Illuminating cognitive dedifferentiation at the end of life

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Terminal cognitive decline refers to the relatively precipitous and widespread drop in cognitive function that occurs in the period preceding death.[1] The concept was originally proposed and investigated by developmental psychologists who were interested in the lifelong trajectories of intellectual and other cognitive abilities.[1–3] Terminal decline change points (inflection points), where cognitive decline accelerates in relation to a future time point of death, have been confirmed among older cohorts free from dementia.[2,4–6] However, it is not clear whether the terminal cognitive decline is due to latent underlying AD or other disease pathology not sufficiently severe enough to cross the clinical threshold, or whether it is attributable to biological processes presumably related to impending mortality.

An important concept and hypothesis linked to terminal decline is the dedifferentiation of cognitive abilities at the end of life. This hypothesis posits that in the course of human aging, cognitive abilities that in the preterminal period (the period before the inflection point of cognitive decline) remain differentiated into discrete systems and domains, become in late life increasingly intercorrelated and dedifferentiated.[7] The hypothesis is not without controversy and over the years has generated a number of conflicting views and reports that reflect differing methodologic approaches and challenges.[8] The issue remains topical, insofar as it is important clinically and scientifically for the field to identify, understand, and treat cognitive decline linked to disease-based, neuropathologic processes (e.g., such as Alzheimer disease (AD), Parkinson disease, and frontotemporal lobar degeneration) as opposed to terminal cognitive decline associated with impending mortality.

In this issue of *Neurology*®, Wilson et al.[8] provide unique insights from their observations on subjects from the Religious Orders Study, a well-characterized cohort with exceptionally high follow-up and brain autopsy rates. The authors compared the rate of change in cognitive test performance during the preterminal and terminal decline periods, and examine its association with AD-related pathologic burden confirmed at autopsy. An innovative and elegant longitudinal statistical design, based on a Bayesian method, is employed wherein each participant's cognitive trajectory (over at least 7 annual assessments) is divided into preterminal and terminal stages using individual specific change points before death. The investigators simultaneously assessed changes in 4 cognitive outcomes (episodic memory, semantic memory, working memory, perceptual speed) and compared within-subject correlations in rates of change among these cognitive functions, before and after the change point. The change point model was originally proposed in the past decade to examine the inflection point in memory function before the diagnosis of AD.[9] The method has been applied to various conceptual models in a wide variety of areas, including noncognitive trajectories such as brain volume[10] and gait speed.[11] However, the use of the technique by Wilson and colleagues is particularly compelling in testing the dedifferentiation hypothesis, as it permits detailed longitudinal examination of cognitive change in multiple domains within individuals across the preterminal and terminal decline periods.

The authors found substantial evidence supporting the dedifferentiation hypothesis. They observe that decline in each cognitive domain began relatively gradually before accelerating rapidly about 2 to 3 years before death. For example, the rate of decline in episodic memory increased 15-fold between the preterminal and terminal periods. The authors also found that changes in cognitive abilities became increasingly intercorrelated during terminal decline before death, with intercorrelations between 0.83 and 0.89 in the terminal phase vs only 0.25–0.46 in the preterminal phase. Interestingly, AD-related pathology (i.e., plaque and tangle burden) was not associated with rates of terminal decline in the different cognitive domains, nor did it modify the correlations among those rates during the terminal period. These

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findings suggest that terminal dedifferentiation of cognitive abilities is not driven directly by pathologic processes related to AD, but rather that this phenomenon may involve novel biological mechanisms at the end of life.

In addition to its scientific importance to the cognitive aging and dementia literature, the article has interesting clinical implications. First, there is the potential clinical application of results obtained from a terminal decline or a change point approach. It would be very useful clinically if algorithms linked to the degree of accelerated cognitive decline could be developed that would allow prospective identification of individuals in the preterminal vs terminal period. Further studies are needed to make possible such translational findings. Second, study findings suggest that treatments that target AD pathologic processes should focus on earlier cognitive changes rather than later, as such processes appear more tightly linked to cognitive changes in the preterminal period than the terminal period.

Cognitive dedifferentiation at the end of life is thus an important research topic whose study deepens our understanding of both disease-based and normal biological aging. The study by Wilson et al. is a substantial addition to the field and makes a strong case in favor of the dedifferentiation hypothesis.

DISCLOSURE

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