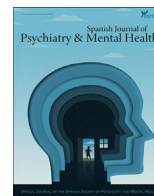




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From Cajal's Desk

### Cognitive performance as a health indicator: Lessons from the Spanish version of the mini-mental

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We have stated that cognitive performance may be an important health indicator, particularly in the elderly. In fact, this perspective has some foundations. My understanding of the relevance of the systematic cognitive assessment began during my residency training at the New York Hospital-Cornell Medical Center, Westchester Division (New York, NY, United States). This journal section, *From Cajal's desk*, provides an opportunity to express gratitude to Ramón y Cajal: I learned that my experimental doctoral thesis on central nervous system mechanisms, conducted “in the country of Cajal”, at the Zaragoza site of the *Consejo Superior de Investigaciones Científicas*, played a crucial role in my acceptance into that competitive residency program in 1973. At the time, Professor Paul R. McHugh—now *Doctor Honoris Causa* by the University of Zaragoza—was the Clinical Director and Director of Residency Education at NYH-WD. He was a firm advocate of cognitive function assessment.

Disenchanted with the American approach to psychiatry in the early 1960s, McHugh received neurological training and then sought psychiatric training under Sir Aubrey Lewis at the Maudsley Hospital and Institute of Psychiatry in London (United Kingdom). His “empirical psychiatry” approach—now commonly referred to as “evidence-based psychiatry”—stood in sharp contrast to the prevailing academic psychiatric paradigms in the United States. McHugh drew many talented American residents to his program, including Marshal F. Folstein, who, at the time, was Chief of the Geriatric Psychiatry wards when I arrived. Along with McHugh, Folstein developed a simple bedside cognitive assessment tool that we residents used systematically. This tool became known as the “Mini-Mental State Examination” (MMSE), which was first validated and published in 1975 in a seminal article.

The MMSE underwent further development at the Johns Hopkins Hospital and Medical School in Baltimore (United States). McHugh and his team were brought in to revitalize the stagnant Psychiatry Department after the Adolf Meyer era. Folstein led the newly established *General Hospital Psychiatry Division*. In 1976, I

joined them in the Johns Hopkins Hospital to pursue a fellowship in liaison psychiatry and engage in research. I was assigned as a consultant to the newly established Oncology Center and the Alzheimer's Clinic organized by Folstein—one of the first of its kind in the United States. Eventually, I was promoted to Attending Psychiatrist and Junior Professor in the Faculty.

Within this academic environment, we conducted the first studies utilizing the MMSE. Alongside my colleagues, we documented a significant prevalence of cognitive deficits among medical patients, often undetected—even by neurologists who later became recognized experts in dementia. Intrigued by the implications of these cognitive deficits, I found empirical support for the hypothesis that cognitive impairment in medical patients is associated with increased mortality. This observation laid the foundation for my position—later substantiated through further research—that cognitive function serves as a health indicator.

Returning to Zaragoza in 1977, I maintained my academic focus and established the core of a *Psychosomatic and Liaison Psychiatry Unit* at *Hospital Clínico Universitario*. Recognizing the need for adaptation due to low education levels and widespread illiteracy—especially among older individuals—I led the development of a Spanish adaptation of the MMSE, initially called the “*Mini Examen Cognoscitivo*,” (MEC) later revised to “*Examen Cognoscitivo Mini-Mental*” (ECMM). The first results were presented at a conference in Granada (Spain) in 1978, and the early publication appeared in 1979. Through a series of studies involving psychiatric, medical, and geriatric patients, we documented the test–retest reliability, procedural validity, and concurrent validity against established cognitive assessments, including the WAIS and Raven's Progressive Matrices. Furthermore, we demonstrated the ability of the test to distinguish patients with brain lesions and EEG abnormalities from those without these entities. Subsequent revalidation in a representative general population sample confirmed the tool reliability (documented in a test–retest conducted at a 2-month interval in the elderly own homes) and validity, with good sensitivity and specificity ratios, and a robust ROC curve (AUC, 0.920).<sup>1</sup>

Of note, our work highlighted the shortcomings of direct translations of the MMSE. For instance, a study conducted by neurologists in Pamplona (Spain) with the MMSE reported an unusually high prevalence of cognitive deficits, suggesting a high rate of false positives rather than genuine dementia cases, which underscored the

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2950–2853/© 2025 Sociedad Española de Psiquiatría y Salud Mental (SEPSM). Published by Elsevier España, S.L.U. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

need for culturally and linguistically tailored adaptations of cognitive assessments.

The impact of the MMSE has been profound. Carol Brayne from Cambridge University summarized its legacy in 1998, acknowledging its widespread use despite criticisms: “*The MMSE has been unexpectedly and wildly successful, whatever the reservations... It is not ideal for any specific purpose but provides a common ground which its users understand. . . .*” “*I expect the Folstein paper to have, at least, a further decade of heavy quotation*” Indeed, a Spanish neurologist Carnero-Pardo, in 2013, said that Folstein’s original article “*is probably the most frequently cited reference in health science literature . . . far ahead of such legendary articles in the history of medicine as Watson and Crick’s description of the structure of DNA or Prusiner’s article describing prions*”.

Following the Spanish validation, the ECMM became an essential tool in clinical, teaching and research contexts. It has been widely used not only in psychiatry, but also across multiple medical disciplines—particularly in primary care and geriatrics, where it is recommended by clinical practice guidelines. Nevertheless, I should mention that initially none of this spared me from my colleagues’ jokes. In retrospect, my internist friends who consulted on their patients would remember: ‘Now we have this guy coming from the States asking patients amusing psychiatric questions, like subtracting by threes.’

Our Department was commissioned by the Government of Aragón (Spain) to investigate psychiatric morbidity in the general population. I led the study on the elderly, employing the ECMM in a 2-phase screening process. The resulting “*Zaragoza Study*” on dementia and depression in the elderly, published in *Archives of General Psychiatry* in 1995, marked a significant milestone in our group triggering international collaborations.

These collaborations included the “*Liverpool-Zaragoza*” study series and participation in the *EURODEM consortium*—an EU-sponsored initiative advancing epidemiological research on dementia across Europe, and influencing policy making in different European countries. Our *ZARADEMP Project*, a 3-phase, 5-wave epidemiological study conducted among a representative sample population of individuals aged 55 and older ( $n = 4803$ ), contributed crucial data on the prevalence, incidence, lifetime risk, and risk factors for dementia, including Alzheimer’s disease.<sup>2</sup> This project also positioned us as one of the leading groups in several international associations. In particular, we were one of the founding groups of the *COSMIC Consortium*, which has harmonized data from cohort studies from 22 countries across the world to enhance the reliability of global estimates on cognitive aging and mild cognitive impairment (MCI), as well as their outcome. A number of new studies are now in different stages of development.

In 2007, we reported a surprising finding: contrary to expectations on an impending dementia epidemic, the adjusted global prevalence of dementia had not increased over a decade.<sup>3</sup> In fact, the prevalence of dementia among men aged 70–84 significantly declined. This result—first reported in the literature—has since been corroborated by subsequent studies. Under the initiative of Carol Brayne, we collected a total of 14 articles identified with similar findings and have reported the results in *The Lancet Neurology* and *Nature Reviews Neurology*. These findings have informed new hypotheses on environmental influences on dementia risk and public health prevention strategies.

Our work with the *ZARADEMP* cohort has also confirmed, in controlled studies, the utility of the ECMM in tracking cognitive

trajectories and their health implications. Longitudinal analyses revealed that cognitive impairment predicts dementia, with a clear gradient of risk corresponding to the degree of cognitive decline. Similarly, in a 17-year follow-up, cognitive impairment was associated with mortality risk. Additionally, this risk increased parallel to the degree of cognitive impairment. The PAF of mortality due to severe cognitive impairment was 3.49%.<sup>4</sup>

Moreover, in our study on MCI, we reported that the rate of progression to dementia in the *ZARADEMP* population cohort is substantially lower than the rates reported in the literature. This finding has sparked controversy in editorials published in *Acta Psychiatrica Scandinavica* and the *American Journal of Geriatric Psychiatry*. However, of greater interest in this essay is the observation that MCI was associated with increased mortality. Specifically, the mortality rate ratio was approximately twice as high in MCI cases diagnosed using DSM-5 criteria vs those diagnosed using Petersen’s criteria.”

A series of articles have also explored cognitive trajectories in healthy older adults using growth mixture models. Variability within each sex and differences between men and women in the identified trajectories and associated predictive factors suggest that gender-specific strategies may be needed to address cognitive aging. Consistent with previous reports, the latest article in the series found that cognitive decline trajectories are associated with increased mortality, with the risk of death following a gradient.<sup>5</sup> Notably, anxiety tripled the risk of death in participants in the low-and-declining cognitive trajectory.

In conclusion, our research underscores the enduring value of the Spanish version of the MMSE as both a clinical and epidemiological tool. Evidence from our studies supports the notion that cognitive function is not merely a reflection of neurological status but an important indicator of overall health and survival in the aging population.

## Conflicts of interest

None declared.

## Declaration of competing interest

None declared.

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