Alzheimer's & Dementia 15 (2019) 1107-1114

Theoretical Article

Paradoxical lucidity: A potential paradigm shift for the neurobiology and treatment of severe dementias

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Abstract Unexpected cognitive lucidity and communication in patients with severe dementias, especially around the time of death, have been observed and reported anecdotally. Here, we review what is known about this phenomenon, related phenomena that provide insight into potential mechanisms, ethical implications, and methodologic considerations for systematic investigation. We conclude that paradoxical lucidity, if systematically confirmed, challenges current assumptions and highlights the possibility of network-level return of cognitive function in cases of severe dementias, which can provide insight into both underlying neurobiology and future therapeutic possibilities.
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Keywords: Alzheimer's disease; Dementia; Lucidity; End-of-life care; Cognition; Consciousness; Recovery

1. Introduction

Anecdotes of unexpected or paradoxical mental lucidity in the days and weeks before death among people with longstanding dementia have been reported over the last two centuries, with sparse scientific investigation. For the purposes of this article, paradoxical lucidity (PL) refers to an episode of unexpected, spontaneous, meaningful, and relevant communication or connectedness in a patient who is assumed to have permanently lost the capacity for coherent verbal or behavioral interaction due to a progressive and pathophysiologic dementing process. Here, we focus on PL in the context of persons with dementia when coherent verbal or behavioral interaction capacity has been documented as being lost by observers (family members, caregivers, health professionals, and/or others). We include all progressive dementias in this consideration that have a presumed or confirmed neurodegenerative etiology. If this phenomenon of PL is systematically examined and confirmed in persons with dementia due to neurodegeneration, our hypothesis is that the current

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https://doi.org/10.1016/j.jalz.2019.04.002
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framework of dementia as an inexorable and irreversible process of structural neuropathology must be revised to include a reversible and functional aspect of pathophysiology, even at late stages. To explore this possibility, the National Institute on Aging convened a workshop in June 2018 to review evidence for and against the existence of PL and to obtain input on a research agenda. Investigators with expertise in PL, dementia, neurology, geriatrics, psychiatry, nursing, neurobiology, consciousness, ethics, linguistics, and clinical research methodology were represented at the workshop. Here, we present the current state of the evidence, review relevant research on the phenomenon of PL as well as its biological plausibility, draw connections across the evidence base to begin to formulate a mechanistic model, discuss associated ethical issues, and provide recommendations for a future research agenda. The ultimate implications of this line of investigation relate to a fundamental reconsideration of the neurobiology and care of patients with dementias.

2. What is known about PL

Cognitive fluctuations in patients with dementia have been observed and documented, but usually in patients with early or moderate stages of the disease [1]. Nahm et al. [2–4] have collected literature reports, and Batthyany [5] collected reports from a 12-month retrospective survey among physicians, nurses, and care providers, usually based on the time shortly before the death of patients. As these studies focused on the time around death, the phenomenon in this context is sometimes called terminal lucidity [2–4], but here, we will retain the designation of PL. Anecdotal reports of dramatic fluctuations of cognitive abilities in severe neurodegenerative diseases that were seemingly not related to dying can be found in nonacademic sources; a population-based study of lucid episodes in patients with severe dementia also contained no mention of episodes that appeared to be specifically related to the death of patients [6]. PL is also reported in patients with tumors, brain abscesses, strokes, and meningitis [3,4], as well as in comatose patients who awaken shortly before dying [7,8]. Our focus here, however, is on cases involving severe dementia and includes the following considerations related to timing and duration.

In a sample of 49 cases, many with dementia, 43% of PL episodes occurred within the last day of life, 41% within 2-7 days before death, and 10% within 8–30 days before death [2]. In the enhanced case collection by Nahm [3], PL in patients with dementia seems to take place predominantly within 1–2 days before death. This is consistent with Batthyany's study [9] of patients with dementia. Of 38 case descriptions, 44% occurred within 1 day before death, 31% within 2–3 days, and 6% within 4–7 days before death. Similarly, in a study of end-of-life experiences, seven out of ten caregivers in a nursing home reported that they had observed patients with dementia and confusion becoming lucid a few days before death during the past five years [10].

Of the 38 cases collected by Batthyany [5], 3% of the lucid episodes lasted less than 10 minutes, 16% lasted 10–30 minutes, 24% lasted 30–60 minutes, 29% lasted several hours, 11% lasted one day, and 5% lasted several days. Nevertheless, episodes of PL may also be brief, lasting only a few seconds, and the patients may only speak a few words that express something meaningful of relevance to a given situation. Hence, PL displays a considerable range of degree and variety. Lucid episodes that occur shortly before death may be accompanied by so-called deathbed visions, for example, visions of deceased loved ones [11].

There is a lack of systematic studies to assess the neurologic underpinnings as well as the epidemiology and phenomenological characteristics of lucid intervals among patients with severe dementia [12]. Similarly, although instruments to assess fluctuations of cognitive abilities of patients with dementia exist [13], a specific scale to describe the extent and qualitative aspects of lucid episodes occurring late in disease progression is not yet available.

3. Related phenomena

There are numerous phenomena related to PL in dementia that have been more extensively investigated, might provide mechanistic insight, and might argue for biological plausibility. The near-death experience (NDE) and unexpected arousal phenomena share the ostensibly paradoxical nature of PL but often have systems neuroscience explanations. In this section, we will consider NDEs and other phenomena of unexpected behavioral recovery or experience.

NDEs have been reported across cultures since antiquity and are arguably the phenomena most closely aligned with PL in dementia, especially when the latter occurs just before death. NDEs represent phenomenologically rich experiences in the setting of clinical death or a hypofunctioning brain [14–16]. Similar to PL in dementia, NDEs were primarily reported anecdotally, retrospectively, or in case studies until the early 2000s. In 2001, two prospective epidemiological studies in cohorts of patients who had cardiac arrest revealed that the incidence of NDEs in this population could be as high as 18% [17,18], which is substantially more common than that might have been predicted from case reports alone. There are a number of general hypotheses regarding physiologically based etiologies of NDEs, including a rapid eye movement sleep-like state [19] or endogenous release of hallucinogen [20].

It has been reported that dying patients in the critical care or operative setting can exhibit a surge of electrical activity in frontal montage electroencephalography [21–23]. However, the relevance of this electrical surge to the phenomenology of the NDE is unclear because such electrical surges could reflect nothing more than a nonspecific discharge attributable to the uncoordinated

activity of neuronal firing in an excitotoxic cascade associated with hypoxia and loss of membrane integrity. Experiments in a rodent model of both cardiac and respiratory arrest replicated the frontal surge of electrical activity but further demonstrated increased functional and directional connectivity between frontal and posterior cortices that were similar to neural correlates of consciousness identified in humans [24]. Follow-up studies in rodents have confirmed this surge of large-scale cortical communication after cardiac arrest and have detailed associated neurochemical surges [25]. The progression of NDE investigation from anecdote to case report to epidemiology to mechanistic investigation could be informative for future research programs of PL in dementia.

There are other forms of paradoxical improvements in cognitive function or arousal of possible relevance to PL. For example, the sleep-promoting drug zolpidem has been shown to enhance arousal and behavioral recovery in patients in a vegetative state [26]. Zolpidem appears to cause what has been referred to as paradoxical metabolic and vascular changes [27,28]. However, such changes have been explained in the context of a mesocircuit model of disordered consciousness [29]. Similarly, children with autism have been found to show signs of recovery across a number of domains in the setting of fever [30]. These two situations (zolpidem in vegetative states and fever in autism) share the common feature of a disordered neural network that recovers function after a perturbation that would typically have a depressive or disorganizing effect in the normal brain.

There has been recent work in anesthetic-induced unconsciousness reporting a phenomenon that has been referred to as paradoxical emergence. In animals anesthetized with isoflurane, the addition of the intravenous anesthetic ketamine induces a deeper state of unconsciousness (as indicated by the appearance of burst suppression) [31]. However, despite the deeper state of anesthesia, the animals treated with ketamine recover from unconsciousness 44% faster than controls. This ostensible paradox, that is, an intervention that more profoundly disables the brain but allows it to recover function more quickly, was associated with enhanced cholinergic tone in the prefrontal cortex. A follow-up study demonstrated that agonizing acetylcholine receptors in the prefrontal cortex could actually reverse the anesthetized state despite the ongoing administration of inhaled general anesthetics [32]. This return of function in the setting of clinical levels of general anesthetic in the brain has also been explained through a mesocircuit model, prominently involving the cholinergic system of the basal forebrain [33].

It is also important to note that there is evidence for preserved consciousness and selfhood in the setting of ostensibly devastating structural brain damage. For example, patients with a diagnosis of vegetative state exhibit such covert consciousness, losing the ability to interact behaviorally with the world but able to demonstrate volition through brain activity, which is identified through functional magnetic imaging [34]. It is thus conceivable that patients with dementia could, in some cases, have a preserved self with the inability to engage behaviorally except in sporadic cases such as PL.

In summary, there are phenomena that, similar to PL in dementia, represent an unexpected or ostensibly paradoxical recovery of neural function with a systems neuroscience explanation. In the next section, we speculate as to how the neurobiology of these related phenomena, which have been studied more extensively, might inform the mechanistic understanding of PL in severe dementia.

4. Possible mechanisms of PL

Several forms of dementia, including Alzheimer's dementia, are largely associated with irreversible degeneration of the cerebral cortex and the hippocampus, resulting in confusion, disorientation, and memory loss, among other symptoms [35,36]. Because the episodes of PL occur rather suddenly, it is unlikely that regeneration of neurons can account for them. Such fluctuations may reflect complex adjustments in signaling cascades, synaptic modifications, neuronal network interactions, and, perhaps, temporary reversal of, or compensation for, chronic functional inhibition due to neurotoxic proteins [37]. We acknowledge that there are different modes of cognitive fluctuation in varying types of dementia [38,39], such as dementia with Lewy bodies. As noted in the Introduction, our focus is on the dramatic behavioral recovery at the time when the functional consequences of the neurodegeneration are thought to be irreversible, although a more comprehensive understanding of mechanisms of cognitive fluctuation across the full disease course for a range of dementias is lacking.

There have been no neuroscientific studies of PL, and thus, any mechanistic framework must be considered speculative. However, the related phenomena described previously speak to the biological possibility of PL and provide some insight into a potential mechanism. Because episodes of PL often occur just before death, the emerging neurobiological data related to NDEs are of relevance. As noted, surges of neurophysiological activity have been observed in humans just before death in the critical or operative care setting [21–23] and in experimental rodent models after cardiac or respiratory arrest [24]. It is thus conceivable that some patients with severe dementia might also experience a surge of neurophysiological activity before death, which is manifested as a lucid episode. Furthermore, extrapolating from studies of rats assessing neurochemistry after two minutes of asphyxia [25], it is possible that as oxygen and glucose levels fall or fluctuate, there is a surge of neurotransmitter levels that results in transient or metastable activation of the brain. However, such surges of electrical activity or neurotransmitter release do not explain how there can be enhanced synchronization or communication across the brain, which has been observed in dying rats and

which could possibly account for a spontaneous recovery of cogent behavior in a patient with severe dementia. A network-level explanation is likely required.

The dynamics of complex networks are of relevance to neural function and have long been studied in the field of physics. There are precedents for the spontaneous recovery of nonbiological networks after periods of inactivity or damage [40]. In fact, network concepts related to "amplitude death" and "oscillation death" might be applicable to the observed surge in neurophysiological coherence just before functional network breakdown in the brain around the time of death. Using a Stuart-Landau model, one investigation described the dynamics of how such oscillations can spontaneously "revive," [41] while another study described how the revival of such oscillations can be accompanied by rhythmicity and dynamic activity across the network [42]. These concepts have also been instantiated in neuronal models, with the conclusion that at a certain point of neuronal inhibition in a sparsely connected network, there is a counterintuitive "rebirth" of neuronal activity [43] that is manifested across the network. Furthermore, conditions for rapid and nonlinear synchronization (sometimes referred to as "explosive synchronization") occur in association with arousal when brain network hubs are suppressed [44], as in dementia [45].

Thus, although the mechanism of PL is unknown, there is evidence that the dying or hypoxic brain can generate neurochemical and neuroelectrical surges that might be associated with the network dynamics of complex systems and that might generate spontaneous network integration manifesting as lucid behavior. We emphasize that this is speculative, but computational modeling studies of large-scale brain networks, which have been applied to Alzheimer's disease, could be investigated to establish foundational credibility for such network phenomena in those with severe dementia. It must also be noted that there may not be a unique mechanism for PL that is restricted to the days before death but rather a mechanism that is common to cognitive fluctuations in less severe stages of the disease [12,13]. Furthermore, changes in systemic factors, rather than intrinsic neural dynamics, might drive the causal mechanisms responsible for lucid episodes. For example, one case report of a patient with Parkinson's disease dementia was able to correlate cognitive fluctuations with paroxysmal episodes of hypotension [46]. Thus, systemic physiologic factors must also be considered in the mechanism of PL.

5. Ethical considerations

In addition to its important neurobiological implications, PL has important ethical implications. Persons with severe dementia are vulnerable, a term that describes a state of being absolutely or relatively incapable of protecting one's rights and interests. One cause of vulnerability is the lack of adequate decisional capacity. Impairments in expressive language may hinder the person's ability to state a choice, and impairments in memory and executive function may cause inadequate understanding or appreciation [47]. As a result, the person may be unable to provide an informed consent to participate in a research study related to PL. Another cause of vulnerability is residence in a long-term-care facility. The person is, in a sense, confined and so unduly influenced by the will of those who run the institution. Substantial ethics scholarship has worked out means to address such causes of vulnerability [40,48]. They include thresholds of permissible research risk called minimal risk, standards for proxy informed consent, and processes for the review and approval of research that involves persons who live or work in long-term-care facilities. Scientists and institutional review boards can also draw on prior studies of persons with severe dementia as precedents upon which they can assess the risks and benefits of studies focused on PL, including neuroimaging in persons with severe dementia near the end of life [49] or testing of pharmaceuticals to modify behavior [50,51].

Research and clinical translation related to PL should draw on an ethical framework. Much of the ethics of care for a person with severe dementia is captured in a framework that recognizes the need to respect the person's "then" and "now" selves [52]. The "then self" describes the values and preferences the person had before dementia or in the early stages of the disease. Some persons record these preferences in documents such as living wills. The "now self" describes the person with more advanced dementia who has distinctly different values and preferences or an inability to express them than when they did not have disabling cognitive impairments. PL arguably closes this tension. An aspect of the "then self" is being presented by the "now self." Future investigators will have to better understand how the observation of PL affects the social and emotional reactions of people who care for a person with dementia and, as a result, the ways in which they care for the person. As we gain insight into the pharmacology and neurobiology of PL, well-intentioned families, researchers, and clinicians eager to bring out the "then self" may experience a zeal to try out interventions to foster the frequency and intensity of its occurrence. This attitude could distort expectations of benefit to a degree that they misunderstand or fail to appreciate the intervention's burdens, risks, and uncertainties.

6. Developing a research program

The current state of understanding the phenomenon of PL is limited to anecdote and case study and is subject to selection bias and recall bias. For PL to represent a critical counter-instance that challenges current paradigms of dementia, systematic research must be conducted. To date, there are few studies of PL or related forms of lucidity [1,6], and there are limitations to the current literature. Validation of family and staff experiences of lucidity when it occurs is a desirable goal of practice, but there is a need to clearly define the phenomenon of PL to distinguish between what family and staff may refer to as a "good day" due to dramatically and unexpectedly improved

cognition versus a "good day" due to improved mood and behavior [53–55]. Similarly, there is a need to distinguish between lucidity and cognitive fluctuations associated with improved attention and alertness that may accompany certain types of dementia (e.g., Lewy body dementia) [12] or delirium resolution [56], but that do not necessarily reflect unexpected levels of cognitive functioning constituting a challenge to current conceptions of dementia.

Given the paucity of literature on PL in dementia, its systematic study poses a number of challenges and opportunities around the use of quantitative and qualitative methods that can describe the phenomenon and its neurobiology, identify potential research participants and settings, and develop valid instruments and technology for data capture.

6.1. Methods for characterizing the phenomenon

Before PL in dementia can be measured or evaluated, it is essential to define what it is to be measured. It is also important to consider what measurement strategies might be appropriate for defining what is currently known as a poorly characterized phenomenon. Two distinct but related approaches are relevant to the measurement of PL in dementia: the clinimetric and the psychometric approaches [50,57]. Clinimetrics is the science of measuring clinical phenomena using expert judgment for the construction of a short and useful clinical index (a heterogeneous set of indicators) that carries face validity. An example of this approach is the development of the Apgar score for assessing neonates. The clinimetric approach, while less familiar to investigators, can advance a field, especially during early stages of measurement development. Psychometric measurement development is the more traditional approach and involves statistical methods (i.e., factor analysis, latent class analysis) that are guided by theory and clinical insight. These measurements are rigorously defined, designed, and used to develop evidence of the construct validity of the theoretical concept.

In addition to the measurement strategy used, several qualitative research methods may be of use in describing PL in dementia itself as well as how this phenomenon is experienced by patients, family, and clinicians. The Delphi method offers a systematic means of determining expert consensus on a phenomenon for which there are not much data available and/or which does not lend itself to experimental methods [58]. Potential uses of the Delphi method to explore PL in dementia include (1) defining it as a foundational concept, for example, how should we define PL? (2) making estimations given incomplete evidence, for example, what is the likely global prevalence? (3) making predictions, for example, what increases an individual's chance of experiencing PL in dementia? and (4) determining collective values, for example, what aspects of PL in dementia should be prioritized for study? A strength of this method is that experts can draw on available evidence as well as their professional and personal experience to contribute to a shared definition [58].

6.2. Methods for explaining the phenomenon

An incompletely characterized phenomenon such as PL requires qualitative and quantitative exploration. Beyond characterizing the lucidity experience and the scope of its expression, a research agenda should also include (1) establishing prevalence estimates; (2) identifying settings and sources of information; (3) identifying methods for combining observational data with those from imaging, pathology, and neurobiology; (4) determining optimal methods for end-user involvement in investigations; and (5) using appropriate methods for data capture. As most cases have been reported at the end of life, long-term-care facilities are a logical setting for its study [4]. Research to establish prevalence might begin with staff estimates based on a predetermined sampling frame of nursing homes, hospices (facility-based and in-home), and "hospital at home" programs [59]. In the United States, for example, there are approximately 15,640 nursing homes that care for 1.4 million people, 65% of whom have dementia [60]. In addition, 70% of people with dementia die in these nursing homes [61]. Consistent assignment of nursing home staff is a best practice in higher quality settings because it gives staff the opportunity to become familiar with residents over an extended period. Thus, instances of lucidity might be more readily observed in these settings that follow this practice [62,63].

Another potential opportunity for the study of PL in dementia is to link research questions to networks for the study of neurodegenerative diseases such as the 27 National Institute on Aging–funded Alzheimer's Disease Centers [64] or the German Center for Neurodegenerative Diseases [65]. These interconnected centers have exponentially increased our understanding of neurodegenerative diseases by systematically following up well-characterized cohorts of individuals living with dementia. They are rich repositories of longitudinal data (clinical and biomarker) that could be combined with observational data and probed for potential causal mechanisms.

6.3. Methods for capturing data

Technology can be used to support longitudinal monitoring, with the potential for capturing and analyzing episodes. Both audio and video recording technology can be used to create an objective record of these events and would complement qualitative methods. Because most of these rare episodes are expected to occur toward the end of life, focusing on capturing data in long-term-care facilities is likely to be most productive. However, using audio and video recording technology in long-term-care facilities presents several technological and logistical challenges.

Technological challenges include selecting and positioning equipment to maximize data quality and minimize intrusiveness on the individual being monitored, for example, caregivers, roommates, staff, and visitors. Socially assistive robotic devices have been investigated for use across a range of dementia severity levels in homes, long-term-care facilities, and day care facilities [66–68]. These devices could be

repurposed to serve as passive recorders of ambient sound and video in addition to their intended therapeutic purpose. Given that monitoring for lucidity events potentially takes a long time, automatic speech recognition and audio and video event detection should be explored for the purposes of indexing and retrieval of information from recorded data. The emphasis in evaluating indexing systems should be on maximizing their sensitivity given the expected low frequency of episodes.

7. Next steps for research and policy

The next steps for systematically characterizing PL could start with funder support for the development of surveillance technologies as described previously. Funders can also facilitate large-scale observational data collection to standardize reporting of suspected PL occurrence to advance description and definition through a newly created registry and/or existing research networks.

The Alzheimer's Disease Centers [58], Alzheimer's Disease Neuroimaging Initiative [69], Brain Health Registry (https://www.brainhealthregistry.org/), and other large comprehensive data-collection efforts in dementia could add PL surveillance modules. Identification of causal, permissive, and/or inhibitory mechanisms would greatly benefit from the longitudinal clinical, genetic, and biomarker data available through these sources. Measures of cognitive fluctuation [17] could be included in ongoing longitudinal studies, helping to establish whether the frequency or quality of prior cognitive fluctuations relates in any way to PL. Such psychometric measures can also serve as the basis for further scale development to enable systematic data collection about PL from providers and family. Collection of dementia-relevant and potentially PL-relevant data, for example, on cardiovascular instability associated with cognitive fluctuation [46], would expand understanding of the phenomenon while also adding to the knowledge about clinical dementia syndromes. As noted previously, computational modeling studies, particularly informed by wider collection of both structural and functional neuroimaging data, could advance understanding of the phenomenon.

Next steps also include leveraging citizen science to encourage individuals to create advance care instructions regarding PL surveillance. A "lucidity watch" may be stipulated in advance care planning documents, for example, as individuals may want to capture and optimize the potential for a meaningful end-of-life event with the potential to connect with the possibility of a premorbid interaction with loved ones. Patient advocacy organizations as well as funders could inform these strategies.

Next steps can also extend to examining guidelines for end-of-life care. Management of pain and agitation at the end of life would require reconsideration, with the potential for modified metrics of care quality, should links between PL and specific clinical and pharmacologic interventions be identified.

8. Conclusion

Unexpected episodes of lucidity occur in patients with dementia for whom the observed loss of coherent communication capacity and associated behavioral sequelae are considered irreversible. If systematically verified, the neurobiological implications are that the brain—even in the setting of severe dementia—is capable of accessing functional networks to generate meaningful communication and interaction with the world. This would motivate reconsideration of current paradigms of dementia, with new avenues in the systems neuroscience approach to therapeutic intervention. We have provided examples supporting the biological possibility of paradoxical manifestations of lucidity as well as systematic and ethical approaches to future studies. Dementia creates a profound burden for patients, caregivers, clinicians, and society. Further investigation of the mechanisms underlying PL is warranted given the potential for unique insights into the nature of neurodegenerative diseases and the potential for mechanistic explanations that could lead to novel interventions.

Acknowledgments

The authors thank Basil A. Eldadah, MD, PhD, as well as his team members from the National Institute on Aging for catalyzing and supporting discussions related to lucidity in dementia.

RESEARCH IN CONTEXT

1. Systematic review: A multidisciplinary panel of experts reviewed case reports and scientific studies related to unexpected or paradoxical cognitive lucidity in patients with severe dementia.
2. Interpretation: Paradoxical lucidity appears to occur, despite what appear to be irreversible functional limitations, and might be explained by systems neuroscience and network science.
3. Future directions: Paradoxical lucidity challenges certain conceptions of severe dementia; the incidence, mechanism, and ethical implications of paradoxical lucidity warrant further study.

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