 participant dyads in BHR, we demonstrated the feasibility of delivering unsupervised online assessments of behavioral and cognitive markers of dementia risk. Utilizing the validated cut off score of >7 on the MBI-C, MBI+ status was associated with significant differences in memory and executive function, measured using memory span, reverse memory span, TMT errors and TMT speed. Further, significant associations were found between poorer objectively measured cognitive performance, in the domains of memory and executive function, and MBI symptom severity. Effect sizes were small, ranging from 0.11-0.20. The findings do suggest that a simple informant reported behavioral measure completed via an online portal might be a relevant addition to neuropsychological testing, warranting further study in BHR. In other work, MBI+ status has demonstrated significant and meaningful associations with incident cognitive decline and dementia across several studies, settings, and populations (Creese et al., 2019; Gill et al., 2020; Ismail et al., 2021; Matsuoka et al., 2019; Taragano et al., 2018; Tsunoda et al., 2021; Wolfova et al., 2021). Thus, while convergent with tests of memory and executive function, behavioral and cognitive markers of risk may be distinct, potentially offering complementary measures of risk.

Our data indicate that the BHR is an effective platform to conduct remote assessments of cognitive functioning with convergence of behavioral and cognitive tests. Poorer performance on unsupervised online neuropsychological testing has been associated with self-report MCI and AD (Mackin et al., 2018). Online participant testing is an efficient and reliable tool for neuropsychological testing, which can identify performance decrements in executive dysfunction and memory (Morrison et al., 2015). Similarly, online informant reports such as those collected in the BHR study partner portal are valuable and informative. Online study-partner reported cognitive decline is comparable to data collected in clinic, is associated with objectively defined participant cognition (Nosheny et al., 2018), and is associated with amyloid, clinical diagnosis of dementia due to AD, and in-clinic cognitive screening test scores (Nosheny et al., 2020). In this study, online informant-reported behavioral symptoms associated with differences in memory and executive function collected via the participant portal. This harmonized utilization of participant and study partner portals is effective and can allow continuation of research activities even during trying times such as the recent pandemic, where consistent in person visits between clinicians and patients were not feasible. Although the COVID-19 pandemic has highlighted the need for alternative infrastructure to allow continued care, the tools that have been developed may permit the assessment of older adults who for physical, social, or cognitive reasons could not previously access care. This approach also allows outreach to areas less accessible to academic centers.

The cognitive domain differences detected with the MBI-C include memory and executive function, which are relevant and important for AD risk (Wilson et al., 2011). Early decline in memory and executive function has been shown to be associated with the preclinical disease process, thus, early detection of reductions in cognitive functioning may be useful in identifying populations at risk (Almkvist et al., 1998; Nagata et al., 2011). Both memory and executive function are important endpoints in AD trials (Vellas et al., 2008). Longitudinal cohorts have demonstrated that an acceleration of decline in memory performance occurs 3-4 years before a diagnosis of MCI and 7 years before a diagnosis of AD, while for executive function an accelerated decline occurs 2-3 years before AD diagnosis (Grober et al., 2008; Mistridis et al., 2015). The finding of small but significant associations between MBI and poorer memory and executive function performance is consistent with the evolving description of the cognitive profile of MBI (Rouse et al., 2021; Wong et al., 2020; Yoon et al., 2019). These findings are consistent with a previous study using the UK online PROTECT study portal in which self-reported MBI, measured with the MBI-C, was associated with faster decline in attention and working memory at one year in older adults with normal cognition (Creese et al., 2019). A subsequent analysis of cognitively normal PROTECT participants, with a median follow up time of 3 years, demonstrated an association between baseline informant-reported MBI+ status and decline in measures of working memory and fluid intelligence (Wolfova et al., 2021). In an overlapping sample, AD genetic risk was determined using polygenic risk scores. AD genetic risk was associated with worse cognition in the informant-reported MBI+ group but not in the MBI− group. The strongest association was in those with more severe MBI, aged ≥65 (Creese et al., 2021a). These convergent findings support leveraging online cognitive and behavioral measures to explore dementia risk. In a recent study of National Alzheimer Coordinating Center data, the combination of informant-reported MBI and subjective cognitive decline (SCD) had a greater risk of incident cognitive and functional decline at three years compared to either MBI or SCD alone (Ismail et al., 2021). Further, in a subsequent study, those with SCD and MBI together had a shorter median time to incident MCI compared to those with SCD in the absence of MBI (Nathan et al., 2020). Taken together the results suggest that individuals with subtle neuropsychological test score differences and MBI together may be at higher risk for cognitive and functional decline.

As the case ascertainment instrument developed to measure MBI in accordance with the ISTAART-AA MBI criteria, the MBI-C was designed to: 1) operationalize the MBI concept; 2) measure a selected list of NPS which may help identify preclinical or prodromal dementia; and 3) predict risk of several dementias (Ismail et al., 2017). This instrument has been validated in an online cohort of cognitively normal older adults (Creese et al., 2020), a primary care sample with SCD (Mallo et al., 2019) or MCI (Mallo et al., 2018a), and a cognitive neurology clinic population with SCD and MCI (Hu et al., 2019; Saari et al., 2021).

This study is the first of its kind, investigating MBI within the BHR. The findings show associations between behavior and cognition, and further support the utility of the study-partner portal. These findings will also serve as a baseline, to assess longitudinal changes in behavior and cognition. Notwithstanding the promising findings of linking behavior and cognition utilizing online study portals, there do exist barriers to this approach. Older

adults may be less likely to use technology to begin with, potentially limiting the sample (Lorence and Park, 2006). Furthermore, lack of computer knowledge, and loss of vision and fine motor skills may affect the ability of older adults to successfully access and operate technology, resulting in negative attitudes and frustration (Gatto and Tak, 2008; Gell et al., 2015; Gitlow, 2014). Socioeconomic status can also influence the ability to utilize online assessments. Limited access to computers or tablets may preclude some from participating, and those without a stable internet connection may not successfully complete online neuropsychological testing due to disruptions or low bandwidth (Darrat et al., 2021). These barriers could also limit the diversity in the sample that does participate in online studies.

Further, study limitations may affect interpretation and generalizability. These limitations include high education levels and restriction to participants and study-partners who can successfully complete tasks online (Nosheny et al., 2018). Since the BHR is an online self-report database, the lack of a clinical diagnosis within the sample group is a potential source of error. BHR participants may have undiagnosed and/or unreported neurodegenerative disease or psychiatric disorders, which may be associated with greater MBI score. While online cognitive testing has been validated (Lim et al., 2015; Mackin et al., 2018), further research is needed, given the lack of supervision or control for test environment, external factors, distractors, or cues. Further, important disease related factors such as severity and time since symptom onset were not controlled for. Although MBI was associated with statistically significant differences in Lumosity neuropsychological test scores, effect sizes were small, and the clinical significance of these differences is difficult to interpret in the largely cognitively healthy population enrolled in BHR. These data are promising but not conclusive, and further research is required. Whether these small differences in cognitive test scores represent greater risk for incident cognitive decline and dementia can be addressed in the future using longitudinal data and a cohort that includes participants with cognitive impairment.

In summary, in this BHR study combining self- and informant-rated measures, the convergence of behavioral risk markers for dementia and cognitive differences was observed, reflected by neuropsychological tests incorporating memory and executive function. The findings lend additional support to online unsupervised administration of cognitive and neuropsychiatric measures, as a low-cost approach to improve access to neurocognitive assessments, potentially identifying at-risk older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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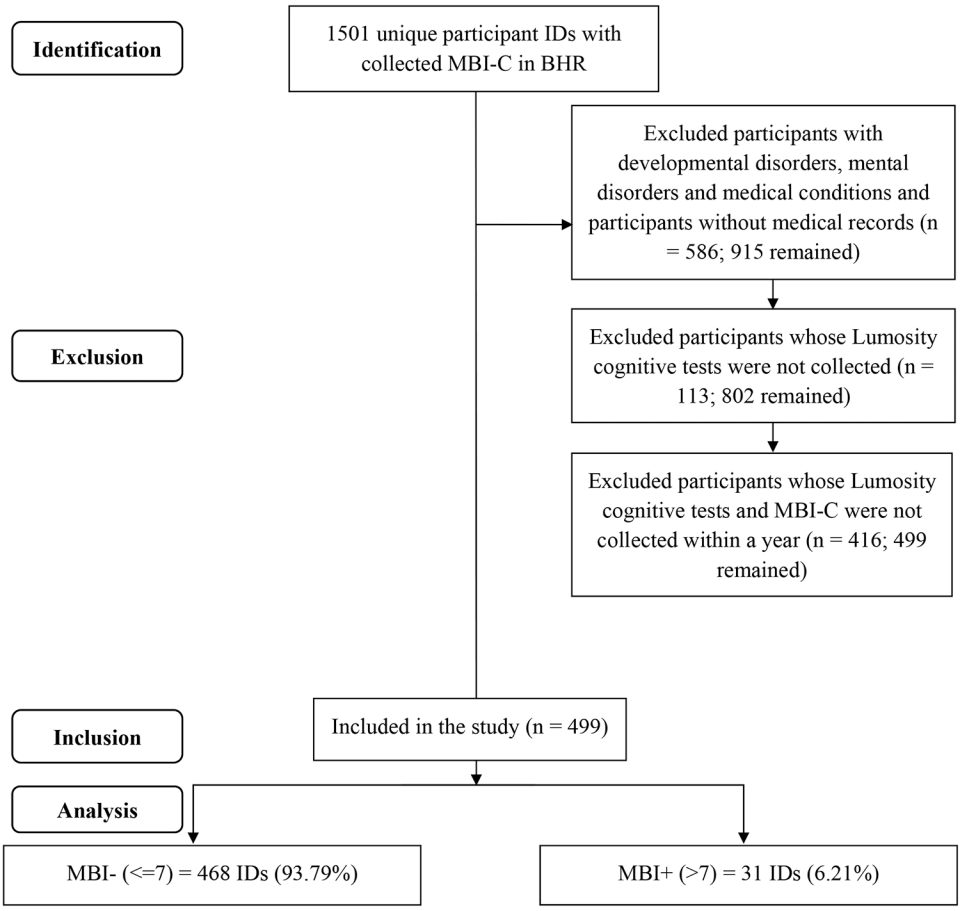

Figure 1-
Flowchart of participants from the BHR included for analysis

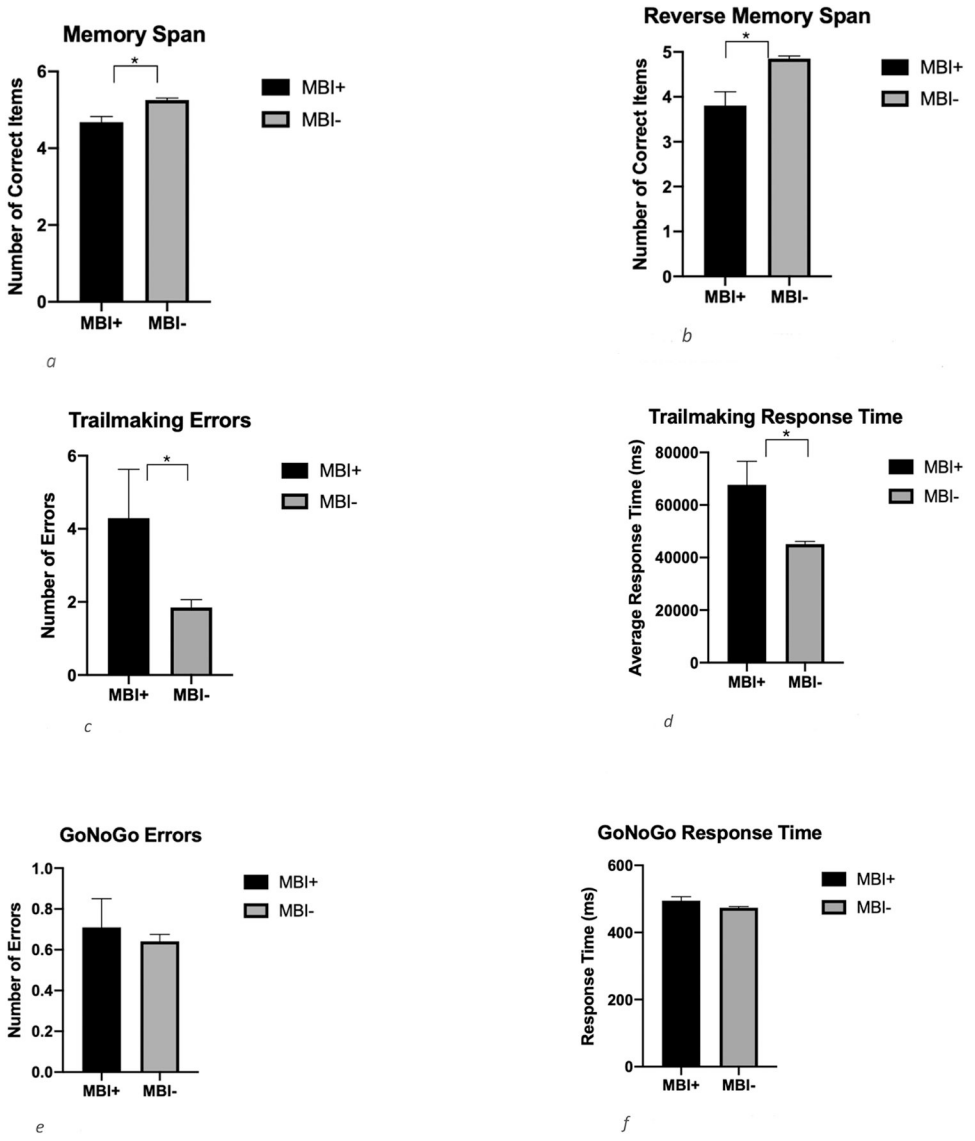

Figure 2.

(a) Positive result (>7) on the MBI-C is associated with shorter Memory Span; (b) positive result (>7) on the MBI-C is associated with shorter Reverse Memory Span; (c) positive result (>7) on the MBI-C is associated with more errors in the Trail Making-B task; (d) positive result (>7) on the MBI-C is associated with longer response time in Trail Making-B task; (e) positive result (>7) on the MBI-C is not associated with the number of errors on a GoNoGo task; and (f) positive result (>7) on the MBI-C is not associated with the response time on a GoNoGo task.

Table 1.

Summary statistics for demographics

Cutpoint of MBI-C > 7				
	MBI+ (n=31)	**MBI− (n=468)**	**Test Statistic**	***p***
Average Age	69.52	67.11	$t(497) = 1.25$	.213
Average Estimated Years of Education	17.58	17.14	$t(497) = 1.13$	.260
Number of Females	11	297		
Percentage of Female	35.48%	63.46%	$\chi^2 = 9.63$	**.002**

Table 2a.

Summary statistics for Lumosity tasks (Cutpoint of 7) (ANCOVA)

Cognitive Measures	Mean (MBI+)	Mean (MBI−)	*F*	*df within*	*df between*	*Partial* η^2 *(effect size)*	*p value*
Memory Span	4.68	5.26	8.11	1	493	0.016 (0.13)	**0.0046**
Reverse Memory Span	3.81	4.85	20.06	1	492	0.039 (0.20)	< **0.0001**
Trailmaking Errors	4.29	1.85	6.81	1	493	0.014 (0.11)	**0.0093**
Trailmaking Response Time (log transformed)	67.67	45.08	19.40	1	493	0.038 (0.20)	< **0.0001**
Go/No-Go Errors	0.71	0.64	0.04	1	491	0.000 (0.01)	0.8386
Go/No-Go Response Time	496.42	473.87	1.98	1	491	0.004 (0.06)	0.1604

Table 2b.

Summary statistics for using MBI-C status (Cutpoint of 7) to predict Trail Making Errors (Negative Binomial Regression)

Cognitive Measure	Beta[1]	95% CI	X^2	*p* value
Trail Making Errors	137.5%	+13.1% to +484.0%	5.312	**0.0212**

[1] Beta coefficients represent the estimate percent difference in Trail Making errors associated with status

Table 2c.

Summary statistics for using MBI-C status (Cutpoint of 7) to predict Go/No-Go Errors (Ordinal Logistic Regression)

Cognitive Measures	Odds Ratio	95% CI	*p* value
GoNoGo Errors	1.058	0.517 to 2.121	0.875

Table 3.

Summary statistics for Lumosity tasks predicting MBI-C total score

Predictor	Beta[1]	95% CI	X^2	*p* value
Memory Span	−26.2%	−41.8% to −7.1%	6.6513	**0.0099**
Reverse Memory Span	−15.7%	−27.7% to −2.6%	5.3765	**0.0204**
Trail Making Errors	5.3%	+0.9% to +11.2%	5.8059	**0.0160**
Trail Making Response Time	0.0012%	+0.0004% to +0.0023%	9.6268	**0.0019**
GoNoGo Errors	−6.2%	−31.0% to +29.0%	0.1594	0.6897
GoNoGo Response Time	0.1%	−0.2% to +0.5%	0.9678	0.3252

[1]Beta coefficients represent the estimate percent difference in total MBI-C score given one unit change in Lumosity task measure.