

Perspective

## Lucidity in dementia: A perspective from the NIA

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### Abstract

In this issue of *Alzheimer's & Dementia*, Mashour et al. propose the intriguing hypothesis that some manifestations of late-stage dementia are reversible, albeit transiently. Calling this phenomenon paradoxical lucidity, their paper follows a 2018 workshop sponsored by the National Institute on Aging that assessed the state of knowledge on lucidity in dementia and identified areas ripe for further study. The National Institute on Aging has since released two funding opportunity announcements (RFA-AG-20-016 and RFA-AG-20-017) to establish the building blocks of such a research program. The potential challenges of conducting such studies are matched by the potential opportunities to open a novel window onto our understanding of dementia. Initial findings from this research may eventually lead to studies that uncover novel mechanisms underlying cognitive decline, identify potential preventive or therapeutic approaches for individuals with dementia, offer more effective strategies for caregivers, and perhaps even expand our understanding of the nature of personhood and consciousness.

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In 1846, a young Hungarian obstetrician named Ignaz Semmelweis landed a job at the Vienna General Hospital, which, at the time, housed the largest maternity hospital in the world. The hospital had two clinics, with expecting mothers admitted on alternate days to either the one staffed by physicians and medical students or the other attended by midwives. When Semmelweis arrived, it was no secret that patients in the medical student-attended clinic were dying from puerperal fever, a rapidly progressive postpartum disease, at a rate several times higher than that of the midwife-run clinic. The medical establishment chalked the disparity up to factors such as imbalances in patients' body fluids and exposure to bad air, reflecting the prevailing medical theories of the day. Semmelweis, an adherent of the growing movement of science in medicine, sought out a more plausible explanation. After methodically eliminating every controllable variable, he concluded that the only difference between the two clinics was the medical students'

morning practice of conducting autopsies on recently deceased mothers before proceeding to their work on the maternity ward. He postulated that "cadaverous particles" riding on the students' hands somehow transmitted the fatal disease. He could not explain his hypothesis—acceptance of the microbial theory of infectious diseases was still decades away. Nevertheless, he instituted a regimen of postautopsy handwashing with a chlorine-containing solution, and immediately, deaths from puerperal fever in the first clinic plummeted. One might think that Semmelweis would have been immediately celebrated as a hero of medical science. However, his superiors scoffed at the prescription for handwashing—after all, the dominant medical theories of the time did not hold a suitable place for iatrogenesis. Eventually, he left Vienna and ultimately wound up in a mental asylum. He died shortly thereafter from pyemia, an overwhelming systemic infection that, ironically, resembles puerperal fever [1,2].

The story of Semmelweis is one of numerous examples from the chapters of medical history that illustrate how dominant paradigms unwittingly create barriers that hinder innovation. Of course, this is how the system is designed.

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Well-keeled science protects us from the volatility of unsubstantiated whims. However, while prevailing theories tend to do best at explaining averages, they can break down at the extremes. And if a theory cannot adequately explain the extremes, then either the extremes are an artifact or the theory needs a second look.

In this issue of *Alzheimer's & Dementia*, Mashour et al. [3] examine a clinical extreme to support the intriguing hypothesis that some manifestations of late-stage dementia are reversible, albeit transiently. According to a sparse literature, comprised mostly of case reports, individuals with longstanding noncommunicativeness due to dementia or other neurological or psychiatric conditions occasionally rekindle in a surprising display of meaningful speech, only to die a short while later. Mashour et al. call this phenomenon paradoxical lucidity because of the unexpected nature of these episodes. They discuss possible explanations for this phenomenon and suggest research avenues for further exploration. Their article follows a 2018 workshop sponsored by the National Institute on Aging to assess the nascent state of knowledge of lucidity in dementia and identify areas ripe for further study. Such studies could conceivably open a novel window of understanding onto the pathogenesis and progression of cognitive impairment, Alzheimer's disease, and related dementias. More proximally, this research could have an impact on the formal and informal care of individuals with dementia, as notions about personhood in the late stages of disease may be reconsidered.

Recently, the National Institute on Aging released a pair of funding opportunity announcements to support research on lucidity in dementia (<https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-20-016.html> and <https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-20-017.html>). These announcements outline an initial set of studies to establish the building blocks of a research program on this topic. Possible outcomes of supported studies might include evidence-based working definitions, development of assessment tools, actual audio and/or video recordings of lucid episodes, tools to quantify verbal output or other objective behavioral evidence of lucidity, and evidence to support further studies on decision-making in dementia. These foundational outcomes could lead to further studies that may eventually point to novel mechanisms underlying cognitive decline, identify potential preventive or therapeutic approaches for individuals with dementia, offer more effective strategies for caregivers, and perhaps even expand our understanding of the nature of personhood and consciousness.

But it won't be easy. A rigorous and systematic study of lucidity in dementia will be demanding for many reasons. A frequently cited challenge is the reported transience and infrequency of lucidity. There is a sense that lucid episodes occur so rarely and fleetingly that it would be difficult to conduct adequately powered studies without very large numbers of subjects, sufficient time, and the requisite funding for both. Of course, we don't know how often lucidity occurs, and determining more accurate incidence estimates

among individuals with dementia overall and in important subgroupings would, in itself, be an important scientific outcome of this research program. It is possible that lucidity happens more often than we think. Its transience, masking by antipsychotics or other medications, social desirability and confirmation biases, and the paucity of scientific reporting channels for most family members and other informal caregiver witnesses may all contribute to underreporting and underappreciation of lucid events.

Another set of challenges involves the lack of a precise definition and phenomenology. What exactly defines lucidity? What makes it paradoxical and not expected? To whom do these definitions apply? These are all crucial questions that will substantially influence the shape and scope of future research studies, and as accumulating data expand our understanding, the terminology will almost certainly change as well. Currently available evidence suggests that paradoxical lucidity occurs shortly before death, in the order of minutes to days, hence the term "terminal lucidity" [4,5]. This is understandable, as reports of lucidity are typically retrospective, and with the benefit of hindsight, cases can be associated temporally to death. However, as research expands into prospective studies, we may find that lucidity occurs over more points along the disease trajectory.

"Paradoxical" reflects an unexpectedness that distinguishes the phenomenon from the waxing and waning course of cognitive function that commonly attends earlier stages of dementia. This term also appropriately reflects our current rudimentary understanding of the phenomenon. When early astronomers measured the movements of heavenly bodies, they found that the planets appeared to advance, reverse course for a time, and then advance again. Entrenched in the geocentric model of planetary motion, they proposed an intricate series of orbits, orbits-upon-orbits, and other adjustments to explain their observations. With enough mental fortitude, the paradoxical movement of the planets could be explained (nearly), but it would take a rather large blackboard and a hefty amount of chalk. Eventually, the heliocentric model bloomed into existence, which, with further refinements, explained planetary motion with elegant simplicity. Paradoxical became logical.

National Institute on Aging's approved funding concept focuses on individuals with dementia. Established cognitive assessment tools and staging criteria make possible to identify this relatively well-defined and large population of potential subjects. Of course, available literature indicates that paradoxical lucidity is not limited to dementia and that individuals with a variety of neurological or psychiatric conditions may also have unexpectedly lucid episodes [5]. Perhaps lucidity is a specific manifestation of a more general, although still unexpected, burst of energy often observed in end-of-life settings that hospice nurses call the "end-of-life rally." As a starting point, however, dementia seems ripe for this initial foray, and whether lucidity in other conditions is associated with similar underlying mechanisms will be an intriguing question for future studies.

Beyond the challenges of definitions and recognition, there may likely be institutional barriers. Nursing home administrators and staff, families, and other caregivers may understandably object to recording devices planted in patients' rooms to capture that unpredictable moment when, or if, lucidity returns. Respecting institutional, cultural, and personal sensitivities, privacy concerns, and ethical boundaries will be imperative. However, it will be a surmountable challenge and a gratifying opportunity to find ways in which all involved win, especially the individual with dementia at the center of these studies.

Research resources, such as the National Institute on Aging's Alzheimer's Disease Research Centers, may offer rich sources of investigator expertise and access to study subjects. Crowdsourcing approaches may offer additional subjects not accessible through usual academic channels. Large cohort studies such as the National Health and Aging Trends Study (NHATS) and the Health and Retirement Study (HRS), or the Alzheimer's Clinical Trials Consortium, may offer avenues for ancillary projects to test assessment tools developed through initial studies.

We look forward to the science that will emerge from this new line of research. There are obviously many more questions than answers at this point, and it is hard to say what the

metaphorical road will look like, as we have hardly left our metaphorical driveway. However, as the history of science has shown, answers to vexing problems can often turn up in previously unappreciated places. Whether lucidity in dementia is one of those places will be determined in due time.

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