Parsing the heterogeneity of mild cognitive impairment

Lumpers and splitters

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The study by Knopman et al.[1] in this issue of *Neurology*® examines how variations in the pattern and degree of mild cognitive deficits, common in older adults without dementia, predict the development of dementia. What the study reveals is not entirely novel and essentially confirms clinical intuition: individuals with broader and deeper cognitive impairments have the highest risk of future dementia. The study's main accomplishment, however, is the light it shines on what is obscured when a categorical construct such as mild cognitive impairment (MCI)[2] is applied to what is clearly a continuous process—the gradual progression of MCI to dementia and Alzheimer disease.

All clinical constructs, including MCI, have limitations that arise as a result of operationalizing the concept for broad use in clinical or research practice. The clinical concept of MCI was created to identify the subset of older persons with mild impairment who are likely to progress to dementia.[3] Cognitive decline is a continuum of gradual and progressive cognitive loss from normality to dementia. MCI is a categorical construct, in the middle of the continuum, defined by the presence of a number of dichotomies: measurable objective cognitive impairment, preserved activities of daily living, and the absence of dementia. Each of these dichotomies has been the source of controversy, in part because of the ambiguity at the threshold that determines their presence or absence, but also because the underlying process is continuous, making the dichotomies essentially arbitrary.

This study examines one aspect of these criteria—the definition of objective cognitive impairment—and how varying that definition changes the predictive abilities in forecasting an individual's likelihood of future dementia. MCI criteria define objective cognitive impairment using cutpoints below which cognitive performance is considered impaired, often 1.5 or 2 SD below the mean of a normative dataset; however, some studies use conceptual cutpoints rather than age-adjusted cutpoints.[4] In this study, the investigators defined low cognitive performance using 4 different cutpoints (0.5, 1, 1.5, and 2 SDs below the mean) for defining impairment in 4 cognitive domains (memory, executive, visuospatial, and language). Thus, individuals were classified both liberally (where more than 50% of the sample was considered deficient at a cutpoint of 0.5 SD below the norm) and conservatively (8%–9% had deficiencies at a cutpoint of 2 SDs).

More than 2,000 dementia-free individuals from 2 independent cohorts (Mayo Clinic Study of Aging and the Framingham Heart Study) were categorized as having cognitive impairment at their baseline evaluation. Participants were followed for an average of nearly 4 years, and more than 10% ultimately developed dementia. The study's primary result was that at any given cutpoint, the risk of developing dementia was highest (1) in those who had amnestic deficits compared with individuals who had nonamnestic deficits, and (2) in those who had impairments in multiple domains compared with those who had impairments in single domains.

The authors draw several conclusions from these data. A more granular appreciation of the cognitive profile of individuals with MCI can add relevant prognostic information that an overly simplistic interpretation of MCI can obscure. A single instrument to detect the presence of MCI is not enough to capture the true risk profile given that it is revealed through the use of multiple tests of different cognitive domains. Thus, by embracing the heterogeneity of an individual's presentation of cognitive changes within certain domains, we can better identify individuals who are more likely to decline.

These findings are conceptually logical and consistent with prior critiques of the MCI construct. The MCI label has been criticized for its ambiguity,[5] primarily at its edges (i.e., where normality ends and MCI begins, and where MCI ends and dementia begins). The findings reiterate that individuals with MCI progress to greater stages of severity at rates that are dependent on the level of cognitive impairment.[5] The data also suggest that MCI generally represents early-stage Alzheimer disease in those with amnestic multidomain presentations.[6]

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While a more refined appreciation of the breadth and depth of the cognitive impairment observed in an individual adds information to the risk profile, this approach remains inherently limited to incremental advances. This approach parses the continuous process of cognitive decline into ever smaller parts, and identifying subsets of MCI into those closer to or further from the dementia line fails to address the underlying process of change.

The etiology of MCI is heterogeneous because it often results from mixed pathologies.[7] Mixed diseases are inherently problematic for taxonomists because they confound our ability to create meaningful all inclusive but mutually exclusive disease categories that correspond to the underlying biology. Furthermore, mixed diseases only account for some of the causes of MCI while others remain elusive. Whether these issues are best solved with broader categories or smaller ones remains to be determined.

Taxonomy is an important aspect of neurology, as with all fields of medicine and many other areas of science. Disease classification allows public health planning and resource allocation, allows us to make prognoses and identify persons in need of particular interventions critical to patient care, and it helps us focus efforts on understanding the underlying biology of disease. However, wherever there are taxonomists, you will find lumpers and splitters. The opinion of Charles Darwin was that each was useful, as evidenced by a statement in a letter to his friend Joseph Hooker in 1857: "it is good to have hair-splitters and lumpers."[8]

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