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GUEST EDITORIAL

Special Issue on mild behavioral impairment and non-cognitive prodromes to dementia

This Special Issue provides a systematic examination of the neuropsychiatric symptoms (NPS) and non-cognitive prodromes of dementia, with an eye toward validating the construct of mild behavioral impairment (MBI).

NPS, also referred to as behavioral and psychological symptoms of dementia, are a common non-cognitive hallmark of neurodegenerative disorders, irrespective of disease etiology (Lyketsos *et al.*, 2011). Their presence is linked to more rapid cognitive decline, earlier institutionalization, and higher mortality rates (Lanctôt *et al.*, 2017). Increasingly, NPS are being cited as an intrinsic aspect of dementia prodromes, and as a marker of impending cognitive decline that precedes the onset of cognitive symptoms (Mortby and Anstey, 2015). Thus, NPS may be an early, and potentially novel, target for intervention.

MBI describes the later-life onset of sustained and meaningful NPS, of any severity, in individuals who do not yet exhibit dementia or who exhibit no cognitive symptoms. MBI is a *neurobehavioral syndrome* that describes an at-risk state for incident cognitive decline and dementia; MBI can precede or emerge in concert with mild cognitive impairment (MCI). Its assessment is operationalized through the International Society to Advance Alzheimer's Research and Treatment – Alzheimer's Association (ISTAART-AA) research diagnostic criteria, developed by an ISTAART expert panel (Ismail *et al.*, 2016), and the MBI checklist (MBI-C, www.MBItest.org) – a rating scale developed specifically for MBI case ascertainment (Ismail *et al.*, 2017). According to the operationalized criteria, MBI is hallmarked by changes in behavior or personality that start after the age of 50 years, representing a clear change from the person's usual behavior or personality. MBI is evidenced by one or more of the following: *decreased motivation and drive*, *affective/emotional dysregulation*, *impulse dyscontrol*, *social inappropriateness*, and *abnormal perception or thought content*.

Using the operationalized diagnostic criteria, Mortby *et al.* (2018a) reported *in this issue* the first population-based prevalence estimates of MBI in 1,377 older adults (aged 72–79 years). MBI criterion A symptoms were reported in 34% of the population across the spectrum from cognitively normal to MCI. Irrespective of the level of cognitive impairment, impulse dyscontrol and decreased motivation were the most frequently reported MBI symptoms.

In a clinical sample of 282 memory clinic patients with MCI and subjective cognitive decline (SCD), Sheikh *et al.* (2018) reported a high frequency of MBI criterion A symptoms (82%). These symptoms were associated with 3.5 higher levels of caregiver burden, thus demonstrating the clinical significance of MBI domains. The findings are of particular importance when considering support mechanisms, the need for family respite care, and the need to include the families in assessments in clinical and pre-clinical settings.

Cieslak *et al.* (2018) presented case studies that illustrate typical presentations of NPS in cognitive clinics, along with neuroimaging findings. These cases emphasize the challenge in primary care of identifying psychiatric symptomatology as part of neurodegenerative disease, as opposed to "typical" psychiatric illness with which clinicians are more familiar. This symptom misattribution often results in unsuccessful treatment of the psychiatric symptoms, with resultant delays to cognitive specialist referral during the treatment process. The cases further illustrate how the MBI-C can be used in a clinical context to help with differential diagnosis of later-life onset psychiatric symptoms, leading to early detection with assessment of dementia risk.

Several papers of this Special Issue address in detail the MBI domains. Reporting on *decreased drive and motivation*, Sherman *et al.* (2018) provided a comprehensive literature review of apathy in pre-dementia states. The authors conclude that there is a need to improve understanding of the neurobiological mechanisms of apathy in MCI and MBI to provide effective treatment to apathetic patients in prodromal dementia. Ismail *et al.* (2018) provided a scoping review of *affective and emotional dysregulation* symptoms, to explore the epidemiology and neurobiological links between affective and emotional symptoms and later cognitive decline. Findings from this paper highlight the prognostic utility of affective symptoms, and

the great importance of understanding the natural history and age of onset of affective symptoms as they relate to neurocognitive disorders.

In their paper relating depression and anxiety to cortical amyloid deposition in cognitively normal elderly, Krell-Roesch *et al.* (2018) provided evidence of an association between anxious and depressive symptoms and cortical amyloid deposition. In a large sample of 1,038 cognitively normal elderly participants in the population-based Mayo Clinic Study of Aging, 379 were amyloid positive. Anxiety was reported in 6.1% of this cognitively normal community sample, and depression in 7.3%. Despite the low prevalence of self-reported anxiety and depression, the results support further need for longitudinal investigation of this association.

Addressing the domain of *social inappropriateness*, Desmarais *et al.*(2018) provided compelling evidence to highlight the importance of social inappropriateness as a first clinical sign of neurodegenerative disease, prior to noticeable cognitive impairment. The authors describe this as an underappreciated issue in pre-dementia populations, recommending more research into this often overlooked feature of MBI.

Finally, Fischer and Agueria-Ortiz (2018) critically evaluated whether *abnormal perception or thought content* is a risk factor, prodrome, or cause of dementia. Their paper focuses on psychotic symptoms in prodromal dementia, concluding that psychosis is more common than previously thought and has a negative impact on clinical course. Research is needed to improve early recognition and treatment. These contributions to the Special Issue provide strong evidence in support of the concept of MBI and provide a good framework to foster domain-specific research.

The final section of the Special Issue focuses more broadly on non-cognitive prodromes and clinical implications of MBI. Kiely *et al.* (2018) provided epidemiological data linking sensory loss (auditory/visual) to clinically relevant NPS in 1,393 older adults with and without cognitive impairment. Among individuals diagnosed with major neurocognitive disorders, any sensory loss was associated with 3+ times greater rates of NPS compared to normal sensory functioning. However, the authors found no evidence of an association between sensory loss and number of NPS in cognitively healthy adults. These findings have particular relevance to the dementia care setting, indicating that individuals with sensory loss are at increased risk of NPS. In a study comparing the diagnostic and predictive utility of various Parkinson's disease (PD) MCI criteria, McDermott *et al.* (2018) also explored the manifestation of NPS in PD. The authors found NPS to be more common in PD than in controls across all cognitive categories. The authors also suggest a neuropsychiatric prodrome to cognitive decline in PD, warranting further longitudinal studies with a rating scale designed specifically for prodromal PD patients, such as the MBI-C.

The last contribution to this Special Issue discusses the implications of the ISTAART-AA MBI criteria, and the MBI-C, for dementia clinical trials (Mortby *et al.*, 2018b). With the low success rate of dementia clinical trials, which have often been limited by poor recruitment and retention of early phase illness, the argument is made that patients with later life emergence of NPS/MBI represent a potentially enriched sample of prodromal dementia. The commentary explores the utility of inexpensive large scale screening for sustained later life emergent NPS as a way of detecting this cohort for biomarker screening, and/or clinical trial enrollment. This discussion highlights the importance of NPS as part of neurodegenerative disease, in advance of cognitive impairment, as opposed to a dementia or MCI-specific phenomenon, which is still often the perspective of clinicians and researchers.

This Special Issue provides a comprehensive overview of the current research agenda to validate the construct of MBI. Studies providing a better understanding of the role and relationship of MBI with pathophysiology are needed to improve early identification, develop interventions, facilitate clinical treatment, and reduce dementia risk. Questions requiring further exploration include the prognostic utility of specific MBI domains, the role of symptom severity, and the description of NPS as a consequence of neurodegenerative disease. This exciting research agenda will increase global awareness of MBI as a syndrome, which serves as a neuropsychiatric parallel to the MCI syndrome, and may be integral to a comprehensive approach to earlier dementia detection and intervention.

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