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Toward harmonization of strategies for investigating lucidity in AD/ADRD: a preliminary research framework

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Abstract

Episodes of lucidity (EL) in Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD), have garnered increasing attention as an important area of research. Efforts to study lucidity suffer from a lack of clear definitional criteria, inconsistent conceptualization and diverse approaches to operationalizing features of these events. To advance systematic investigation of EL in AD/ADRD, there is a need for clarity and precision in labeling event attributes, markers, and specific measurement strategies that enable operational harmonization across distinct approaches to investigating the relatively broad and nascent phenomenon. To that end, we propose a preliminary research framework to guide harmonization of approaches to investigating EL in AD/ADRD. Our goal is to provide an initial schematic that encourages uniform labeling of operational decisions about EL.

There is a vast literature that describes the irreversible downward trajectory in cognitive abilities that people living with AD and related dementias (AD/ADRD) experience. Included in the literature are anecdotal reports of unexpected and transient returns of lost abilities [1]. These episodes of lucidity (EL), referred to as paradoxical lucidity when referring to people with advanced neurodegenerative disease with deficits assumed to be permanent,

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have not been studied systematically, and may require a paradigm shift in our historical understanding of the natural course of AD/ADRD. We believe a turning point in thinking occurred with the 2017 Lancet Commission on Dementia Prevention, Intervention and Care Report [2]. This Report and other publications indicate a growing willingness to consider novel explanations to persistent and intractable challenges in understanding AD/ADRD [3, 4]. With that context, the broader phenomenon of lucidity represents a unique opportunity to expand our knowledge of neurobiology and to challenge the presumed irreversibility of cognitive losses that have characterized our understanding of AD/ADRD [1, 5].

Episodes of lucidity have been commonly reported near end of life, leading to an active topic of debate regarding the degree of distinction from and potential overlap with a related clinical phenomenon, terminal lucidity [6–8]. More broadly, EL are suggested to constitute the broader phenomenon within which more specific types of lucidity, such as paradoxical and terminal lucidity, occur. Evidence for EL is largely limited to case studies and retrospective reports, but new evidence is expected to result from a series of grants awarded by the National Institute on Aging (NIA). Together, the funded studies aim to establish foundational scientific knowledge for future research on lucidity in AD/ADRD [9]. As a relatively new area of scientific inquiry, these studies are—appropriately—using varied conceptual and operational approaches for understanding the phenomenon of lucidity. As others have noted, definitional (and thus conceptual) clarity of phenomena is necessary for operationalizing those variables in clinical research [5]. Simultaneously, progress in conceptualizing EL in AD/ADRD must rely significantly on emergent data, and thus operationalization.

In an attempt to resolve this inherent tension and to move the science of lucidity in AD/ADRD forward, we introduce guiding questions to stimulate discussion regarding conceptual and operational considerations in the investigation of lucidity and propose a preliminary research schematic that builds on the provisional [1] and refined [5] definitions of EL put forth by investigators. Distinct from a theoretical framework which is designed to define or explain lucidity, we propose a “research framework,” which serves to facilitate uniform labeling for operationalization of attributes, markers, and/or measurement strategies used to detect or characterize EL. We begin with background on the call for a new line of research on EL. We then present considerations for operationalizing the phenomenon of lucidity across a series of guiding questions which illuminate implications for how various attributes of EL (such as meaningfulness and connectedness) and markers (directly observable indicators) are considered, measured, and labeled [5]. A broad goal of the proposed preliminary framework is to make what is implicit to investigation of EL explicit, thus equipping the field for more rapid advancement in both depth and precision of conceptual and operational understandings.

Background

The NIA sponsored a workshop in 2018 where experts reviewed extant literature on lucidity in AD/ADRD, made recommendations for future research, and ultimately introduced a preliminary definition for guiding early research [1]. The 2019 definition provisionally offered by Mashour and colleagues and in the funding announcement describes *paradoxical*

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lucidity as 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 pathophysiological dementing process” [1]. The NIA later published a funding opportunity on “unexpected” episodes of lucidity, which acknowledged the provisional nature of this definition, stating “current evidence does not permit an accurate definition,” and prioritized progress toward conceptual and operational definitions [10]. Scientific papers that have followed exemplify the challenges in defining and conceptualizing the phenomenon of paradoxical lucidity and lucidity more broadly. A recent concept analysis drawing on published literature evaluated key attributes of lucidity and suggested they include (a) presence of advanced neurodegenerative disease, (b) cognitive clarity and return of memories inconsistent with the individual’s resting state, (c) ability to share insights with others in intelligible ways; and (d) presence of meta-awareness—defined as insight into one’s own condition during the lucid episode [11]. Other commentaries have cautioned that the use of definitions not informed by empirical data may prematurely limit the ability of investigators to capture the phenomenon of EL in the most valid and reliable manner [12]. A critique of the 2019 provisional definition for paradoxical lucidity considered various interpretations for concepts within the definition and outlined an approach to specifying previously undefined parameters for interpreting concepts within the definition [5]. These include specifications for who can reasonably display paradoxical lucidity, and the meaning of spontaneity, meaningfulness, communication, and connectedness. They conclude by suggesting an analytic process of questioning implications of definitional parameters for concepts to inform the design of future studies. They also highlight the need for further debate regarding provisional definitions and concepts therein to strengthen the quality of rapidly evolving science in this area [5].

Concept advancement

Because data on EL are very limited and attributes included in the provisional definition for paradoxical lucidity, such as meaningfulness and connection, are not well developed, it is critical at this juncture in scientific inquiry to raise questions about what they mean and how they are measured. At this early stage, potential refinements to provisional definitions have appropriately included conceptual reasoning around potential attributes and markers of lucidity, but many of them remain abstract because they have not been examined in the context of EL [5–7]. As conceptual terminology often varies across disciplines contributing to AD/ADRD science and the study of lucidity, we provide our working definitions in Table 1 (column 2).

We applied principles used in concept advancement to derive guiding questions and facilitate development of a sufficiently unambiguous yet flexible research framework [13]. Concept advancement uses principles from conceptual reasoning to design and guide strategic refinement of concepts through an iterative, progressive process that evolves with integration of new data and subsequent concept-focused assessments. Distinct from concept analysis, concept advancement does not focus on the current state of understanding of a concept, but rather on incremental gains in specifying units of conceptual meaning, such as attributes that enhance the quality, precision, and coherence of research in an area that are then used

to further evaluate gaps in understanding [14]. The extant literature on EL in AD/ADRD is currently inadequate to support a traditional concept advancement process. The principles of concept advancement, however, are well suited for identifying gaps in understanding and/or reasoning around the phenomenon of EL through the development of guiding questions [13, 15]. Guiding questions address the study of EL broadly, and serve to stimulate debate regarding conceptual and operational understandings of EL with implications for approaches to inquiry. Questions are not designed to advance a uniform argument or definitional standard; however, they may support hypothesis development. A summary of guiding questions, the considerations they raise, and examples of testable hypotheses are in Table 2.

Guiding Question 1: Do episodes of lucidity exist along a continuum that extends throughout the disease trajectory?

Inquiries about EL that are restricted to “remarkable” and “spontaneous” events may prematurely narrow boundaries of what is and what is not EL. First, attention to EL in narrow contexts may also be subject to informant and/or expectancy biases, wherein an informant’s views regarding what is or is not remarkable influences their interpretation of observed expressions in the person with AD/ADRD. To that end, it is possible that the emphasis on studying paradoxical EL in the setting of advanced AD/ADRD—and consequentially predominantly near end of life wherein events are largely considered “remarkable” and “implausible”—has constrained opportunities to detect potential variability in the presentation of EL in earlier stages of AD/ADRD.

Second, current conceptualizations of EL are largely constructed around an assumption of the discontinuous emergence of EL, where events are perceived to have an abrupt presentation, and thus, denoted by attributes of spontaneity and unexpectedness. Again, spontaneity may be largely influenced by how the events are experienced or interpreted by informants [5] whose own knowledge/preconceptions about the degree of cognitive loss and/or irretrievability of certain abilities may shape their interpretation of what behaviors or communication are unexpected or unpredictable. In a sense, this conceptualization glamorizes EL as remarkable and unique.

For paradoxical lucidity in particular, as currently defined, episodes may be relatively rare, remarkable, and spontaneous. However, it is plausible that even these episodes exist along a continuum of lucidity that extends throughout the disease trajectory, but simply has not been systematically characterized or observed. As preliminary definitions focus on events that are “paradoxical” in nature, it may be argued that inquiry that includes earlier stages of disease is beyond the scope of investigation. We would suggest that at this stage of conceptualization it is worth considering whether such narrow boundaries are premature or should be revisited following emergent data. This is particularly relevant in the context of a set of conditions for which pathophysiologic processes are active decades prior to clinical symptoms, as is the case in AD/ADRD. Identifying presence of prodromal stages that precipitate clinical AD/ADRD required observing changes beyond the timeframe of active impairment [16]. It is reasonable to consider that these processes may intersect with or activate pathways that promote EL. It is also plausible that EL take place in moderate disease stages that could also

be interpreted as “remarkable” or substantially different from an individual’s current/typical state. Conversely, as suggested by Mashour and colleagues, drivers of routine cognitive fluctuation in mild to moderate disease may evolve into drivers of paradoxical lucidity [1].

It is also plausible that changes in abilities or expression that accompany various presentations of lucidity may have distinct and/or shared underlying mechanisms. These may be precipitated by multiple determinants that are environmental (i.e. familiar surroundings), social (i.e. personally meaningful interactions), and/or neurobiological in nature (i.e. continuous/discontinuous synchronization) [1, 17]. Specific mechanisms may be variably accessible or “active” across different AD/ADRD etiologies and at different stages in the disease process. Similarly, some neurobiological mechanisms could be shared with events described as terminal lucidity, which some hypothesize is a specific type of paradoxical lucidity or may be an inter-related but distinct phenomenon [6–8]. It is equally plausible that underlying mechanisms are more active at other disease stages and thus not considered as “remarkable”. In light of these possibilities, expanding our perspectives of inquiry to accommodate degrees of impairment outside of the setting of advanced disease may be particularly useful for clarifying boundaries around various types of lucidity and their distinct and/or shared determinants. Expanded inquiry may also be broadly useful in clarifying underlying mechanisms that facilitate expressiveness more broadly—and potentially access to retained abilities— throughout the course of AD/ADRD.

Guiding Question 2: Are episodes of lucidity situated within individually defined parameters?

EL are generally described as meaningful by virtue of the considerable degree of change from routine abilities at an individual’s current/typical state. Individuals living with AD/ADRD exhibit heterogeneous underlying pathologies and clinical presentation, and co-existing conditions can influence speech production or communication. Even in the case of paradoxical lucidity, it is important to recognize that while people with severe dementia have commonalities in the extent and range of their impairments, they do not have a homogenous clinical presentation. Therefore, the specific ways EL are manifested are potentially diverse because of the interaction of conditions and an individuals’ unique retained abilities/strengths and impairments [18–20]. In this sense, EL are intrinsically situated within individually-defined parameters. Specific attributes or markers of EL may be differentially relevant depending upon an individuals’ unique retained abilities and current/typical state. For example, very small movements that are contextually congruent (present in a logical rather than aberrant manner) may be perceived as meaningful in one individual who has substantially limited control of their extremities, but interpreted differently in an individual who routinely demonstrates goal-directed motor function. In this regard, assessment of the perceived relevance of distinct attributes/markers specific to the individual or context surrounding the EL may provide a degree of conceptual clarity that can account for broad variations in individual presentation and thresholds for observed shifts surrounding EL.

To guide development of individually responsive assessments of EL, a distinction between predominantly nomothetic and idiographic approaches to inquiry may be useful. Nomothetic approaches generally aim to generate explanations for phenomenon among a group or population while idiographic approaches emphasize intensive assessment of individual experiences. Idiographic approaches may be particularly important for initially detecting and characterizing EL, and nomothetic approaches may be more appropriate in measures focused on characterizing attributes/markers of the events once identified. For example, a shift in expression – such as a smile or sustained eye gaze – may be a small gesture but indicate a significant return of communicative ability in one individual with advanced AD/ADRD, but indicate nothing in another. The implication of this consideration is that EL are unlikely to present as homogenous and uniform events, but rather events comprised of heterogeneous attributes and markers whose presentation may vary over time and within and across individuals. This has implications for development of standardized measures and further refinement of provisional definitions.

Guiding Question 3: Is meta-awareness or insight a distinct attribute of lucidity?

Meta-awareness, or insight into one's own situation and condition has been identified by some as a key attribute of EL [11]. Meta-awareness and insight are not explicitly addressed in Mashour and colleagues' provisional definition, but may be implied in "connectedness," contingent upon how one interprets that attribute [1]. Peterson and colleagues suggest a broad interpretation of connectedness that may not just define the person with AD/ADRD's sense of connection to their milieu [5]. As prior descriptors of EL are often accompanied by shifts in degree of awareness or insight, specifying this as a potential attribute for investigation may help clarify its relevance to other attributes and to occurrence of EL overall. Shifts in degree of awareness or insight may also be evidenced or accompanied by a return of memory or recall abilities specifically. This is not to suggest that every EL necessarily need evidence of a shift in awareness or insight; but that this may be a predominant attribute in some events. It is also possible that shifts in meta-awareness or insight are themselves a distinct phenomenon which share attributes central to the study of EL.

Guiding Question 4: Are speech, language and communication measures necessary and/or sufficient to identify presence of an EL?

Direct measurement of attributes/markers of EL from the person with AD/ADRD are focused largely on variation in speech, language and communication [21]. Provisional definitions for EL emphasize qualities of communication, specifying display of meaningful *and* relevant communication or connectedness. We draw upon the fields of both speech-language pathology and linguistics to distinguish among these communicative attributes, and define discrete aspects of each in Table 3.

Peterson and colleagues emphasize the utility and implications of semantic and pragmatic language for specifying the criterion of "meaningfulness" and "relevance" of

communication during a paradoxical EL [5]. We add to this approach by expanding upon the multiple aspects of communication (linguistic, extra-linguistic, nonverbal) that can contribute to identifying episodes of EL. While measurement of speech, language, and communication are frequently intertwined and integral to perceptions of meaningfulness and relevance, discrete elements of each may yield distinct knowledge regarding corollary or antecedent characteristics surrounding an EL independent of informant appraisal. That is to say that measures of speech, language and communication may contribute relevant data that reflect quantitatively notable variations from an individual's routine patterns irrespective or absent external appraisal of meaning. If data for capturing speech and language is exclusively contingent on external appraisal of "meaningfulness" or "relevance" it may constrain inquiry in ways that limit detection of both idiographic and nomothetic variability. This may also limit attention to potentially sensitive and meaningful non-verbal communication behaviors as well as non-communicative behaviors that may be relevant to EL. Included in Table 3 is the concept of "coherence," which we propose as a related yet distinct alternative to Mashour et al.'s concept of "relevance." Coherent communication can be characterized as logically organized and connected verbal and nonverbal language, where there are conceptual links among the units of language within given words and sentences [22]. In contrast, relevant communication must also be accurate in relation to the topic as well as being related to- and informative about the content of the topic [23]. As coherence is dependent upon another person's ability to derive logical communication from the interaction, EL may be characterized by marked changes in coherence of communication, whether or not relevance to the situation, topic, or informant is also noted [24]. Multiple approaches to measurement, ranging from clinical judgement scales to computational linguistic methods, have been described for coherence [25, 26].

We further assert that the cultural context of pragmatic language—the shared rules of "use" of language in a social context (e.g., eye contact, conversational turn-taking) is critical in determining coherence [27, 28]. A lack of cultural humility in interpretation of language may lead to something being deemed non-meaningful based on biases about social language use [29, 30]. As an example, an absence of eye contact may be appropriate for certain conversational pairs in one culture, while another culture may interpret a lack of eye contact as disengagement.

In sum, it may be optimal for research frameworks to accommodate broad variability in approaches and interpretations of speech, language, and communication while simultaneously distinguishing between features that are contingent on subjective interpretation, direct measures obtained from the person living with AD/ADRD, and/or triangulation of both.

Guiding Question 5: Are dimensions of temporality and magnitude intrinsic to assessment of lucidity necessary to differentiate EL from other events?

An important consideration for clarity of a phenomenon is the ability to readily recognize unique manifestations of its core features, and to easily discriminate them from other related phenomena, such as routine fluctuations. Explicit integration of EL attributes/markers

assessment that account for temporal dimensions and magnitude (the degree of change) may aid with the task of more objectively disambiguating remarkable shifts from more routine fluctuations, or clarify areas in which they may overlap. For example, an individual may occasionally produce more speech content during a certain period. Observational data sources, such as audio or video data, may facilitate recognition and quantification of these fluctuations, and informants may indicate it is evidence of a return of abilities. Because this individual has multiple occasional episodes of increased speech production around the same time period, however, it may be challenging, absent an assessment of how each episode relates temporally and in magnitude, to distinguish the features that are within the boundaries of an EL. Implicitly, episodes of lucidity, and perhaps in particular paradoxical lucidity, are notable because of the degree or magnitude of the shift, not just because a shift occurs. However, the degree of variability exhibited within a specific attribute/marker (e.g., connectedness or verbal fluency) may vary considerably over time in ways that are not uniform. Inclusion of dimensions of temporality and/or magnitude to the assessment of specific attributes/markers may serve to help pinpoint the boundaries between shifts that more constitute routine fluctuations, cognitive fluctuations [31], and pronounced fluctuations (common to some etiologies), and lucid episodes [32].

Temporal dimensions of EL attributes and markers may also be useful in other ways. Specifying temporal dimensions of EL such as timing of event onset/offset and duration, can clarify associations between and across events and their attributes, along with temporal antecedents and/or consequences, thus facilitating disambiguation of potentially overlapping events. Temporal sequencing of events may enable close assessment of communication patterns, including initiatory (communication initiated by person with AD/ADRD) vs. responsive speech or behavior (communication by person with AD/ADRD is in response to stimulus) which may play a role in whether events themselves are experienced as surprising—which may be more likely when the person with AD/ADRD initiates communication sequence [33]. Thus, delineating antecedents and consequences surrounding EL and discrete attributes can also help shape our understanding of the contexts within which EL occur.

Another aspect of temporal dimensions in measurements relates to specification of timeframes applied for informant appraisals of EL, which implicitly rely on comparisons of the abilities or expressiveness of the person with AD/ADRD at other periods of time, and potentially to longitudinal familiarity with the individuals' habits and personality. Having referent timeframes of EL, therefore, is likely critical for informants to determine the presence of an EL and to appraise, validate and interpret it. These temporal qualities are important for uniform interpretation of data and resultant inferences. While not addressed explicitly in existing definitions, the fundamental relevance of temporal dimensions and magnitude surrounding attributes and markers and informant appraisal of EL merits further consideration.

Provided the absence of direct data sources capturing these events, it is premature to assume rigid boundaries that constrain assessment of potential co-occurrence, or temporal proximity with other more routine or pronounced fluctuations, or related phenomenon. Measurement strategies that take frequency, duration, sequential presentation, and magnitude of attributes/

markers into account may provide useful relative comparators for disambiguating these events.

Considerations for a Preliminary Research Framework

Based on guiding questions informed by concept advancement, we outline an initial research framework capable of lending common labels and interpretive clarity in this rapidly evolving area of investigation. The framework accounts for hypotheses of continuous vs. discontinuous emergence of EL, nomothetic and idiographic approaches to detecting and characterizing EL, the potential relevance of insight or meta-awareness as an attribute and/or inter-related phenomenon, the role of speech, language and communication approaches to studying EL, and specificity in elements of time and magnitude of change from a “normal state”. Our intent in introducing a preliminary research framework is to provide a schematic to elucidate the multiple lines of inquiry that may prove relevant to EL in AD/ADRD. Provisional definitions for paradoxical lucid events and guidance on approaches to interpretation of attributes (e.g. spontaneity, meaningfulness, connectedness), such as those provided by Peterson and colleagues, offers valuable insights for shaping rapidly evolving research in this area [5]. The high degree of ambiguity regarding interpretation of definitional attributes makes evident the prematurity of establishing concrete definitional criteria for any given attribute of EL. It remains unclear which specific attributes provide a necessary and sufficient combination of indicators for capturing the phenomenon of lucidity, and which specific markers evince or confirm sufficient presence of these attributes. Thus, we suggest a research framework that adopts the broadest possible perspective regarding potentially relevant avenues to inquiry while maximizing precision and clarity in labeling specific measurement approaches. Such an approach may facilitate comparability and ultimately harmonization at conceptual and operational strata.

At this early stage, specificity in the data sources from which discrete attributes/markers are derived will be essential as the field progresses. Progress in these areas will benefit from a research framework for guiding and labeling measurement strategies and the specific event attributes/markers to which they are aligned. In particular, a framework can help to specify which attributes are directly evidenced by the person with AD/ADRD and which are informant-derived or contingent on subjective appraisals of event-level features or event content.

The preliminary framework (Figure 1) organizes domains of inquiry broadly into those characterized at the event-level or within the event level. In a particular study design, a different organization of assessment levels may be necessary and we encourage investigators to specify in all cases whether attributes are assessed at a global event level and/or within discrete events.

An *event-level characterization* is an EL appraised as an entire event, contingent perhaps on the duration of the shift or impact it had on informants. Conversely, *within-event characterization* includes markers evidenced *during* the EL or the *content* or substantive features of the event. This may also include assessments of the magnitude or degree of shifts in expression. Delineation of the level(s) at which attributes or markers are appraised

is likely important to interpret and compare events across different studies, however, few efforts have been undertaken to combine data applying different levels of analysis. An *event-level characterization*, for example, may be an event where speech is transiently recovered. A *within-event characterization* may be such that *within that speech recovery*, the content of the speech reveals uncharacteristic retrieval from episodic memory, or a demonstration of declarative learning based on current events. An event presenting a more multilayered retrieval of abilities may be appraised as a higher level of magnitude or intensity of the EL. Variation in within-event features across these two instances may ultimately be relied upon to engender appraisal of its meaningfulness. Informants may apply distinct markers within an event *or* may refer collectively to the entirety of markers that comprise the event. Delineating level(s) of assessments in the preliminary research framework provides a level of specification in measurement strategies necessary to disambiguate co-dependence or interaction across attributes/markers. This will ideally facilitate interpretability and harmonization across diverse interpretations of events that are attributable to perceptual differences associated with various levels of assessment.

The framework specifies three categories of attributes/markers, those that are evidenced by the person with AD/ADRD, those that are evidenced through an informant, and those that could potentially be measured using both approaches. Within the domain of attributes evidenced by the person with AD/ADRD, areas of inquiry include various markers related to verbal and non-verbal speech, language and communication attributes, non-communicative behaviors or actions, and neurobiological attributes that could be associated with EL. Emerging evidence suggests that actions that are functional and not communicative in nature may also be relevant to EL in AD/ADRD and as such, was integrated as a potential marker [21].

Within the domain of attributes that are measured via informant appraisal, are assessments of the spontaneity or unexpectedness of an EL, appraisal of meaningfulness, the influence of the event on the informant, appraisal of a shift in insight or awareness, coherence, and event antecedents and consequences. There remains opportunity for considerable variation in how each of these aspects of EL are conceptualized and operationalized, for which the approach presented by Peterson and colleagues may prove useful to investigators [5].

Orthogonal dimensions that may be specified include the degree or magnitude of shift in discrete expressive actions (or communication behaviors, contingent upon approaches chosen), as compared to an individually specified current/typical state (i.e. degree of return or recovery of abilities) and temporal qualities surrounding temporally sensitive markers. Depending upon assessment method, determining the degree of shift from individual current/typical state may depend upon assessment from informants. To date, there are no standards for the quantity or duration of data required to comprise a “comparison window” thus explicitly specifying timeframes used will aid in comparability.

This preliminary research framework presents just one approach to facilitating broader harmonization across lines of inquiry and measurement strategies. While there are provisional definitions for paradoxical lucidity in AD/ADRD, frameworks to guide uniformity in labeling measurement strategies across investigational approaches to studying

EL broadly are lacking. The ongoing work in EL being done by NIH-funded scientists should bring us closer to a more precise definition of EL, its attributes and markers. This work is foundational to the development of theoretical frameworks that will further describe and explain EL. Examples of existing theoretical frameworks that may be salient at that point and may help to inform a theoretical framework for EL include Cognitive Reserve Theory and the Delirium Systems Integration Theory [34, 35]. Both theories attempt to explain the mechanisms by which cognitive function varies across individuals (cognitive reserve) and within individuals over time (delirium systems integration) [34–36]. These other theoretical perspectives, however, are broad in scope and perspective. On the contrary, the proposed preliminary framework is narrowly focused on specifying how lucidity is operationalized. Other broader frameworks such as these may prove useful in efforts that extend beyond building uniformity in operational labels toward trying to understand the contexts in which it occurs, or to more specifically promote refinement of definitions for the phenomenon at large. Strengths of the present framework include the flexibility and breadth of attributes, markers, and measurement strategies incorporated that can be tailored to support labeling of operationalization across a range of study designs and perspectives.

Because of the lack of data surrounding EL in AD/ADRD at any disease stage, the development or adoption of any standard definitional criteria is premature at this point. However, as research on this phenomenon progresses, we expect that this initial framework for specifying attributes, markers, and measurement strategies for investigating EL can help guide concept advancement, harmonization and specificity in specifying areas of study, as well as interpretation of findings across studies. The proposed framework may also prove broadly useful to other areas of inquiry focused on consciousness. Ideally, emergent evidence surrounding EL will yield a broader understanding of which attributes are central and/or defining attributes and markers of these events, and potentially shed light on other interrelated phenomena or concepts that should be disambiguated or separated from the study of EL in AD/ADRD. Most notably, the framework may prove useful in informing more consistent disambiguation between terminal lucidity and paradoxical lucidity; and perhaps other types of lucid episodes that are not well characterized. Similarly, guiding questions and the hypotheses they might inform may provide an opportunity to identify and question assumptions that underlie our current thinking around lucidity in AD/ADRD; and to foster an openness to the development of new understandings as new knowledge is acquired. It is our expectation that this framework should and will be revised and expanded upon as this field grows and that, critically, this evolution incorporate the perspectives of people living with AD/ADRD and their caregivers.

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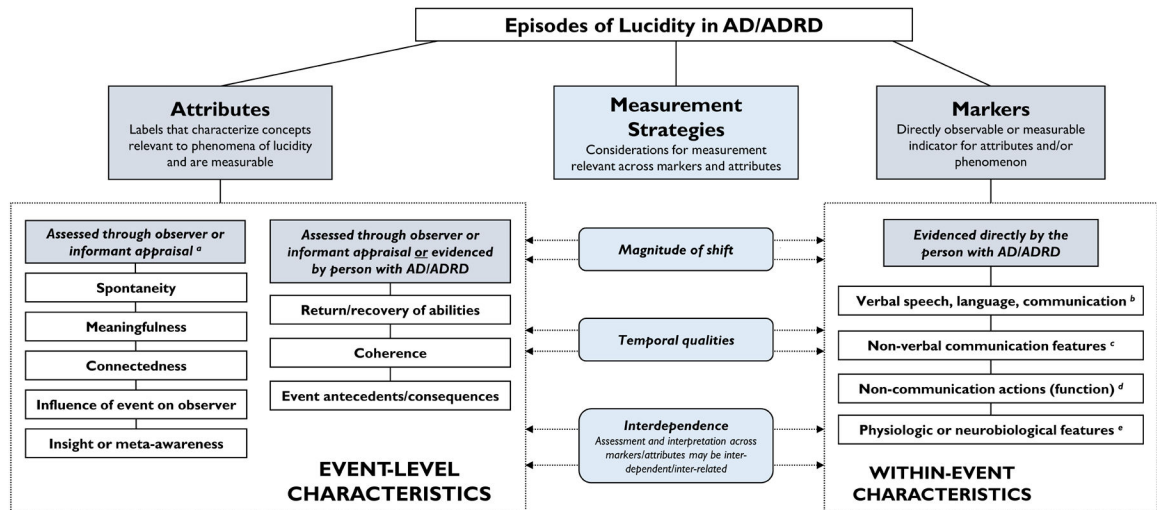
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Footnote: ^a Absent standard definitions for subjectively appraised domains, investigators may wish to refer to recommendations from Peterson and colleagues
^b Various markers can be used to characterize verbal output and its speech, language, and communicative features, which may include measurement of semantic/lexical content, syntactic complexity, and pragmatics
^c Affect, eye gaze and gestures are examples of common markers of non-verbal communication.
^d Markers for non-communicative behaviors may include engagement in functional tasks or gross motor activities
^e Markers of interest may include electrocortical beta, alpha, theta, delta, and gamma activity and functional near-infrared spectroscopy

Figure 1.
 A Preliminary Research Framework for Harmonizing Approaches to Investigating Lucidity in AD/ADR

Table 1.

Glossary of Conceptual Terminology

Term	Definition	Examples
Attributes [37, 38]	Labels that characterize concepts which may be empirical, inferential, or abstract in nature, generally described in terms of properties of events that can be operationalized	<ul style="list-style-type: none"> • Meaningfulness • Connectedness • Spontaneity • Return to prior level of abilities
Phenomenon	Observable event articulated according to a theorized organization of discrete concepts, attributes and propositions	<ul style="list-style-type: none"> • Episodes of lucidity <ul style="list-style-type: none"> – Paradoxical lucidity – Terminal lucidity
Markers	Refer to directly observable or measurable indicators that specify the presence of certain attributes	<ul style="list-style-type: none"> • Characteristics of verbal output • Non-verbal communication behaviors
Antecedents [38]	Situations or contexts that precede emergence a phenomenon and often shape conceptual boundaries, or provide insight into determinants of an event	<ul style="list-style-type: none"> • Familiar music playing prior to an episode of lucidity
Consequences [38]	Situations or contexts that follow emergence a phenomenon and often shape conceptual boundaries	<ul style="list-style-type: none"> • Reactions of other persons to the episode of lucidity
Measurement Strategies	Specific approaches and techniques employed to assess markers and attributes	<ul style="list-style-type: none"> • Physiological measures • Video observations • Informant appraisal • Multi-dimensional assessments incorporating temporal and magnitude

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Table 2. Guiding Questions Informing a Preliminary Research Framework for Investigating Lucidity in AD/ADRD

Guiding Questions	Considerations	Potential Testable Hypotheses and Implications
<p>1. Are episodes of lucidity remarkable events or a continuum of shifts in expression?</p>	<ul style="list-style-type: none"> • Mechanisms driving ELs may be present and potentially active at all disease stages • Conceptualization of EL as remarkable and spontaneous events may be shaped by biases in how people with AD/ADRD are viewed and the specific contexts in which ELs arise • Constraining investigation to the setting of advanced disease may prematurely constrain investigations that could clarify whether lucidity operates along a continuum 	<ul style="list-style-type: none"> • Hypothesis: Mechanisms that drive lucidity in advanced disease (paradoxical lucidity) are present and more active in moderate disease stages • Implications: Mechanisms may become more inhibited with disease progression, identifying presence of shared mechanisms at other disease stages may clarify pathways by which they are altered over time and open lines of investigation to timeframes more amenable to intervention
<p>2. Are episodes of lucidity individually-defined events?</p>	<ul style="list-style-type: none"> • ELs are denoted as meaningful due to the considerable degree of change from an individual's "normal" suggesting emergent features of ELs may be unique to each individual • Idiopathic (peculiar to an individual) and nomothetic (descriptive of a group of individuals) approaches to investigating ELs should be distinguished • At early stages of inquiry, idiopathic approaches may be optimal for facilitating detection of ELs and nomothetic approaches more appropriate in measures focused on characterizing attributes/markers of the events once identified 	<ul style="list-style-type: none"> • Hypothesis: Measurement approaches that apply uniform thresholds for indicating presence of ELs are less sensitive than measurement approaches that apply individually specified thresholds • Implications: Differential accuracy across measurement strategies may clarify whether and what proportion of cases of EL present in ways that are unique to a specific individual and would be overlooked by more general measures. This knowledge can inform advances in measurement approaches including delineation of tools that are specific to detection and characterization and potentially different types of ELs
<p>3. Is meta-awareness or insight a distinct attribute of lucidity?</p>	<ul style="list-style-type: none"> • Meta-awareness may be an attribute of ELs, a concept related to connectedness, or a separate but related phenomena to ELs such as routine fluctuations • ELs may not be homogenous and uniform events that necessarily include the presence of all attributes thought to describe it 	<ul style="list-style-type: none"> • Hypothesis: Meta-awareness will occur during some ELs and will also occur at other times • Implications: Clarifying when meta-awareness is present in relation to and apart from presence of EL will inform whether it is an important attribute to assess in measuring ELs
<p>4. Are speech, language and communication measures necessary and/or sufficient to identify presence of an EL?</p>	<ul style="list-style-type: none"> • Descriptions of ELs demonstrate they are commonly exhibited by the person with AD/ADRD through speech, language and communication • Distinguishing which attributes and markers of ELs are measured directly from the person with AD/ADRD and which are subjective interpretations of informants will aid harmonization efforts • Speech, language, and communication can be evaluated directly for meaningful change both with and without informant appraisal 	<ul style="list-style-type: none"> • Hypothesis: Discrete measures of speech, language and communication will identify ELs that are not identified via informant appraisal • Implications: Whether ELs can be evidenced by exclusively by changes in speech, language and communication can clarify the relative importance of these domains in detecting ELs and the role of appraisal in efforts to surveil/detect ELs
<p>5. Are dimensions of temporality and magnitude intrinsic to assessment of lucidity necessary to differentiate ELs from other events?</p>	<ul style="list-style-type: none"> • Temporal dimensions (frequency, duration, antecedents and consequences of EL episodes) are both implicit to and useful in specifying features of EL occurrence • Specification of timing of events as well as magnitude of change for specific attributes/markers may help disambiguate more routine fluctuations from ELs and clarify temporal antecedents/consequences 	<ul style="list-style-type: none"> • Hypothesis: Measurement approaches that do not incorporate temporal dimensions will demonstrate comparable discriminatory accuracy between EL and routine fluctuation on time-specified measures • Implications: If performance between measurement approaches that do and do not address temporal dimensions of ELs is

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Guiding Questions	Considerations	Potential Testable Hypotheses and Implications
	<p>Informant appraisal implicitly relies on comparisons to an individual's "normal" and may benefit from explicit specification of referent timeframes for uniform interpretation across studies</p> <ul style="list-style-type: none"> • 	<p>equivalent, this would suggest that event dimensions of event frequency and duration are not required to detect an event, but may be used to characterize it</p>

Abbreviations: EL, Episode of Lucidity; AD/ADRD, Alzheimer's Disease and Alzheimer's Disease Related Dementias

Proposed concepts and terms relating to speech, language and communication that can be directly measured from spontaneous utterances

Table 3.

Term or Concept	Definition	Potential units of measurement
Phonological system [39]	The set of sounds (phonemes) and the rules necessary to combine sounds into words	Articulatory precision ratings; number of phonological paraphasias [40]
Lexical diversity [41, 42]	The variety of word forms used in language production	Type-token ratio: unique words to total words
Semantic system [39, 42]	The concepts that word forms represent	Open class vs. closed class words; correct information units
Morphologic system [43]	The rule system that mediates assembling word forms from the basic elements of meaning (morphemes)	Mean length of utterance based on morphological analysis
Syntactic system [40, 44]	The set of rules that govern ordering words into sentences	Syntactic complexity based on number of clauses, verbs and verb forms
Speech fluency [40, 42, 44]	The rate, rhythm and ease with which speech is produced in context	Words per minute; filled and unfilled pauses, repetitions, revisions
Pragmatic language system [41, 43]	The system of rules and knowledge regarding use and interpretation of language in social settings.	Number and type of speech acts (greeting, requesting), number of conversational turns, eye contact, use of conversational repair strategies; prosodic features
Cohesion [45]	The linguistic means by which words and sentences are meaningfully linked to each other within discourse	Number of cohesive ties per utterance (e.g., pronouns, conjunctives, reiterations)
Global Coherence [46, 47]	The organization and structure of spoken language that conveys overall meaning of the message; either at the utterance level or at the level of the entire discourse sample. How words and utterances together create a unified whole	4-point Global Coherence Scale, rating scales of verbal and nonverbal devices
Local Coherence [47]	Macrolinguistic skill that reflects the extent to which each utterance is conceptually linked to the previous one	Local coherence rating scales
Relevance [23]	Words or communicative actions that are intelligible in context, accurate in relation to the topic, and related to and informative about the content of the topic	Speech connectedness to situation, topic, or informant