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COMMENTARY

Mild behavioral impairment: challenges facing a quickly developing evidence base

The past decade has seen the recognition of later-life emergent neuropsychiatric symptoms (NPS), referred to as mild behavioral impairment (MBI) (Ismail *et al.*, 2016, Taragano *et al.*, 2008), as a novel dementia-risk marker and a potential early clinical intervention target (Mortby *et al.*, 2018a). Leveraging the well-known behavioral prodrome of frontotemporal dementia (FTD), MBI was first proposed by Taragano and colleagues (2008) as a pre-dementia (primarily FTD) construct where a primarily behavioral presentation (late-life behavioral changes in the absence of major cognitive symptomatology) was associated with greater dementia risk, when contrasted to a primarily cognitive presentation (i.e. mild cognitive impairment). This definition was substantially revised by the MBI Working Group of the Alzheimer's Association (AA) International Society to Advance Alzheimer's Research and Treatment (ISTAART) Neuropsychiatric Syndromes Professional Interest Area, and published in 2016.

The fundamental changes to the MBI construct, as described in the ISTAART–AA criteria, come from the harmonization of cognition and behavior, not as competing constructs but as parallel ones (a neurobehavioral axis and a neurocognitive axis), that can manifest concurrently or sequentially (as opposed to either/or). Further, these new criteria are explicit in that MBI can be a prodrome to dementia of any etiology, including Alzheimer's disease, moving away from the prevailing belief that behavioral prodromes are uniquely associated with FTD. Additionally, specific behavioral domains were described, allowing the opportunity to distinguish between behavioral endophenotypes, potentially allowing for greater prognostic precision. The criteria exclude psychiatric illness a priori and require the onset of symptomatology in later-life and the presence of the behaviors for 6 or more months (Ismail *et al.*, 2016).

The AA–ISTAART MBI criteria provide the research field with a structured framework through which relevant NPS can be examined for their impact on cognition (Ismail *et al.*, 2016). The five behavioral domains, which can be examined independently or collectively, include: (i) impaired drive and motivation (apathy); (ii) emotional dysregulation (mood and anxiety symptoms); (iii) impulse dyscontrol/agitation/abnormal reward salience (changes in response inhibition and self-regulation); (iv) social inappropriateness (impaired social cognition) and (v) abnormal thoughts/perceptions (psychosis e.g. hallucinations and delusions). The development of these construct-specific criteria has been crucial in the elucidation of the relationship between MBI and cognitive impairment.

A concerted global research effort has since focused on the validation of the MBI construct as a neurobehavioral syndrome (e.g. Sherman *et al.*, 2018, Ismail *et al.*, 2018, Bateman *et al.*, 2020, Desmarais *et al.*, 2018, Fischer and Aguera-Ortiz, 2018, Mortby *et al.*, 2018b, Sheikh *et al.*, 2018, Creese *et al.*, 2019). The ISTAART–AA MBI criteria, and the subsequent development of a construct-specific case ascertainment tool – the MBI Checklist (Ismail *et al.*, 2017), have underpinned a paradigm shift, with greater recognition of MBI as a pre-clinical marker of dementia risk.

These criteria have underpinned a rapidly growing international body of evidence linking MBI to accelerated cognitive decline/progression to dementia (e.g. Taragano *et al.*, 2018, Creese *et al.*, 2019, Matsuoka *et al.*, 2019), validated Alzheimer's disease genetic loci (Andrews *et al.*, 2018, Creese *et al.*, 2020) and neurobiological correlates (e.g. Naude *et al.*, 2020, Lussier *et al.*, 2020). Within this rapidly evolving research field, the work presented by Rouse and colleagues (2020) in their article "Mild Behavioral Impairment as a Predictor of Cognitive Functioning in Older Adults" provides a valuable addition to the current research paradigm and a starting point for longitudinal follow-up.

Using data from the Florida Alzheimer's Disease Research Center (FL-ADRC), the authors conducted a secondary data analysis of 497 cognitively healthy older adults and individuals with mild cognitive impairment and provide valuable insight into unique cognitive phonotypes associated with MBI. This was done by examining the impact of MBI on specific cognitive domains (executive function, attention, short-term memory and episodic memory) and further investigating the role of cognitive status (i.e. normal cognition vs. mild cognitive impairment) within this association. The authors

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hypothesized that those with MBI would perform worse on tests of executive function and attention, and that when an MBI diagnosis is superimposed on mild cognitive impairment, performance would be worse across all cognitive domain tasks.

In a 2 (MCI: presence or absence) × 2 (MBI: presence or absence) Multivariate Analysis of Co-Variance, Rouse *et al.* (2020) showed that, regardless of cognitive status, MBI was associated with poorer executive function, attention and episodic memory; and that co-morbid presentation of MBI and mild cognitive impairment resulted in significantly poorer performance on tasks of episodic memory when compared to a mild cognitive impairment only cohort. The authors conclude that the current findings not only corroborate the notion of MBI as an at-risk state for cognitive decline (e.g. Ismail *et al.*, 2016, Taragano *et al.*, 2018) but also contribute to the growing evidence base that MBI is associated with "unique cognitive phenotypes" (e.g. Creese *et al.*, 2019).

While the study methodology is generally well described and utilizes data from the comprehensive battery of cognitive tests collected by the FL-ADRC, there are a number of methodological considerations that need to be considered. Firstly, the authors describe that participants were included if at baseline they had complete information on cognitive status, full Neuropsychiatric Inventory Questionnaire (NPI-Q) data, and mostly complete data for the neuropsychological assessments. The authors note that individuals were excluded if they lacked a consensus conference diagnosis, had subjective cognitive complaints, a diagnosis of dementia or incomplete key demographic information (i.e. missing age, gender, race and education). While these inclusion/exclusion criteria are plausible, there is a lack of clarity around what exactly is meant by "mostly complete data". Secondly, the authors' decision to exclude individuals with subjective cognitive complaints (n = 46) seems somewhat over-simplified. The study methodology provides no clear guidance as to how these individuals were identified and the only rationale provided for their exclusion was a lack of formalized criteria for subjective cognitive decline at the time of data collection. It therefore begs the question how these participants were identified for exclusion. Finally, given the increasing research focus on MBI and subjective cognitive complaints (e.g. Sheikh *et al.*, 2018, Mallo *et al.*, 2019, Ismail *et al.*, 2020), it would have been beneficial to the study if this cohort had been included in the current study design. Future research will be needed to evaluate whether the findings from this study are also maintained in the context of subjective cognitive decline.

Some consideration needs also to be given to the prevalence rates of MBI reported in the current study, as the original study was not designed to investigate MBI, and thus did not include the novel MBI-Checklist. Similar to other population-based cohort and clinical studies which have used data collected prior to the development of the MBI-Checklist, Rouse *et al.* (2020) assessed MBI using a previously published MBI operationalization matrix (e.g. Mortby *et al.*, 2018b, Sheikh *et al.*, 2018, Andrews *et al.*, 2018). This operationalization matrix maps 10 of the 12 NPI-Q domains (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviors) onto the MBI criteria.

Using this operationalized matrix and a 1-month reference range, Rouse *et al.* (2020) reported MBI prevalence rates in 38.6% of cognitively healthy participants and 67.9% of participants with mild cognitive impairment. These prevalence rates lie between those reported by Mortby *et al.* (2018b) in an Australian population-based sample taken from the Personality and Total Health (PATH) Through Life study (27.6% in cognitively normal and 48.9% in mild cognitive impairment) and by Sheikh *et al.* (2018) in a Canadian clinical sample taken from the Prospective Study for Persons With Memory Symptoms (PROMPT) study (85.3% in mild cognitive impairment). Given the FL-ADRC dataset includes participants from both population-based and clinical settings, the reported prevalence rates seem perfectly plausible.

Having said that, the prevalence rates reported across all three studies (Mortby *et al.*, 2018b, Rouse *et al.*, 2020, Sheikh *et al.*, 2018) need to be interpreted with caution, as they may in fact represent inflated prevalence rates. The reason for this is the discrepancy between the reference timeframes used by the assessment tools. While the Neuropsychiatric Inventory and its derivatives (i.e. the NPI-Q) are traditionally considered the gold-standard assessment tool for NPS in dementia, they use a 1-month reference range for the reporting of symptoms. In contrast, the MBI criteria and the MBI-Checklist mandate a 6-month reference range of behaviors. Differences in the reference timeframes of the assessment tools may thus be resulting in inflated prevalence rates of MBI as transient and reactive symptoms are more likely to be captured when using this transformation matrix and assessment tools that mandate a shorter reference timeframe.

Nonetheless, the utility of this operationalization matrix should not be prematurely discarded as a tool for retrospective assessment of MBI in pre-existing datasets. For example, using this operationalization matrix, Rouse *et al.* (2020) also identified impulse

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dyscontrol and affective dysregulation as the most commonly observed MBI domains in the FL-ADRC. These findings not only align with those reported in both the PATH (Mortby *et al.*, 2018b) and PROMPT (Sheikh *et al.*, 2018) studies but also with findings from novel prospective studies which have utilized the more sensitive MBI-Checklist (e.g. Lussier *et al.*, 2020, Mallo *et al.*, 2018). This suggests that despite discrepancies in reference timeframes, the operationalization matrix still shows some merit to identify MBI and its subdomains. For this reason, future research will need to focus on the development and refinement of the operationalization matrix to enhance accuracy in retrospective assessment in previously existing population-based and clinical studies.

In summary, the study by Rouse *et al.* (2020) provides new and important additions to the fast advancing research field on MBI. The identification of cognitive phenotypes of MBI is a crucial building block in better understanding MBI as an at-risk state for cognitive impairment and dementia as well as the development of early identification and risk reduction strategies. The study raises a number of interesting questions for the field of research, especially in relation to the effective assessment of MBI in studies, which were not originally designed to assess this novel construct. It is therefore incumbent on the field that a focus is placed on better understanding the temporal patterns and timeframes of MBI and that dedicated efforts are made to improve the operationalization of existing data to inform the research field.

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