

Using Behavior to Catch Early Signs of Brain Degeneration

George J. Augustine

With the ever-increasing rates of neurodegenerative disorders worldwide—and the resulting increases in dementia burden—there is a need for better biomarkers to anticipate neurodegeneration early, before irreversible symptoms set in. Neurodegeneration in disorders such as Alzheimer’s disease causes thinning of numerous cortical areas, including the orbitofrontal cortex, medial frontal cortex, anterior cingulate cortex (ACC), and insula (1,2). However, the best way to measure cortical thickness in the living brain—magnetic resonance imaging (MRI)—is prohibitively expensive, making measurements of cortical structure impractical as a routine diagnostic biomarker for neurodegeneration. One potential alternative is to target the mild behavioral impairment (MBI) associated with the early stages of neurodegeneration (3). While there are numerous ways to assess MBI, one convenient assay is the Mild Behavioral Impairment Checklist (MBI-C). The MBI-C is a simple (34-question) self-administered test that evaluates changes occurring over 6 months in several behavioral domains: decreased motivation (apathy), emotional dysregulation (mood/anxiety), lack of impulse control, social inappropriateness, and abnormal beliefs or thought content (4). Previous work has established that the MBI-C can detect behavioral changes associated with neurodegeneration; indeed, the MBI-C has been used as an early-stage biomarker for dementia (5).

But how do MBI-C results compare with the gold standard, namely MRI-based measurements of brain structure? In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Leow *et al.* (6) address this question by examining the relationship between MBI-C scores and cortical thinning in a Southeast Asian cohort in Singapore. The authors found that MBI-C scores are associated with thinning in several cortical areas. In particular, cortical thinning was preferentially associated with high scores within the MBI-C abnormal belief domain. This domain assesses abnormal perception or thought content and is probed by questions such as “Has the person developed beliefs that they are in danger, or that others are planning to harm them or steal their belongings?” and “Does she/he have unrealistic beliefs about her/his power, wealth or skills?” It is therefore notable that thinning was most noticeable in cortical areas—including the posterior banks of the superior temporal sulcus, fusiform gyrus, superior temporal gyrus, and transverse temporal gyrus—that are involved in emotional regulation, belief formation, and cognitive control. This correlation suggests that MBI-C scores in the abnormal belief domain are a useful measure of thinning in such cortical areas.

Significant cortical thinning was observed only in the right hemisphere of the brain. This parallels the role of this hemisphere in belief evaluation and other processes that are affected in early-stage dementia (2,7). Several other independent lines of evidence implicate preferential disruption of the right hemisphere in dementia (8) and in aging (9). Thus, it is likely that cortical thinning in the right hemisphere is responsible for the observed elevation of MBI-C Belief scores.

Leow *et al.* (6) are not the first to establish a correlation between behavioral impairment and cortical thinning. Studies of other cohorts have shown that thinning of the orbitofrontal cortex, ACC, and insula is associated with poorer cognitive outcomes and dementia progression in MBI (1). Further studies have also associated cortical thinning with the neuropsychiatric symptoms of neurodegenerative diseases (2,10). Beyond confirming previous work, the value of the Leow *et al.* study comes in its use of a prodromal multiethnic Southeast Asian cohort, indicating that the MBI-C—particularly its abnormal belief domain—is useful as a biomarker for neurodegeneration in diverse populations. This lends support to the idea that the MBI-C could become a standard tool for early detection of MBI.

Like all clinical cohort studies, the Leow *et al.* (6) article has several limitations that the authors describe in earnest detail. In particular, the correlation between MBI-C abnormal belief scores and cortical thinning does not establish causality, although—as mentioned above—the fact that other studies have reported similar correlations strengthens the case that cortical thinning is indeed the cause of the observed MBI. A longitudinal experimental design, where subjects are examined over repeated time points, could bolster the argument by establishing another potential dimension of correlation. In addition, the use of self-reported MBI-C results may introduce bias; having close informants (such as a family member or caregiver) complete the MBI-C could provide a more objective assessment and strengthen reliability. It would also be useful to consider other behavioral measurements that could more objectively assess the 5 domains of MBI. For example, decreased physical activity could be used to reflect decreased motivation. Finally, it would also be valuable to have anatomical parameters beyond cortical thickness for assessing brain structural changes and their relationship to MBI.

In conclusion, the study by Leow *et al.* (6) is a valuable contribution to the field because it aligns with mounting evidence that behavioral changes can precede detectable neurodegeneration. It is the largest cohort to date showing a correlation between cortical thinning and MBI-C scores and further establishes the utility of the MBI-C in detecting the

SEE CORRESPONDING ARTICLE ON PAGE 70

early stages of Alzheimer's disease and other dementias. Future studies using additional multiethnic cohorts will strengthen the value of this approach, while longitudinal analyses of the temporal relationship between MBI and changes in brain structure will help strengthen our ability to catch—and eventually treat—the earliest stages of neurodegenerative disorders.

Acknowledgments and Disclosures

The author was supported by core funding provided by the Temasek Life Sciences Laboratory.

The author reports no biomedical financial interests or potential conflicts of interest.

Article Information

From Temasek Life Sciences Laboratory, Singapore.

Address correspondence to George J. Augustine, Ph.D., at george_augustine@tlsl.org.sg.

Received Nov 2, 2025; accepted Nov 3, 2025.

References

1. Gill S, Wang M, Mouches P, Rajashekar D, Sajobi T, MacMaster FP, *et al.* (2021): Neural correlates of the impulse dyscontrol domain of mild behavioral impairment. *Int J Geriatr Psychiatry* 36:1398–1406.
2. Donovan NJ, Wadsworth LP, Lorius N, Locascio JJ, Rentz DM, Johnson KA, *et al.* (2014): Regional cortical thinning predicts worsening apathy and hallucinations across the Alzheimer disease spectrum. *Am J Geriatr Psychiatry* 22:1168–1179.
3. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, *et al.* (2018): NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 14:535–562.
4. Ismail Z, Agüera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE, *et al.* (2017): NPS Professional Interest Area of the International Society to Advance Alzheimer's Research and Treatment (NPS-PIA of ISTAART). The Mild Behavioral Impairment Checklist (MBI-C): A rating scale for neuropsychiatric symptoms in pre-dementia populations. *J Alzheimers Dis* 56:929–938.
5. Leow Y, Soo SA, Kumar D, Zailan FZB, Sandhu GK, Vipin A, *et al.* (2024): Mild behavioral impairment and cerebrovascular profiles are associated with early cognitive impairment in a community-based Southeast Asian cohort. *J Alzheimers Dis* 97:1727–1735.
6. Leow YJ, Saffari SE, Vipin A, Tanoto P, Shaik Mohamed Salim RB, Qiu B, *et al.* (2026): Mild behavioral impairment and cortical thinning: Biomarkers of early neurodegeneration. *Biol Psychiatry Cogn Neurosci Neuroimaging* 11:70–79.
7. Gainotti G (2018): Anosognosia in degenerative brain diseases: The role of the right hemisphere and of its dominance for emotions. *Brain Cogn* 127:13–22.
8. Kim KW, Park S, Jo H, Cho SH, Kim SJ, Kim Y, *et al.* (2020): Identifying a subtype of Alzheimer's disease characterised by predominant right focal cortical atrophy. *Sci Rep* 10:7256.
9. Dolcos F, Rice HJ, Cabeza R (2002): Hemispheric asymmetry and aging: Right hemisphere decline or asymmetry reduction. *Neurosci Biobehav Rev* 26:819–825.
10. Ozzoude M, Varriano B, Beaton D, Ramirez J, Adamo S, Holmes MF, *et al.* (2023): White matter hyperintensities and smaller cortical thickness are associated with neuropsychiatric symptoms in neurodegenerative and cerebrovascular diseases. *Alzheimers Res Ther* 15:114.