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Impacts of Alzheimer's Disease on Identity and Potential Therapeutic Approaches for Mitigating Identity Loss

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ABSTRACT: Alzheimer's disease (AD) is a devastating neurodegenerative disorder that profoundly affects an individual's identity. This review examines the multifaceted aspects of identity and how they are impacted by AD. Identity is constituted by a variety of factors, including cognitive function, morality and autobiographical memory, all of which undergo significant changes as the disease progresses. Qualitative and quantitative approaches have been used to measure these identity-related changes. Cognitive function decline, particularly in learning, reasoning, and attention, is associated with identity changes in AD. Morality is also closely linked to identity and is affected by the biological mechanisms of AD, as seen in responses to moral dilemmas. Autobiographical memory, a key component of identity, is disrupted as well, as evidenced by performance on autobiographical memory interviews and fluency tasks. Finally, this review discusses potential treatments tackling cognitive, moral, and memory impairments to help preserve identity in Alzheimer's patients.

KEYWORDS: Behavioral and Social Sciences, Neuroscience; Alzheimer's disease, Identity, Cognitive function.

Introduction

Human beings have a fundamental need to know and understand who they are, to take pride in their abilities and to feel respected by other people. However, these basic experiences can often be hard to achieve for people with dementia, primarily due to symptoms of dementia and the responses of those around them, particularly as the disease progresses.[1] There are several types of dementia diseases, with the most common type being AD.[2] The disease progresses from a mild stage, via a moderate stage, to an advanced stage, where those affected become increasingly dependent on others for daily care and support.[3]

AD is characterized by the gradual decline of cognitive function, changes in morality and loss of memory.[4] This deterioration ultimately forces individuals to relinquish who they once were, which leads to a loss of identity. This causes those with AD to experience a profound sense of disconnection from their former self and the world around them.[5] This not only poses challenges for those with AD to stay rooted to their past and present, but also hinders communication and connection between those with AD and their caregivers, family and friends, impacting their interpersonal relationships,[6] and further alienating them from their personal history and the societal contexts that once defined them. Therefore, understanding how identity is affected in AD can provide valuable insights into the complex processes underlying the formation and disintegration of self, so as to find potential therapies that could combat or slow down the progressive debilitating effects of AD on identity.

This paper begins by discussing the factors forming identity, as well as qualitative and quantitative measurement methods for identity. Then, the paper addresses how the three components of identity, namely cognitive function, morality and autobiographical memory, are impacted by Alzheimer's disease in terms of their biological mechanism, as demonstrated in findings through various specific measurement approaches. Finally, this paper identifies potential therapies and treatments that could be used to stagger the decline in the three components of identity by exploring their benefits and disadvantages.

Discussion

Identity:

- ***Factors constituting identity:***

Identity is complex and always evolving. The construction of one's identity is a continual, life-long process in which maintenance and transformation occur in daily interactions with other people and the environment. In a relationship with another person, the members of the dyad develop a set of unique gestures, nuances, and idiosyncrasies of everyday living that communicate their perceptions of each other, which in turn influence each member's identity. Interactions with the environment also contribute to identity formation. Identity is founded on three main components during one's interactions with the environment: existential coordinates, which are significant events that alter the person's perspective or worldview; paradoxical meaning, which is meaning that emerges from a field of mundane daily tasks; and memories of consequence, which are past experiences that have a lasting impact on identity.[7]

The awareness of one's identity is composed of two parts: self-knowledge and narratives. Self-knowledge refers to self-identifications and perceptions about oneself, such as knowledge of one's traits, commonly measured by the Tennessee self-concept scale, which consists of 100 items that assess 15 different dimensions of self-concept, including physical, social and emotional and family.[8] Meanwhile, narratives refer to stories about oneself regarding one's life and experiences, commonly measured by the Twenty statements test, which

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takes the form of a survey, with respondents asked to give up to twenty responses to the prompts, "Who am I?" or "I am…".[9] Identity is also conceptualized as a product of coherence and continuity over time, which is achieved by the integration of past, present, and future selves.[10] This in turn leads to links between the self in the past and the self in the present, creating connections between discrete moments, which generates a sense of psychological continuity and connectedness.

Identity is displayed multidimensionally, encompassing personal, mental, intellectual, and social dimensions. Most notably, in the prognosis of AD, the decline of three factors in the human mind, including cognitive function, morality and autobiographical memory, contribute significantly to the progressive loss of identity of patients. This research aims to understand the effects of AD on identity loss, with a specific focus on the three aforementioned key factors, as well as exploring the potential interventions and therapeutic approaches to mitigate their decline and preserve identity.

- ***Methods of measuring identity:***

Identity is usually measured by researchers using qualitative and quantitative approaches. There are several qualitative approaches to be used in researching identity, including the social constructionist model, which emphasizes the use of interviews, and embodied selfhood, which emphasizes the study of bodily actions.[11] The majority of these approaches focus on verbal interactions involving people with dementia, while some concentrate on their non-verbal behavior.

The social constructionist model emphasizes the role of language in shaping an individual's reality and identity, and that the way in which people acquire and use language skills can influence the organization of thought and experience.[12] There are three types of 'self identity' as suggested by this theoretical model. Self 1 is an individual's sense of self as being continuous and singular. This can be displayed through the use of personal pronouns such as "I", "me", or "mine" and is measured by counting frequencies of first-person singular pronouns in text data.[13] Self 2 consists of how one perceives his or her own beliefs and attributes, which can also be exhibited through verbal communication,[14] such as through adjectives used to describe themselves. Self 3 is the multiple social personae which become apparent during interactions with others, which can be seen through actions or inner dialogues.[15] Therefore, based on the premises of such a model, researchers can determine an individual's identity through analyzing the extent to which the individual demonstrates the three types of self, which are achieved by conducting interviews and conversations with the subjects under research. Interviews and conversations can be used in such studies to examine self or identity through the exploration of personal narratives of individuals with dementia. This information has been analyzed using a variety of methods, including a constructivist grounded theory approach.[16] Grounded theory is a systematic qualitative research method that collects empirical data first, and then creates a theory 'grounded' in the results. Data collection methods often include in-depth interviews using open-ended questions. This method is used to uncover things such as social relationships and behaviors of groups, known as social processes. Since the narratives of the subjects may become compromised due to cognitive impairments associated with AD, the grounded theory approach is suitable in identifying whether the subjects give a fragmented narrative that is not necessarily in chronological order, or may consist of repeated events or the omission of salient events.

Moreover, taking into account patients who are in more severe stages of AD and may lack the ability to use language skills, another qualitative approach to research identity is Embodied selfhood, which focuses on the idea that selfhood resides in the body itself.[17] Ethnographic studies have observed selfhood in bodily actions of thirteen people with moderate to severe AD.[18] The data presented illustrate how selfhood can be observed in behaviors associated with appearance, social etiquette, caring, dancing, and gestural communication.

On the other hand, there are quantitative approaches to investigating self and identity, including experimental techniques and questionnaire measures. These methods often target specific components of self or related abilities rather than examining self as a unified construct.

For example, several studies have focused on self-knowledge as a component of self, including personal knowledge such as one's name and past job, and more frequently, knowledge of one's own personality traits. Studies based on the concept of self-knowledge of personality as a component of self have used discrepancy scores in order to measure a person's knowledge of his or her own personality traits, which are calculated by a person's self-ratings of current personality traits and ratings from relatives.[19] This approach is relatively quick and easy to use, and has the advantage of not only checking how accurate a person's current self-knowledge is, but also whether inaccurate current self-knowledge might be due to an outdated sense of self. However, the main disadvantage of this type of measure is its reliance on relatives to accurately rate the person's personality traits.

The Self-Identity in Dementia Questionnaire examines role identities in people with dementia, covering four types of self-identity roles, which are occupational roles, family roles, leisure activities and attributes.[18] This questionnaire offers several advantages for researchers studying self-identity in dementia. Firstly, it allows for information to be gathered from multiple sources, enabling a more comprehensive understanding of how self-identity is expressed in people with dementia. Secondly, it is particularly relevant for individuals in the more advanced stages of dementia, as it considers both verbal and behavioral manifestations of self. Studies have shown that there are multiple outcomes from this questionnaire, including that all role identities had either been forgotten, or had reduced in significance from past to present while some were preserved to some extent, notably the familial role. These results hold true regardless of the informant group, suggesting the presence of a sense of self, even in later stages of the illness. The occupational role appears to be the one that experiences the most significant decline in importance.[18]

In summary, qualitative approaches primarily focus on observing and analyzing interactions involving individuals with dementia to gather evidence of self-identity. These studies of-

fer valuable insights into how self is expressed and experienced in people with dementia, often using the participants' own words. However, they tend to overlook the impact of cognitive and brain changes on self-identity and primarily focus on individuals with intact verbal abilities, limiting the generalizability of their findings. Moreover, these studies often seek evidence supporting the persistence of self, rather than a deterioration in self, potentially reflecting researchers' pre-existing beliefs about the effects of dementia on the self.

On the contrary, quantitative approaches to studying self in dementia encompass a range of methods, including experiments and questionnaires. These approaches tend to focus on specific aspects of self rather than considering it as a unified concept. Certain quantitative techniques, particularly questionnaire measures, offer the advantage of capturing evidence related to the extent of self-identity remaining in individuals with dementia. Some quantitative studies are more suitable for those in severe stages of dementia as they do not rely on verbal abilities, such as self-recognition studies or gathering information from relatives and caregivers, such as studies on role identities. Additionally, quantitative measures have the potential to explore relationships between self-identity and other variables like cognition, mood, and quality of life, which can have significant clinical implications. However, some quantitative approaches may be complex and challenging for individuals in severe stages of dementia, such as questionnaires or structured interviews that require comprehension and verbal skills.

Cognitive Function:

- ***Factors constituting cognitive function:***

Cognitive function is a broad term that refers to high-level mental processes that allow individuals to acquire knowledge, manipulate information and make judgements based on the information.[21] It includes multiple mental abilities, including learning, thinking, reasoning, remembering, problem solving, decision making, and attention.

In AD patients and those at increased risk, accumulation of amyloid in the brain may influence cognition indirectly through neurodegenerative processes. The extent of changes in cognitive functioning can also be influenced by other measures of brain health, including vascular health, as well as individual differences in brain structure and connectivity throughout a lifetime.[22]

- ***Biological mechanism of cognitive function and effects of it on identity:***

Executive function and memory are cognitive functions that are especially impacted by AD. Executive function depends on three types of mental processes: working memory, mental flexibility, and self-control. These functions are closely interconnected, and the effective use of executive function depends on these three mental processes working together in a coordinated manner.[23] However, in AD, these three mental processes of executive function are disrupted to a certain extent.

Some studies have related hippocampal health to cognition. In particular, a study done on AD patients discovered that global cognition is associated with hippocampal radial distance, which is the distance from each point on the hippocampal surface to the medial core of the hippocampus.[24] Since the hippocampus in the brain is important for working memory and is found to degenerate early in AD due to early deposition of neurofibrillary tangles,[25] with hippocampal damage in incipient AD, there is decreased synchronization between the hippocampus and the left posterior cingulate, leading to large declines in working memory performance.[21]

When looking beyond the hippocampus and analyzing the broader brain, including the neocortex, studies have found that higher rates of atrophy in the medial temporal lobe atrophy in controls are linked to a greater decline in global cognition. Furthermore, frontal lobe atrophy is associated with declines in executive function, including emotion regulation difficulties and declining self-control.[21] Apart from that, semantic memory, which is the memory of meanings, understandings and concepts related to facts, information and general knowledge about the world, is also impacted negatively due to AD. Studies show that declines in semantic fluency are related to atrophy rates in a broader network that includes the bilateral temporal lobe, left frontal lobe, and left anterior cingulate.[26]

Decline in cognitive function also impacts the vascular aspect of the brain. Among neuroimaging measures, the structure of the lateral ventricles is one of the most effective for distinguishing AD patients from healthy controls. By comparing AD patients and older adults without dementia, differences in the surface of the lateral ventricles were linked to overall cognitive functioning, longitudinal cognitive decline, and cerebrospinal fluid levels of Aβ42 protein levels, a biomarker used in AD, which AD patients have reduced levels of. Specifically, enlargement of the right frontal and left temporal horns of the lateral ventricles in AD patients has been associated with declines in executive function abilities.[18]

Declining cognitive function exacerbates the loss of identity through several mechanisms. Due to worsened mental flexibility, AD patients have trouble finding the right words to express themselves, affecting their communication with others. This often leads to poorer social relationships, causing patients to experience prolonged periods of isolation and loneliness, ultimately weakening their sense of community. The result of this is a decline in perception in Self 3, the multiple social personae that become apparent during interactions with others. Furthermore, struggling to engage in conversations can lead to social withdrawal and diminishing self-esteem,[27] which erodes Self 2, the self that is shaped by the way one perceives his or her own beliefs and attributes.

Patients with worsened working memory and self-control also often find it more challenging to make decisions or perform everyday tasks, which leads to increased dependency on others like caregivers and family members. This results in a loss of autonomy for AD patients, causing their self perception to shift from being an active participant in life to feeling like a burden.[28] This poses substantial damage to their self-esteem, increasing their sense of helplessness and diminished Self 2, negatively impacting their sense of self.

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- ***Methods of measuring cognitive function:***

Cognitive function changes throughout one's life. The dominant approach in lifespan developmental psychology for measuring and conceptualizing cognitive functioning is the psychometric approach. This approach emerged based on efforts to define, measure, and quantify cognitive abilities using fundamental constructs like traditional intelligence (g), fluid intelligence (Gf), and crystallized intelligence (Gc), as shown in Figure 1. In particular, g represents a single common factor underlying all cognitive abilities; Gf refers to reasoning, processing speed, and problem-solving in novel situations, independent of acquired knowledge; Gc represents accumulated intellectual knowledge and achievements, often measured through tasks like vocabulary. Lifespan psychologists have described these dimensions as "cognitive mechanics and pragmatics". This psychometric method relies on administering and scoring multiple cognitive performance tests, which has had a significant influence on applied psychological research. Using this approach, studies have shown that the most significant cognitive changes observed with normal aging are declines in Gf, leading to diminishing performance on tasks that require rapidly processing or transforming information to make decisions. This includes measures of processing speed, working memory, and executive functions. In contrast, Gc remains largely intact, where cumulative knowledge and experiential skills gained over a lifetime tend to be well-maintained even into advanced age. This implies that older adults may show decrements in tasks requiring fast, flexible thinking, but can often leverage their extensive knowledge and life experience to compensate and maintain overall cognitive function.[21]

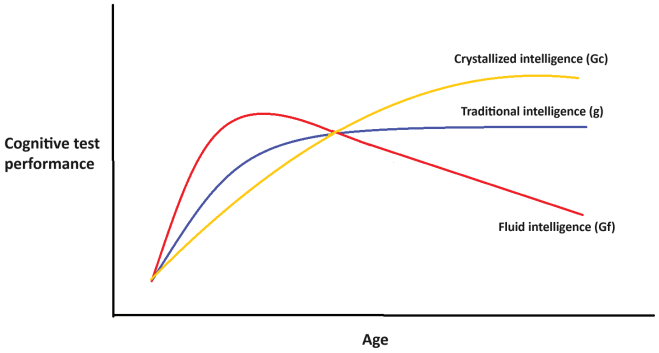

Figure 1: Graph showing cognitive test performance for crystallized intelligence (Gc), traditional intelligence (g) and fluid intelligence (Gf) in a normal adult.

However, in AD patients, cognitive function has declined to a much larger extent, and more sophisticated methods can be used to measure cognitive function at this stage. One approach is the Mini-Mental State Examination (MMSE), which is a brief cognitive assessment test that evaluates attention, orientation, short-term memory recall, language abilities, and visuospatial construction skills.[29] The test takes about 5 to 10 minutes, with the top score being 30, where a score of 25 or higher is said to be normal. Participants will be asked to do a set of tasks such as:

1. Trying to remember a few objects and then repeating the list back later.
2. Copying a drawing.
3. Writing a short sentence with correct grammar. An example could be: "the dog sat on the floor".
4. Correctly saying the current day of the week. You may also be asked to say the date, month, season and year.
5. Correctly saying where you are.

However, there are some limitations of the MMSE. There are instances in which a low score does not mean that one has cognitive impairment. This is because low scores can also be caused by physical problems, intellectual disability, education level, cultural differences, language, or speech problems, especially since the MMSE has a strong emphasis on verbal abilities, with many of the test items relying on language-based tasks. This is why other tests are needed to supplement the results from the MMSE.[30]

Another test that can be done is the Montreal Cognitive Assessment (MoCA). The MoCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. It is also rated on a 30-point scale. Compared to the MMSE, the MoCA is more sensitive in detecting subtle cognitive deficits, especially in conditions like Parkinson's disease and mild forms of AD. The MoCA is considered a more difficult test, with tasks like a clock-drawing test and a trail test, whereas the MMSE has a heavier language component. The MMSE is also better suited for more severe cognitive impairment, while the MoCA is more useful for detecting mild cognitive impairment or early stages of dementia. Nevertheless, both have limitations as both have ceiling and floor effects, meaning they may not accurately capture the cognitive abilities of highly educated individuals or those with severe impairment respectively. They are also not designed to be differential diagnostic tools for different types of cognitive conditions.[31] Therefore, other tests can also be considered in measuring cognitive impairment for higher accuracy.

Tests that recognize cognitive decline may indirectly suggest a shift in identity perception, allowing us to track the progression of cognitive decline and its impact on identity over time. This monitoring can inform adjustments in care strategies and provide insights into the effectiveness of interventions aimed at preserving identity.

Morality:

- ***Factors constituting morality:***

Morality is about ideals of human conduct based on both interactions with society and on innate traits. Morality is made up of different dimensions, with each dimension containing traits that define an individual's moral code. One large dimension of morality emphasizes traits related to warmth, which enhances interpersonal connection through traits like tolerance, good naturedness, sincerity and friendliness. Other dimensions that are less relevant to warmth and are more associated with justice include traits like trustworthiness, courage, fairness, modesty and loyalty.[32] There is also a continuum in terms of how important different traits are, which shape how individuals perceive one

another. The presence of this continuum is explained by the inherent concern of people about others' moral character, as the goodness of another person's character determines whether they are likely to be harmful or helpful to the self.

- ***Biological mechanism of morality and effects of it on identity:***

From different research findings, it is observed that there hasn't been much research in particular about the relationship between AD and morality, but there has been more research about the relationship between morality and frontotemporal dementia, another form of dementia, which could give some insights into how morality is affected in AD, so it is worth investigating the difference between affected brain areas of both dementias.

FTD patients have a decreased emotional responsiveness to others and a tendency to respond to moral dilemmas in a calculated fashion. In studies, they are also more likely to approve emotional moral violations and show a transgression of social norms including sociopathic behavior compared to the patients with AD and normal controls, but it is not certain whether it is change in morality that causes this difference in results or other factors, such as change in cognition.[33]

In particular, the behavioral variant of frontotemporal dementia (bvFTD) is a neurodegenerative condition predominantly affecting socioemotional function and, as a result, moral reasoning.

Such a disturbance may result from progressive deterioration of the frontal and anterior temporal lobes, particularly the ventromedial prefrontal cortex (vMPFC), as well as the orbitofrontal and anterior temporal cortex. This supports the presence of a "morality" network in the brain, predominantly in the right hemisphere, as can be seen in the "social intuitionist model" where moral judgements result from fast and automatic emotional intuitions of the actions of themselves or others.[34] Functional MRI studies indicate that discomfort at the prospect of causing direct harm to another drives automatic, emotionally based moral responses which are associated with increased activity in the medial vMPFC.[35] Although there are other systems for moral emotions, especially an orbitofrontal striatopallidal brain system with a reward role,[36] this vMPFC system appears to have primacy for immediate moral decision making. The vMPFC mediates a rapid, emotional response that signals potential moral violations of social norms and that attributes feelings of blame and wrongdoing.[37] This suggests that similar brain areas and their connections are damaged in other dementias like AD, impairing an emotionally based moral system.

Changes in morality can ultimately lead to a decreased sense of self. When a person experiences changes in their moral values or ethical beliefs, it can lead to confusion about who they are, altering self-perception. This shift may create a dissonance between their former self and their current beliefs, undermining the basis of Self 2 and contributing to an identity crisis.

Moreover, morality change can impact relationship dynamics. If a person's values shift from a change in morality, the patient may become unfamiliar to initially close companions. This change may even create tension or conflict with their family, friends, and colleagues, who may not share the same views. This results in social isolation and a further erosion of identity, as Self 3, which is founded on social connection, is diminished.

- ***Methods of measuring morality:***

There are multiple methods to assess morality. One method involves using the Moral Behaviour Inventory, a questionnaire that consists of 24 items originally derived from the Moral Behaviour Scale.[38] Another method involves evaluating morality by analyzing patients' responses to ethical dilemmas, which helps distinguish between reasoned and emotionally driven moral judgments. These dilemmas can be categorized into four paradigms: trust versus loyalty, individual versus community, short-term versus long-term, and justice versus mercy. In this method, participants are presented with ten moral dilemmas, five of which are reasoned (e.g. the 'Standard Trolley Problem'), where the conflicts do not result in direct harm to others, with harm only being caused due to a logical, non-personal deflection of any existing threat onto fewer people. The other five dilemmas are emotional (e.g. the 'Footbridge Dilemma'), where subjects may cause direct harm to another through their own actions.[39]

One study utilized the aforementioned methods to assess emotionally-based moral behavior in individuals with FTD. The results showed that FTD patients were more likely to endorse emotional moral violations compared to the control group. However, they still retained knowledge about moral values and conventional rules. These findings suggest an impairment in emotional moral judgment in FTD, despite the preservation of moral knowledge and the ability to discern right from wrong. FTD serves as a model for understanding the relationship between morality and the brain.

It has been reported that FTD patients often exhibit early loss of social tact and propriety and may engage in sociopathic behaviors, such as shoplifting, traffic violations, acts of violence, and even pedophilia.[37] Consequently, individuals with FTD have been characterized as more inclined toward ethically questionable actions compared to healthy individuals. However, an alternative perspective suggests that their endorsement of instrumental harm choices, such as being willing to sacrifice one person to save five, is motivated by striving for the greater good. This type of choice is commonly referred to as "utilitarian."[40]

A study revealed that some of the utilitarian responses of FTD patients could be considered prosocial choices, where they sacrificed their own self-interest to promote the greater good. Individuals with bvFTD were more likely to support prosocial values like kindness and service to the greater good as important personal values that contextualize their moral decisions. Furthermore, they exhibited significant positive emotionality even in challenging moral dilemmas. Importantly, individuals with bvFTD did not display antisocial or cold tendencies in their moral reflections when asked to contemplate their values, suggesting that their motives were not as self-centered as previous literature might imply.[40]

By understanding how morality impacts identity using the above methods, targeted therapeutic interventions can be

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developed. Clinicians can create strategies that address both moral and identity concerns, helping individuals navigate their experiences more effectively.

Autobiographical Memory:

- ***Factors constituting autobiographical memory and effects of it on identity:***

Autobiographical memory (AM) typically involves two distinct components, which are personal incident memory and personal semantic memory. Personal incident memory refers to the episodic memory component and constitutes memory for specific personal events, while personal semantic memory encompasses non-event-based personal information, including factual knowledge about an individual's own past such as home addresses and names of teachers, friends or colleagues.[41] In AD, AM involves temporal gradients of impairment.

The relationship between AM and identity is regarded as bidirectional,[7] with identity influencing the selection, reconstruction, and interpretation of autobiographical moments. Simultaneously, AM contributes to building self-awareness and personal narratives, enabling the integration of the past and present self and fostering identity continuity.

AD patients undergo AM loss, impacting various aspects of identity such as its strength, richness, complexity, and continuity. This AM loss is mainly characterized by a loss of associated episodic information, which results in de-contextualization of memories and a shift from vivid recollection of past events to a vague sense of familiarity. This decline mainly exacerbates retrograde amnesia, but it can also impact the strength of newly acquired memories,[42] affecting anterograde amnesia. AD patients may experience a reminiscence bump,[43] which refers to the overrepresentation of autobiographical memories from early adulthood, ranging from 16 to 25 years. Since memories from other time periods are less strong, early adulthood memories play a critical role in identity.

In AD, the overall decreased access to memories which shape self-consciousness, self-knowledge, and self-image, impairs the construction of a coherent identity. This results in more abstract and less specific statements in AM tests, as explored in the sections below. The close relationship between autobiographical decline and compromised sense of self in AD can also disrupt the connections between past memories, current goals, and personal beliefs, further affecting the overall coherence of identity and self-understanding.

- ***Biological mechanism of autobiographical memory:***

Studies investigating the biological mechanisms of AM have pinpointed a left-lateralized network in the brain involving key regions in the frontal, temporal, and posterior cortices, as well as the cerebellum and a number of subcortical structures.[44] These studies have also delved into factors impacting this network, such as the dynamic process of long-term memory formation encompassing several temporal and functional phases like encoding, consolidation, retrieval, storage, and reconsolidation. Additionally, glucocorticoid receptors, which are crucial for autobiographical memory formation, regulate essential intracellular signaling pathways necessary for memory consolidation, including those activated by CREB, mitogen-activated protein kinase, calcium/calmodulin-dependent protein kinase II, and brain-derived neurotrophic factor.[45] Such processes and pathways are impacted with increasing severity in AD patients.

Apart from AM formation, AM retrieval is also vital for the preservation of one's identity. Preliminary evidence suggests that the medial temporal lobe's role in recalling autobiographical events can be influenced by the passage of time, both directly and indirectly. Qualitative aspects of memories, like personal importance, level of detail, and vividness, which seem to impact the activation of the medial temporal lobe significantly, can sometimes diminish with time's passing,[46] leading to loss in perception of self.

- ***Methods of measuring autobiographical memory:***

AM has been measured both with neuroscientific studies and psychological measures. Neuroscientific studies on AM typically involve comparing event recollection with various reference conditions that engage different cognitive processes. By contrasting activation patterns between the target task (e.g. AM retrieval) and reference tasks (e.g. rest), these studies can identify the memory processes that cause hippocampal activation.

In terms of psychological measures, AM, specifically retrograde amnesia for personal memories in AD, is commonly assessed using two main methods: the Autobiographical Memory Interview (AMI) and the Autobiographical Interview (AI). Studies have shown significant impairments in AD patients' performance on both memory tests, indicating changes in the strength, quality, and direction of identity compared to healthy individuals.[47]

In the AMI, participants are asked to recall memories from three specific periods of their life: childhood, early adulthood, and recent adulthood. Modified versions may include up to five periods. Questions in the interview focus on specific episodic events related to each period (autobiographical incident schedule) as well as personal semantic facts from each time period (personal semantic schedule). The autobiographical incident schedule asks for three memories of specific events for each time period, while the personal semantic schedule requests 12 to 15 autobiographical facts for each period.[47]

On the other hand, the AI probes for memories from five time periods (early childhood, adolescent-teenage years, early adulthood, middle age, and the previous year), with participants typically asked to report only one memory for each period. Each memory is then evaluated for the amount of episodic and semantic details provided.[48]

Studies using the AMI in AD patients have shown a decrease in the frequency and specificity of autobiographical incidents from middle childhood to the present, with relatively preserved early memories. In contrast, studies using the AI have often reported a similar level of episodic memories across different time periods in AD.[49] These discrepancies may be attributed to methodological differences, such as the number of time periods assessed and the number of memories requested for each period.

While the predominance of older memories identified in AD patients using the AMI initially supports the standard consolidation model of retrograde amnesia, which suggests a temporal

gradient with earlier memories being better preserved, further research has challenged this notion. Increasing the number of time periods in the AMI from three to five has revealed a more complex distribution of memories in AD patients, including indications of a peak in memories from late childhood to early adulthood, known as the "reminiscence bump", which is mentioned above.[49]

In summary, the assessment of autobiographical memory in AD through the AMI and AI methods has provided insights into the temporal distribution and characteristics of memories in individuals with AD. The reminiscence bump observed in AD patients highlights the significance of memories from late childhood to early adulthood, while methodological differences can influence the observed temporal gradients and patterns of memory retrieval. These interviews help identify specific deficits in autobiographical memory, which is crucial for constructing personal identity, as they help to explore how changes in memory impact an individual's self-concept, values, and life narrative, revealing the extent to which identity is tied to remembered experiences. Therefore, understanding what memories are intact versus what has been lost can provide insights into how memory loss affects an individual's sense of self.

Potential Treatments for Identity Loss of Alzheimer's Disease:

After discussing how identity is lost in AD through the domains of cognitive function, morality and autobiographical memory, it is crucial to explore treatments that can mitigate identity loss, with slowing the decline of these three domains in mind. There are several approaches for treatment towards AD. These include therapies targeted at treating cognitive impairment, morality deterioration and memory loss. These three types of therapies have their respective effectiveness and may overlap in their potential use in aiding patients with AD.

- ***Therapies targeted at treating cognitive impairment:***

Cholinesterase inhibitors are medications prescribed to manage symptoms associated with memory, thinking, language, decision-making and other cognitive processes.[50] Cholinesterase inhibitors were developed based on substantial neurochemical evidence that there is a significant acetylcholine deficit in AD. One of the primary mechanisms of these drugs is to inhibit the enzyme acetylcholinesterase, which breaks down acetylcholine, thus effectively increasing the level of the acetylcholine in the brain.[51] Three cholinesterase inhibitor drugs have been established for AD and are currently used: donepezil, rivastigmine, and galantamine.[52] These drugs vary in their pharmacological action, and while they cannot stop the damage AD causes to brain cells, they may help mitigate or stabilize symptoms for a limited period of time by influencing the chemical processes involved in transmitting messages between the brain's nerve cells.

Donepezil and rivastigmine are important because of their lack of liver-related side effects and the convenience of once-daily dosing. In a multinational study, both drugs showed a protective effect against cognitive decline compared to placebo and led to some improvements in global functioning.[52] Galantamine, on the other hand, has a unique dual mechanism of action – in addition to its cholinesterase inhibition activity, it also has a modulating effect on nicotinic acetylcholine receptors in the brain, which appears to play a role in enhancing the response to acetylcholine. Extension studies of galantamine found that patients receiving the 24 mg/day dose had better cognitive function compared to those on placebo, suggesting that the drug's additional nicotinic receptor modulation may contribute to stabilization of symptoms. Direct comparison trials have been conducted to evaluate the relative advantages and disadvantages of donepezil, rivastigmine, and galantamine. For example, donepezil's long half-life allows for once-daily dosing, while galantamine may delay the onset of behavioral and psychiatric symptoms in dementia. Rivastigmine seems to have fewer drug interactions and has demonstrated efficacy in dementia with Lewy bodies. However, it is worth noting that all these cholinesterase inhibitor drugs can potentially cause side effects, such as nausea, vomiting, diarrhea, anorexia, and dizziness, with rivastigmine and galantamine being more likely to induce such adverse events.[51] Therefore, each of these cholinesterase inhibitors carries its own set of advantages and potential drawbacks, so caution should be taken before administration. Other kinds of cholinesterase inhibitors with fewer side effects can thus be investigated and put into practice.

However, cholinesterase inhibitors have been in use for quite some time, and there are other treatments currently being developed to address cognitive impairment, one of them being Lecanemab (brand name Leqembi). Lecanemab is a humanized IgG1 monoclonal antibody that targets soluble aggregated amyloid-beta protofibrils. It is designed to reduce amyloid plaques in the brain, which are associated with AD. Clinical trials have also indicated that Lecanemab can slow cognitive decline in individuals with early AD, as measured by standardized cognitive assessments. In a phase 3 trial, Lecanemab demonstrated a statistically significant 27% reduction in cognitive decline as measured by the Clinical Dementia Rating Scale sum of boxes over 18 months compared to placebo. Secondary cognitive and functional measures also showed significant improvements favoring Lecanemab treatment. Moreover, Lecanemab has shown signs of clinical benefit, as after 18 months of treatment, approximately 68% of participants treated with Lecanemab showed complete clearance of amyloid-β as confirmed by PET imaging, indicating its possible clinical applications.[53]

Nevertheless, as with any developing treatments, there are reasonable concerns about the efficacy and safety of Lecanemab. Firstly, Lecanemab shows only modest clinical benefits. This is because the removal of amyloid-β might not be as thorough as shown by PET scans or other tests, meaning Lecanemab may not target all important forms of amyloid-β. Additionally, once neurodegeneration spreads beyond certain brain areas, it may become independent of amyloid-β accumulation, suggesting that therapies targeting other aspects of neurodegeneration might be necessary for better outcomes. For amyloid-β removal alone to be effective, it may need to start before symptoms appear.

Moreover, there is a need to consider whether Lecanemab can still carry out its function after 18 months. The modest reduction in rate of clinical decline may not be evident to most

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affected individuals. Longer-term observations are needed from the ongoing open-label extension trial. There is limited and complicated evidence about the benefits of lineman beyond 18 months from an earlier phase 2 trial,[54] which suggested Lecanemab's slowing of decline may be sustained, though not amplified, even after drug cessation and reinstitution 2 years later.

An additional issue is comorbidity, as treating cognitive impairment in older adults is complicated by the presence of multiple brain issues. Many elderly individuals experience mixed dementia, where factors like cerebrovascular disease or other neurodegenerative conditions contribute to cognitive decline alongside amyloid-β.[55] This complexity may explain the limited effects of Lecanemab in patients with mild cognitive impairment and dementia, indicating that other pathological processes may be at play. Understanding these various contributing factors is crucial for developing effective treatments.

One study has suggested Lecanemab is associated with risks like amyloid-related imaging abnormalities (ARIAs), which included both the edema and microhemorrhage types in 21.5% of treated individuals. About 9% of placebo-treated individuals also experienced new cases of ARIAs—mainly microhemorrhages. There was no excess mortality during the 18-month double-blind period of the trial, but in the subsequent open-label extension phase, three affected individuals had brain hemorrhage-related deaths that could be attributed to Lecanemab treatment combined with anticoagulant therapies.[56]

Overall, Lecanemab treatment avidly removed amyloid-β and produced some clinical benefits. Lecanemab may have succeeded because its amyloid-β targets were better than prior efforts, and it was deployed in the right dose. However, its limitations show that treatment of late-life cognitive impairment will require more complex approaches, so more research will be needed to address the therapeutic challenges of this treatment.

- ***Therapies targeted at treating moral deterioration:***

While there is limited research on specific treatments to halt the deterioration of moral functioning, one potential approach is to prevent the atrophy of key brain regions involved in morality. Elevated levels of homocysteine, which is an amino acid broken down by folate, vitamin B12 and B6 to create chemicals needed in the body, signify vitamin B deficiency and have been identified as a risk factor for brain atrophy, increasing the risk for dementia.[57] Thus, by using B-vitamin supplementation to lower elevated plasma homocysteine levels, it may be possible to modify this nongenetic risk factor. In an initial randomized controlled study conducted on elderly individuals with increased risk of dementia, high-dose B-vitamin treatment (folic acid 0.8 mg, vitamin B6 20 mg, vitamin B12 0.5 mg) was found to significantly slow the shrinkage of total brain volume over a two-year period. Furthermore, the B-vitamin intervention was shown to reduce cerebral atrophy in gray matter regions that are particularly vulnerable to AD, including the medial temporal lobe, by as much as sevenfold.[58] These findings suggest that targeting modifiable risk factors, such as homocysteine levels, through B-vitamin supplementation may represent a promising strategy to help slow the deterioration of brain regions critical for moral reasoning and decision-making in individuals at risk of developing dementia.[59] Future research is necessary to determine the individual effects of each of the three B vitamins used in the study.

Nevertheless, there are some concerns about using vitamin B to slow down brain atrophy. Firstly, there is a need for more extensive long-term studies to determine whether the benefits of B vitamin supplementation in slowing brain atrophy are sustained over time. Many existing studies focus on short-term outcomes, which may not reflect the long-term effects of supplementation.

Another issue is that high doses of B vitamins, particularly B6 and B12, can lead to adverse effects. For example, excessive vitamin B6 can cause neuropathy, and there are concerns about the safety of high-dose vitamin B12 supplementation in certain populations. These risks may outweigh the potential benefits for some individuals. These effects are shown in one study, which presented a case of a man who developed a neurogenic detrusor contractility because of too much Vitamin B6 or pyridoxine intake. He developed voiding dysfunction and sensory neuropathy in both legs (numbness). The analysis gave no other explanation for the development of his complaints than the intake of excessive multivitamins, resulting in a supraphysiologic vitamin B6 level associated with neurotoxicity.[60] Focusing on B vitamin supplementation might lead to neglecting other essential nutrients that are important for overall brain health as well. Therefore, a balanced diet is crucial, and relying solely on supplements could result in deficiencies in other areas.

It is also important to note that the effectiveness of B vitamin supplementation can vary significantly among individuals due to genetic factors, existing nutrient levels, and overall health. This variability means that not everyone may experience the same benefits from supplementation, and some may not have any response at all. Additionally, B vitamins can interact with certain medications, potentially altering their effectiveness or leading to adverse effects. Thus, this necessitates careful consideration and consultation with healthcare providers before starting any new supplementation regimen.

- ***Therapies targeted at treating memory loss:***

The amyloid hypothesis proposes that the accumulation and spread of beta-amyloid in the brain, starting in the hippocampus, plays a central role in progressive memory loss seen in AD.[61] One pharmacological approach to address this involves reducing the formation of beta-amyloid peptides by inhibiting the beta-secretase and gamma-secretase enzymes, which are responsible for cleaving the amyloid precursor protein (APP) to form beta-amyloid peptides. However, some studies show that developing effective beta-secretase inhibitors is challenging because this enzyme has many substrates beyond just APP, such as neuregulin-1 which is involved in myelination of the peripheral nerves. Indiscriminate inhibition of beta-secretase could therefore lead to adverse side effects.[62] Additionally, the structure of beta-secretase, as an aspartic protease, makes it difficult for its inhibitors to cross the blood-brain barrier effectively, since the beta-secretase inhibitors must be large, hydrophilic molecules.[63] Currently, researchers are examining

various compounds to overcome these obstacles and discover beta-secretase inhibitors that can treat AD. The same challenges exist in developing inhibitors for gamma-secretase as with beta-secretase. However, an alternative approach seeking to prevent the undesirable impacts caused by these inhibitors is exploring the use of selective gamma-secretase modulators.[64] These modulators alter APP processing by gamma-secretase while sparing its signaling effects on other pathways like the Notch pathway, which involves gene regulation mechanisms that control multiple cell differentiation,[65] so as to avoid adverse effects.

Nevertheless, several potential biases and gaps can be identified in this research. The discussion primarily emphasizes the amyloid hypothesis, which posits that β-amyloid accumulation is the main driver of AD. This perspective can overshadow other contributing factors, such as tau pathology, neuroinflammation, and vascular issues. Moreover, the supposed evidence about the efficacy of gamma-secretase modulators mainly comes from studies that may not adequately address long-term effects or outcomes of modulators, so longitudinal studies should be conducted to better understand the chronic impact of these treatments. Many studies also do not include diverse populations, which can limit the generalizability of findings since variations in genetics, lifestyle, and environment among different demographic groups can influence disease progression and treatment efficacy.

In addition, both passive and active immunotherapies have been developed to inhibit the aggregation of beta-amyloid peptides, as there is substantial evidence indicating the neurotoxic and synaptotoxic effects of amyloid deposits.[66] Active immunotherapy involves vaccination against Aβ42, which is the predominant form in amyloid plaques. These trials typically involve stimulating T and B cells and generating an immune response through activating microglia to clear amyloid using their phagocytic capacity. This approach has shown promise in transgenic animal models of AD.[67] While initial results in humans were encouraging, some patients developed meningoencephalitis, leading to the partial suspension of these trials.[68]

Passive immunization, on the other hand, involves the intravenous administration of monoclonal or polyclonal antibodies targeting Aβ. This approach elicits an anti-Aβ immune response without provoking a pro-inflammatory T-cell-mediated reaction.[69] Studies in transgenic animals have demonstrated that passive immunization can reduce the amyloid buildup in neurons and improve cognitive function, even before the elimination of neuronal amyloid plaques. This may be attributed to the neutralization of soluble amyloid oligomers, which are believed to play a crucial role in the pathophysiology of AD.[68] Therefore, both active and passive immunotherapies show promise as potential strategies for clearing beta-amyloid in the brain, slowing memory decline in AD.

Conclusion

AD significantly alters multifaceted aspects of identity, including cognitive function, morality and autobiographical memory. Measuring these changes through qualitative and quantitative approaches has provided important insights into the complex relationship between identity and the progression of AD. As a result of these insights, developing effective treatments to address the cognitive, moral, and memory impairments in Alzheimer's patients is crucial for preserving a sense of self and identity. Ongoing research in these areas holds promise for improving the quality of life for individuals living with AD, so this section discusses in more depth regarding gaps that future research should address, practical implications and specific recommendations for clinical practice.

Research on Lecanemab, aimed at slowing the progression of cognitive impairment, reveals several areas necessitating further exploration. More investigations should be done on the long-term effects of Lecanemab beyond 18 months, including potential sustained benefits or risks after treatment cessation. Studies should also be conducted to assess the effects of Lecanemab on patients with mixed dementia or other comorbidities, which can enhance understanding of Lecanemab's broader applicability. From a practical standpoint, implementing regular monitoring for ARIAs in patients receiving Lecanemab is vital, especially those on anticoagulant therapy. Management protocols for potential side effects and comorbid conditions that could complicate treatment should also be developed, while awareness campaigns encouraging patients to promptly report symptoms of ARIAs could foster proactive management. Furthermore, it is possible to consider initiating Lecanemab treatment before significant neurodegeneration has occurred, as early intervention may enhance efficacy.

The role of Vitamin B in mitigating moral deterioration warrants further investigation to address gaps in current literature, particularly concerning the adverse effects associated with high-dose vitamin B6 and B12. Comprehensive studies focusing on long-term safety profiles across various populations, particularly those with existing health conditions, are critical. The mechanisms behind adverse effects like neuropathy could be studied with more detail to develop safe dosing guidelines. Furthermore, exploring the effects of a comprehensive dietary approach that includes a range of nutrients in conjunction with B-vitamins, as well as the specific effects of each B-vitamin (B6, B12, folate), could also yield insights into their impact on brain health and cognitive function and the application of using Vitamin B in clinical practice. To address potential practical implications of Vitamin B, guidelines should be established for monitoring plasma homocysteine levels and B-vitamin levels in at-risk populations to make informed decisions about supplementation. Promoting awareness of the importance of maintaining adequate B-vitamin levels can also encourage individuals to focus on dietary sources of B vitamins alongside considering supplementation. As for some specific recommendations for clinical practice, individualized supplementation plans based on patient assessments can be developed, including genetic testing and existing nutrient levels, so as to tailor interventions effectively. Another recommendation is to regularly review and adjust supplementation based on patient responses and health changes.

Regarding the use of gamma-secretase modulators, future studies should expand beyond the amyloid hypothesis to in-

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tegrate research on tau pathology and neuroinflammation, offering a more comprehensive understanding of AD mechanisms. A need also exists for thorough risk-benefit analyses of gamma-secretase modulators to better understand their therapeutic window and identify patient populations that may benefit most. Long-term studies are necessary to evaluate the chronic effects and outcomes of these modulators on memory loss. With research into gamma-secretase modulators, there could be practical implications with this treatment method. More research insights into genetic and environmental influences on AD could inform personalized treatment strategies, while a focus on selective modulators may lead to safer therapeutic options that minimize adverse effects associated with indiscriminate enzyme inhibition, potentially improving patient compliance and treatment outcomes. To ensure the largest benefits and least risks when implementing this treatment, clinicians should closely monitor patients on gamma-secretase modulators for side effects and adjust treatment protocols based on individual responses and emerging evidence.

Considering passive and active immunization, more research is warranted to understand the role of soluble amyloid oligomers in AD and how passive immunization can effectively neutralize them before significant plaque formation occurs. Standardized monitoring protocols for patients receiving immunotherapy are essential for the early detection of adverse effects related to T-cell activation or antibody administration. In clinical practice, clinicians should carefully evaluate which patients are most likely to benefit from active versus passive immunization based on their health status, history of adverse reactions, and cognitive function. Strategies should also be implemented for managing potential side effects, particularly for active immunization, which may include pre-treatment evaluations and close monitoring during treatment.

Overall, future research in the above treatment methods should prioritize longitudinal studies to assess the long-term safety and efficacy of these therapies, with a particular focus on identifying potential side effects. It is also essential to include diverse populations in these studies to understand how demographic factors, such as age, ethnicity, and comorbidities, impact treatment efficacy, safety and outcomes, thereby broadening the applicability of therapies. Furthermore, investigations into how genetic and phenotypic variations among patients, including APOE ε4 status, influence therapy outcomes will be critical for optimizing treatment strategies. Combination therapies represent a promising avenue for AD treatment by exploring the potential synergistic effects of integrating treatments explored in the sections above that target various pathologies, such as tau pathology and neuroinflammation. This multifaceted approach may enhance the management of AD's complex pathology. By tailoring combination therapies to individual patients based on their specific disease characteristics, genetic profiles, and responses to prior treatments, healthcare providers can offer more personalized and effective care.

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