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Hypothesis

The Proactive Self in Space: How Egocentric and Allocentric Spatial Impairments Contribute to Anosognosia in Alzheimer's Disease

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Abstract. In addition to impairments in episodic and spatial memory, anosognosia (i.e., loss of awareness of the deficient aspect of own cognitive functioning) may be considered an important cognitive marker of Alzheimer's disease (AD). However, although a growing body of interesting models have been proposed to explain this early symptom, what is still missing is a unifying framework of all the characteristic signs occurring in patients with AD that may guide the search for its causal neuropathological process and, ultimately, the etiological process. This contribution will first show how anosognosia may be related to the above-mentioned episodic and spatial memory impairment through a unifying framework of all these characteristic signs, i.e., the continuous interaction between different spatial representations. Second, we hypothesize that a break in the interaction between different spatial representations, as we suggest occurs in AD, may contribute significantly both to the early impairments in spatial and episodic memory, and to a deficient self-awareness since it may interfere with the capacity of the brain to detect predictive errors.

Keywords: Allocentric reference frame, Alzheimer's disease, anosognosia, egocentric reference frame, episodic memory

INTRODUCTION

> "*Depending on where you set your sights, Alzheimer's disease is a scientific puzzle, a medical whodunit, a psychological tragedy, a financial disaster, or an ethical, legal, and political dilemma. The disease quietly loots the brain, nerve cell by nerve cell, like a burglar returning to the same house each night*" [1], p. 20).

The theme of self-awareness, defined as the awareness of one's own mental state [2], has been a central topic of philosophy, but it recently has become a crucial issue for both the experimental investigations and theoretical speculations of cognitive neuroscience [3]. In simple terms, in the same way I am aware of a variety of things, for example, I am aware of the cup of coffee in front of me at this moment with its intense brown color and pleasant smell; I am also aware of

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myself, my physical and mental states, namely the events that occur inside and around me. I am aware of an *I* that belongs to *me*, that is self-awareness. Secondly, the continuous positive experience of having coffee allows me to "add" a piece of my personal identity: I love coffee. Accordingly, one of the main issues in this research field is to understand the link between the sense of self and personal memories, since this link permits an answer to the question, "Who am I?".

The lack of self-awareness of deficient aspects of own cognitive functioning in individuals with dementia has important consequences for their diagnosis, treatment, and safety. This condition–usually known as "anosognosia"–is quite common in patients suffering from Alzheimer's disease (AD), affecting between 20% and 80% of the total number of individuals diagnosed with the disease [4–6]. Despite the complex clinical presentation of anosognosia in AD, especially in the different phases of the disease [7, 8], its presence dramatically affects the management and quality of life of the patients [9, 10]. Moreover, it has been shown to be predictive of the progression of the disease from the so-called transitional stage of mild cognitive impairment (MCI) [11, 12] to AD [13].

However, although a growing body of interesting models have been proposed to explain this early symptom, what is still missing is a unifying framework of all the characteristic signs occurring in patients with AD that may guide the search for its causal neuropathological process and, ultimately, the etiological process. Using a "disease perspective" as proposed by McHugh and Slavney [14], the first step is to identify all the characteristic clusters of signs that occur in many patients. The second step is then to identify the pathological process that explains the characteristic clusters of signs with a particular neuropathology (i.e., the nature, extent, and localization of a neuropathological process in the brain). Finally, the third step is the discovery of an etiological agency, i.e., genetic mutation, neurodegeneration, etc.

Beyond the unquestionable role of biomedical research in identifying well-validated AD-related biomarkers (see for example [15]), neuroscientific cognitive research continues to provide indicators that appear crucial for both early and differential diagnosis, for improving the evaluation of the efficacy of clinical trials, and for designing and testing non-pharmacological interventions. Indeed, using the words of Khachaturian [1], the "burglar returning the same house each night" leaves a trail of clues: cognitive neuroscience uses these clues in an effort to solve the "scientific puzzle" of AD.

The "first clue", i.e., the first cognitive characteristic sign of AD, is traditionally considered prominent episodic memory deficits, in the context of more subtle perceptive, language, and executive deficits [16, 17]. In addition to progressive difficulties in encoding and storing spatio-temporal located past events with a specific reference to themselves as participants to those events (i.e., episodic memory impairment [18]), topographical disorientation is another important cognitive sign in the first phases of AD [19–21], suggesting an early deficit in spatial memory functioning [22, 23]. With regard to the underlying pathological process and possible etiological agency, the AD-neurodegenerative process usually starts in the medial temporal lobes, particularly in the hippocampus [24–28], which is a key structure for both episodic and spatial memory since it is involved in the retrieval of past experience by providing a spatial coherent framework that acts as pointer or index [29] thanks to repeated associations between hippocampal sparse patterns of activity and distributed neocortical representations allow the storing of episodic memories [30–32].

In the current work, we will present how self-awareness deficit should be considered as another important "clue" to be understood in disentangling the puzzle of AD. Expanding the "mental frame syncing hypothesis" [33, 34], we will first show how anosognosia may be related to the above-mentioned episodic and spatial memory impairments through a unifying framework of all these characteristic signs, i.e., the continuous interaction between different spatial representations. Second, we hypothesize that a break in this interaction between different spatial representations, as we suggest occurs in AD, may contribute significantly both to the early impairments of both spatial and episodic memory, and to a deficient self-awareness, since it may interfere with the capacity to detect predictive errors.

ANOSOGNOSIA IN AD: LESSON LEARNED SO FAR

Babinski originally coined the term "anosognosia" [35] to refer to a loss of awareness observed in patients suffering from hemiplegia who seem to be unaware of the left-sided paralysis that affects them. Beyond hemiplegia (for an historical review see also [36]), this term has been used for the loss of awareness that may occur in other clinical cases, such as hemianopia or dementia. As specifically concerns AD, different conceptual models of anosognosia were developed to explain disorders of self-awareness [37, 38]. The Dissociable Interactions and Conscious Experience (DICE) model was the first neuropsychological model of the underlying mechanism of anosognosia in AD, later reformulated in the Cognitive Awareness Model (CAM) [38, 39]. The DICE model introduced the role of the conscious awareness system (CAS) located in the parietal lobes [40], which collects and brings to consciousness the output of separate functional modules for each cognitive function, including both episodic and semantic memory. If a disconnection between one of these specific modules and the CAS occurs, a domain-specific loss of awareness follows. CAM proposes a mechanism linking awareness of cognitive functioning with the sense of self [38, 39]. According to CAM [38, 39] when a failure in performance occurs, this information is sent to a “mnenomic comparator” to compare it with the so-called “personal database” (PDB), which contains information about the self, and in which the semantic representations of our own abilities are stored (“I cannot go to the swimming pool because I can’t swim”). If an incongruence between current performance and semantic representations of own abilities is perceived, this information is sent back to the PDB to provide an update, and the updated information is directed to the Metacognitive Awareness System (MAS), allowing for awareness of a deficit. Accordingly, anosognosia would directly result from a memory dysfunction, which prevents updating of self-knowledge and thus leads to an outdated sense of self (termed “*petrified self*” [41]. The most reliable aspect of this model is that it highlights a major role of memory in explaining the causes of anosognosia. For AD, it is the peculiar pattern of memory dysfunction, with an early episodic memory deficit in the context of a more preserved semantic memory function, since patients fail to update the self with new episodic information regarding cognitive functioning and at the same time use outdated semantic representations of their abilities as a basis for evaluating performance.

Another intriguing hypothesis is that anosognosia in AD may originate in both memory and perspective-taking impairments [42]. Salmon and colleagues [43] found that a cognitive discrepancy score (i.e., a measure of anosognosia that is the result of the difference between patient’s and caregiver’s evaluation of the patient’s cognitive status) was inversely correlated to metabolism in the temporoparietal junction. According to this framework, it is possible to interpret anosognosia in AD as the result of an impaired ability to see oneself within a third-person perspective (i.e., knowing how another person sees you). This is consistent with what emerged in a recent review that explored the neural correlates of anosognosia in AD [44]. From one side, it is noted the role of the medial prefrontal cortex and the medial posterior cingulate, which are critical areas for self-referential processing (judgments targeting the self versus the other person) [45]. On the other side, however, another line of functional magnetic resonance imaging (fMRI) studies have highlighted the involvement of the medial frontal and lateral parieto-temporal regions (especially the temporo-parietal junction), areas known to be critical in the ability to understand another’s mental status, namely the ‘theory of mind’ (ToM) or mentalizing [46]. Moreover, this is in line with recent results obtained with patients who were anosognosic of their hemiplegia. An incredible improvement in awareness of hemiplegia has been shown in patients who had the opportunity to see a visual feedback of their paralysis from a third-person perspective, i.e., using mirrors or video replays [47–49]. Following these results, Fotopoulou suggested that patients with anosognosia for hemiplegia have an impairment in the ability to use a third-person perspective to inform and update their first-person perspective on their state [50]. Adopting a predictive processing theory of cognitive function [51–53], Fotopolou affirmed that “anosognosic phenomena can be linked to an antagonism between ‘prior beliefs’ (predictive internal models of the world formed on the basis of prior learning and genetics) and ‘prediction errors’ (discrepancies between expected and actual inputs based on ascending interoceptive and exteroceptive signals) at different levels and domains of the neurocognitive hierarchy.” ([54], p. 12). In this view, anosognosia can be considered a functional disconnection between top-down, premorbidly learned predictions regarding a property of the self and the processing of bottom-up perceptual information regarding its current state [50, 55]. The difference between self-awareness deficits in AD and in other pathologies can be related to the characteristic of the self that is disconnected: spatial reference frame processing in AD, body experience in anorexia nervosa [55], etc.

Indeed, a possible explanation for taking into account both episodic memory and perspective-taking impairments is the introduction of a unifying framework connecting them, i.e., the continuous interaction between different spatial representations.

A UNIFYING FRAMEWORK FOR ALL CHARACTERISTIC SIGNS OF AD: THE "MENTAL FRAME SYNCING"

To understand how anosognosia may be related to other fundamental early signs of AD, the first step to disentangle is the distinction between the egocentric and allocentric spatial representations. Indeed, the relationship between the self and the world in spatial terms may result in two types of spatial representations, according to the two reference points used to encode and store spatial information [56–58]: egocentric and allocentric. Egocentric representations are transient spatial representations useful for guiding immediate actions in peripersonal space, since they are constituted of subject-to-object spatial relations, integrated mainly in the posterior parietal lobes [59–61]. Allocentric spatial representations are useful for long-term storage, since they are constituted of object-to-object spatial relations, which are elaborated in the hippocampal areas [62–64]. Parallel egocentric and allocentric spatial processes create a flexible and highly adaptive inner space that permits an effective interaction with our surrounding space. From a neuroscience perspective, Burgess and colleagues [65, 66] argued that when stimulated by external (perceptual) or internal (cognitive) inputs, we are engaged in a process of retrieving an egocentric scenario, known as a "parietal egocentric window." We extract pieces of information from our experiences and recombine them in a flexible manner according to our different needs. This process recruits the activity of different brain regions, such as the frontal lobes, the retrosplenial cortex (RSC), and the parietal areas, which highlight the key role of the medial temporal lobes, specifically the hippocampus [67–70]. In particular, according to this neuroscientific model [65, 66], a crucial role was assigned to RSC, which is responsible for the continuous transformation between these two spatial representations by compensating for the rotational offset of different coordinates (self-centered versus world-centered).

An interesting fMRI study carried out by Zhang and colleagues [71] helped to clarify the role of RSC in the translation between allocentric and egocentric reference frames. Participants learned spatial layout in two different ways, by active navigation (i.e., egocentric reference frame) or by learning with an aerial-view map (i.e., allocentric reference frames). While undergoing the fMRI, participants were asked to perform a traditional spatial pointing task involving judgments of relative direction (JRD) (see for example [72]). In this task, participants were required to imagine themselves at a specific object X, facing object Y, and to point to object Z. This task was dependent on allocentric knowledge of the relative position of spatial locations in relation to each other and not only to the correct matching of the individual's orientation with the immediate environment. Results showed a greater activation of the RSC following the egocentric condition, suggesting that this area is involved in translating egocentric coordinate information acquired during a first-person perspective navigation to an object-to-object relationships representation. Dhindsa and colleagues [73] expanded these findings by investigating how brain activity correlated with accuracy in judging the direction of an object in three different conditions: 1) without a change in viewpoint; 2) with a rotation in viewpoint; 3) with a rotation and translation in viewpoint. In the first condition, participants were asked to imagine if their position and viewpoint were identical to the reference viewpoint they had learned previously before pointing to the cued object. In the second condition, participants were required to imagine their position being identical to the position in the first condition, but instead they were facing one of the objects and asked to point to a second object. The last condition is the JRD paradigm previously described. Results demonstrated that the RSC was more active during imagined transformations involving both rotation and translation of viewpoint (JRD) compared to transformations involving only a rotation of viewpoint.

To understand all these relevant results, it is crucial to reflect that in the JRD task, participants were asked to indicate the bearing of each object from a new position, but still in relation to their heading, that is what Klatzky called the "ego-oriented bearing" [58, 74]. In other words, when confronted with two objects in space, the inter-object direction is coded with respect to the individual's current heading, resulting in an "ego-oriented bearing" from one object to the other, that is the angle between the self's position and the vector connecting the two objects [58, 74]. It would be difficult to solve the JRD task if the stored egocentric heading was not aligned with the objects' bearings [33, 34]. In order to account for the role of this alignment principle centered on the self, starting from this theoretical framework [65, 66, 68], we suggested that *mental frame syncing* may be included as a neurocognitive mechanism of the egocentric-allocentric transformation to support the recall of a spatial scenario.

The starting point is the evidence that there are two regions within the hippocampus involved in processing allocentric information [76, 77]: the region CA3 receives inputs from the entorhinal cortex and elaborates an allocentric representation containing information about the individual's viewpoint within the spatial scene (i.e., *allocentric viewpoint-dependent representation* [34,77]), while the region CA1 receives inputs from CA3 via Schaffer's collaterals and encodes allocentric representations containing pure object-to-object information of the spatial scene (i.e., *allocentric viewpoint-independent representation* [34,77]). More specifically, when we memorize the pure object-to-object relationship included in a spatial scene (i.e., *allocentric viewpoint-independent representation* [34,77], we also encode the inter-object direction with respect to our egocentric heading, resulting in the above-mentioned "ego-oriented bearing" [58, 74]. Accordingly, when we have to recall this spatial scene, we have to re-establish our ego-oriented bearing on the first pure allocentric representation by mentally computing the bearing of each relevant "object" in relation to the stored heading in space (i.e., information about our viewpoint contained in the viewpoint-dependent representation), and this process facilitates the translation into the egocentric representation. This means a synchronization between the allocentric viewpoint-independent representation (i.e., including the above-mentioned object-to-object information) with the allocentric viewpoint-dependent representation (i.e., comprising information about our heading in the space), that is the "mental frame syncing" [33, 34].

From these theoretical and experimental premises, Serino and Riva [78] specifically investigated the mechanism underlying this process, namely how the interaction between allocentric viewpoint-independent and viewpoint-dependent representation works in spatial retrieval. Participants were asked to navigate in virtual environments to memorize the position of one hidden object in two different conditions: in an egocentric condition and with an interactive aerial view of the city. Results showed that the presence of an interactive aerial view of the city facilitated the retrieval of spatial information, since it furnishes information about the current egocentric heading in the space; this may facilitate the matching of the stored egocentric heading with the current egocentric heading in the spatial scene.

WHEN THERE IS A "BREAK" IN THE "MENTAL FRAME SYNCING": PRELIMINARY EVIDENCE FOR A PATHOLOGICAL PROCESS IN AD AND RELATED ETIOLOGICAL AGENCY

At this point we can introduce the main claim of our hypothesis: a break in the continuous interaction between different spatial representations may contribute significantly both to the early impairments in spatial and episodic memory, and to a deficient self-awareness in AD.

As concerns the first point, namely how a break in the mental frame syncing may contribute to the early impairments in spatial and episodic memory in AD, it has been suggested that when it occurs, the reconstructed egocentric image retrieved from allocentric memory is useless because the egocentric heading is not aligned with the bearing of each relevant "object" that cued the retrieval [33, 34] (see Fig. 1).

In support of this idea, a recent study demonstrated that patients suffering from AD performed significantly more poorly when compared to the cognitively healthy age-matched controls in a task requiring them to memorize the position of an object in a virtual room and then to retrieve its position starting from another viewpoint of an empty version of the room, indicating a specific impairment in storing a viewpoint-independent representation, and then syncing it with the viewpoint-dependent representation [22].

Consequently, first of all, a deficit in mental frame syncing may explain both the spatial and episodic deficits in patients with AD, since it did not allow to place their stored egocentric heading in relation to other objects within the "memorized space", a function that is crucial to navigate (i.e., spatial memory deficit) and to retrieve our past experiences (i.e., episodic memory deficit).

As concerns the second point, namely how a break in the mental frame syncing may contribute to a deficient self-awareness in AD, a useful theoretical starting point is the predictive account to brain function [51–53]. Indeed, it has been suggested that our brain is essentially a "predictive brain" since it is constantly engaged in making predictions about future states and comparing them with actual perceived states [51–53]. In this direction, recent empirical works and theoretical proposals have emphasized the relationship between the retrieval of personal past

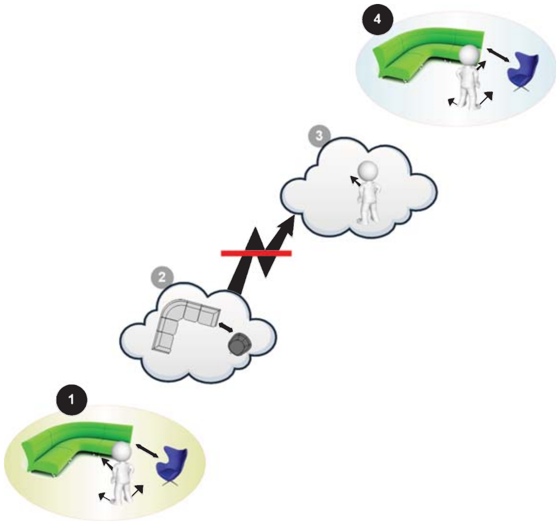

Fig. 1. When a cue prompted the retrieval of a personal experienced event (1), if the mental frame syncing does not work, the reconstructed egocentric image (4) is useless, because the allocentric viewpoint-independent representation (i.e., including the above object-to-object information) (2) is not aligned with the allocentric viewpoint-dependent representation (i.e., comprising information about our heading in the space) (3). This may cause difficulty in correctly orienting bodily position ('orienting toward the sofa') in the space that had been memorized ("memorized space"), making easy the translation of it into a "lived space" that needed to navigate and remember the past.

events and predictions of future events (for a review, see [52]). Here, we advance the idea that a break in the mental frame syncing may affect also possibility to detect errors in predictions. Prediction errors, which can be detected internally (thanks to a mismatch between predictions and perceptions) or externally with cues, which are usually used to adjust behavior in the immediate context or to update internal models, allowing more accurate predictions in the future [52]. Comparison between predictions and perception is processed outside of awareness; however, when a mismatch is detected typically it reaches the self-awareness.

However, as previously explained, a break in the mental frame syncing implies that the stored egocentric heading (i.e., our direction in the world) is not aligned with the objects' bearings (i.e., the stored object-to-object relationships) in the "memorized space". In other words, we are not able to re-establish a new ego-oriented bearing on a pure allocentric representation by elaborating the bearing of each relevant "object" in relation to the stored heading in space. This in turn may imply that we do not have sufficient information to generate accurate predictions about the spatial position of self in his/her "future space", and then to detect errors in predictions allowing for self-awareness of cognitive functioning. In particular, we refer to the so-called "episodic prediction" [79], namely "the estimation of the likelihood of, and/or the reactions to, a specific autobiographical future events" (p. 25). Using the words of Freton and colleagues [80], this means that the "remembering self" (i.e., the subject who is remembering a past event) is no more able to use information about the "remembered self" (i.e., the agent of the remembered event) to predict the "future self" (see Fig. 2).

Some interesting evidence may give specific support for the idea that a break in the mental frame syncing may also contribute to the deficient self-awareness in AD. First of all, as previously explained, a peculiar aspect of autobiographical memories is related to the visual perspective adopted during the recall [80–82], namely the *field perspective* (i.e., first-person perspective; the person remembering sees the event through his own eyes) and *observer perspective* (i.e., third-person perspective; in which the person remembering sees himself and the event from the point of view of an external observer). Traditionally, the distinction between two types of visual perspective permits in turn a distinction between episodic and semantic aspects of autobiographical memories [80, 83, 84]. The first-person perspective, indeed, is a feature of the episodic autobiographical retrieval, whereas the third-person perspective is traditionally associated with a semantic autobiographical recall. This is in line with studies showing that remote semanticized autobiographical memories are usually retrieved from a third-person perspective, while more recent memories are usually recalled from the same perspective as the encoding [80, 84]. Although the first-person perspective is more immediate and natural, studies have demonstrated that people may adopt a third-person perspective [85], and this implies a cognitive translocation of our egocentric viewpoint to locate ourselves into another point in space [85]. With regard to "spatial characteristics" of the two retrieval modes, in a recent study undergraduate students were instructed to retrieve an experienced event either from a first or a third-person perspective to investigate whether a specific vantage point may influence its mnemonic content [86]. The results showed that memories recalled from a third-person perspective included more "spatial details", such as where the participants looked, what they did, or where things were.

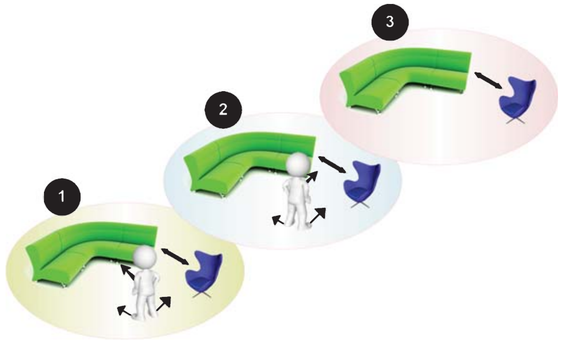

Fig. 2. A deficit in mental frame syncing affects the retrieval of a personal experienced event (1) since a person is not able to correctly orient his/her bodily position ("orienting toward the sofa") in the space that he/she had memorized ("memorized space") (2), and this in turn may imply that he/she does not have sufficient information to generate accurate predictions about the spatial position of self in his/her "future space", and to then to detect errors in predictions allowing for self-awareness (3).

This supports the idea that the third-person perspective may be useful for updating self-knowledge since it offers the possibility of acquiring new information on the self, taking into account previous stored information [50]. It is possible to argue that these "spatial details" would be essential to establish an ego-oriented bearing on a pure allocentric representation since they furnish essential information about the egocentric heading in relation to the bearing of each relevant "object" within the spatial scene, taking into account both episodic memory and perspective-taking impairments. With regard to the impaired ability of in AD to see themselves from another perspective, a recent study [87] investigating autobiographical recall in patients with AD found that 31.4% of retrieved memories were visualized via "general" off-tangent imagery without an explicit reference to the self or to the original event that cued the recall. Moreover, 16% of memories were recalled without any visual spatial details indicating the visual perspective. These results may provide evidence to support the difficulties of patients with AD in adopting an accurate third-person perspective of themselves during recall, a compromised ability which may reflect pathology in the medial parietal areas [88], known to be critical for egocentric spatial processing in the context of autobiographical retrieval.

As specifically concern the ability in imaging future personal events, Addis and co-workers [89] found that also patients with AD had difficulties in simulating future autobiographical events, generating fewer internal and external episodic elements in comparison to a matched control group. Moreover, Gamboz and co-workers [90] asked 14 patients with amnestic MCI (aMCI), and 14 matched controls to mentally retrieve and simulate autobiographical events. The findings showed that patients suffering from aMCI produced fewer event-specific details for both past and future events.

These data on patients suffering from aMCI are interesting since it is has been shown that these patients have a higher likelihood of progressing to AD (e.g., [91]), but it is crucial to underline that although a reduced self-awareness is often reported among patients suffering from MCI [92, 93], the question about level of awareness about own cognitive functioning in patients with MCI is still under debate, and literature has not yet reached a clear consensus [94, 95]. In addition to the heterogeneity of self-awareness deficits found in MCI, one of the main concerns regards the validity of the existing methods for the evaluation of anosognosia [96, 97]. However, an interesting study using a multimodal assessment of anosognosia found that this symptom was equally frequent in both patients suffering from aMCI and in mild AD [98]. These findings may provide some support to the idea that impaired self-awareness in MCI may share common underlying mechanism with that reported in AD.

Overall, these data may corroborate the hypothesis that patients with AD may have an impaired ability to simulate autobiographical future scenarios of themselves in a third-person perspective, which may prevent the update of the first-person perspective on one's own state [50], and in turn, the update of self-knowledge [41]. This is consistent with results showing that the ability to simulate future autobiographical scenarios is based on the activity of medial temporal lobes [99–101], which is the earliest area affected by the neuropathological process in AD. A first step to give further support to this hypothesis is to investigate whether patients with AD would manifest an improvement in their anosognosia if they have the opportunity to see themselves in future autobiographical scenarios from a third-person perspective. How is it possible to experimentally simulate autobiographical future scenarios in a third-person perspective? A possible solution is offered by virtual reality (VR). Recently, Friedman and co-workers [102] proposed an innovative method for generating the illusion of "time travel" using VR: participants took part in an event with a dramatic outcome (i.e., the deaths of stranger) and they had to choose between saving five people or one. Then, in the “Time Travel Condition”, they relived these events for three times, having the possibility to see the embodied version of their past selves doing what they had previously done. Besides the opportunity for controlled, valid, and secure testing environments (for a review, see [103]), with VR it would be possible to set-up an innovative and objectively valid method to experimentally simulate autobiographical future scenarios in a different perspective. Specifically, VR has proven to be a valid tool to assess large-scale navigation strategies in patients suffering from MCI and AD [104]. Moreover, as highlighted in a recent review, it appears useful to detect allocentric and egocentric impairments that appear since the first phases of the AD, and also in individuals suffering from MCI, particularly from aMCI [105]. Future research in this field should focus on this population, considering also the individuals with one or two alleles of the apolipoprotein E (ApoE4), which is the only genetic variant accepted as increasing the risk of developing AD [106]. In particular, indeed, some interesting studies have found that individuals who met the clinical criteria for aMCI and were also ApoE4 positive showed the same spatial impairments as patients with AD [107, 108].

CONCLUSION

The fortunate combination of a rapid increase in population growth (the Baby-Boom generation) and in life expectancy has resulted in a consequent increase in the aging population (aged 65 and over). The flip-side of the coin, namely the negative effect of this growth, is that the prevalence of neurodegenerative diseases is also expected to increase. In 2005, an estimated 24.3 million of individuals suffered from AD [109]. It has been estimated that each year 4.6 million new cases of AD will be diagnosed, and that the number of the elderly with AD will reach 81.1 million by 2040. In the United States, recent epidemiological data has estimated that 5.3 million of U.S. individuals suffered from AD [110, 111], a number that is projected to grow by nearly 10 million by mid-century [111]. Based on these premises, it is evident why a major goal of health policy worldwide has become the continuous identification of early indicators of cognitive decline in the elderly [112].

Here, we suggest a new unifying framework of all the characteristic signs occurring in AD related to the interaction between different spatial representations. In particular, we hypothesized that a break in this interaction may contribute significantly both to the early impairments of spatial and episodic memory and to deficient self-awareness. Specifically, it is proposed that continuous synchronization (namely, “mental frame syncing”) of an allocentric viewpoint-independent representation (i.e., including only abstract object-to-object relations) and an allocentric viewpoint-dependent representation (i.e., comprising information about our egocentric heading) may permit me to correctly orient my bodily position in the space I have memorized (“memorized space”) making it easy to translate it into a “lived space” that I need to navigate and remember the past [33, 34]. If mental frame syncing stops, as we suggest occurs in AD, the reconstructed egocentric image from the allocentric memory will be useless, because our egocentric heading will be not aligned with the objects’ bearings. Moreover, this may provoke an impairment in our ability to use this “memorized space” to predict our future based on our personal past episodes, namely to place our self in a “future space” and consequently to see ourselves from the outside, and in turn to detect errors in predictions and then use this information to update our first-person perspective allowing for self-awareness.

From a clinical viewpoint, the elaboration of a unifying framework of all the characteristic signs occurring in patients with AD opens crucial possibility also for non-pharmacological interventions. In the last few decades, an increasing number of studies found that the non-pharmacological interventions, such as cognitive training, may play a role both for patients with AD or for their caregivers, as a complement to the pharmacological approach [113]. In a recent study, 61 patients suffering from mild stage AD patients were assigned to an experimental group to receive a Multi-Intervention Programme (i.e., a combination of cognitive tasks, training in daily life, and recreational activities) or to the waiting list. Results showed that patients with AD and with awareness of their deficits had positive effects on all outcome measures when compared the waiting list group, whereas patients with AD and unawareness demonstrated improvements only in non-cognitive symptoms [114].

Even if these claims are supported by a growing number of studies, further research is still needed to provide more evidence for this theoretical proposal. Any further improvement in this direction may also help cognitive neuroscience to bridge the still existing gap between two key questions related to our self: “Where am I?” and “Who am I?”.

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