BioEssays

WILEY-VCH

BioEssays

HYPOTHESES OPEN ACCESS

Memory Gate Controlled by Contexts: Potential Key Structure That Could Link Small Associative Failures With Severe Cognitive Disorders

Eduardo Mizraji[1] | Juan Lin[1,2] | Andrés Pomi[1]

[1]Group of Cognitive Systems Modeling, Biophysics Section, Facultad de Ciencias, Universidad de la República, Montevideo, Uruguay | [2]Department of Physics, Washington College, Chestertown, Maryland, USA

Correspondence: Eduardo Mizraji (emizraji@gmail.com; mizraj@fcien.edu.uy)

Received: 16 February 2025 | **Revised:** 28 May 2025 | **Accepted:** 3 June 2025

Keywords: Alzheimer's disease | associative contexts network | memory gate | memory recall | transient forgetting

ABSTRACT

Can the banal and transient forgetfulness that we all experience at some point in our lives give us clues about the neural mechanisms underlying the onset of severe dementia, such as Alzheimer´s disease (AD)? The hypothesis we propose suggests an affirmative answer. If access to the memory system (MS) depends on matching key input patterns to appropriate contexts, we postulate that if the matching does not occur, the MS is blocked by a neural gate. From empirical observations, we shift to neural models of memories and their modulation by contexts. Our approach provides a possible explanation for transient memory failures but also suggests that the memory gate (MG) can be a crucial neural module that triggers a cascade of events leading to conditions where AD becomes irreversible and catastrophic. This hypothesis suggests ways to slow down the progression of this disease and may be explored with currently available techniques.

> "Science is built up of facts, as a house is built of stones; but an accumulation of facts is no more a science than a heap of stones is a house."
>
> "Science and Hypothesis," Henri Poincaré (1905)

1 | Introduction

It is to memory that human individuals owe their sense of personal identity. Also, it is to memory that they owe their ability to store linguistic codes and, with them, establish the systems of communication on which our society is based. In memory reside the procedures that at the beginning of humanity were transmitted from generation to generation and that allowed for the creation of instruments, art, child-rearing strategies, and the ability to defend oneself from the weather and predators. The historical and current life of humans owes everything to the existence of their privileged memory. The codes of memory and our ability to transmit information give us our identity as humans. This makes the nature of memory a prominent objective of scientific research, both for its intrinsic scientific interest and the challenging enigmas it poses, as well as for its profound philosophical implications [1].

However, in our time, when social and scientific advances have increased human life expectancy, a more dramatic motivation is added to the above: the appearance of different forms of dementia at relatively advanced ages, where memory deterioration is the primary factor. These severe cognitive disorders have devastating consequences for the affected individuals and their families and are currently a topic of research at multiple top-level laboratories [2–4].

In this work, we assume that certain types of transient memory deficits, which constitute a common experience for all people, can be a clue to uncover the existence of a neuronal gate that conditions the access of information to memories. If this neural gate turns out to be true, it may be relevant to the process of attaining new approaches to understand, and perhaps prevent, the onset of extremely severe impairments that occur in neurodegenerative processes such as Alzheimer's disease (AD). In describing this hypothetical "memory gate," (MG) we will assume that contexts are essential components for accessing memories.

MGs have been postulated for specific situations on several occasions, both in theoretical and experimental research. As far back as 1989, a neural model of context-dependent associative memories showed that contexts could operate as gates capable of triggering chains of associations like episodic or procedural memories [5]. More recently, Chatham and Badre [6] analyze gates for the input and output of working memory (WM) and their possible neuroanatomical substrates. Verschooren et al. [7], in experiments where various perceptual inputs are presented to participants, propose a MG that opens and closes while WM interacts with long-term memory. Coelho et al. [8] have found evidence in experiments with mice that the dentate gyrus in mice may be a key structure supporting a gate that establishes contextual modulation of memory access. Also, most recently, Liu, et al. [9] proposed a model, which they call GATE, where a MG in the CA3 area of the hippocampus may be responsible for mammal adaptive learning.

The MG we postulate here is a complex structure that receives the key pattern already associated with its contexts as paired inputs coming from the WM and subsequently sends this key pattern-context pair to the memory system (MS) involved. However, a central point of our hypothesis is that this MG is dynamically linked to a rich contextual network that, failing recognition, causes a random context replacement process until the appropriate context-key pattern is recognized by the MS.

The paper is organized as follows: first, some of the most accepted MSs and their possible neurofunctional bases are described. Then, we show another way of looking at the nature of memory, mostly based on mathematical models of neural networks developed since the 1970s, which are precursors of the artificial intelligence (AI) systems that predominate today. These neural models are based on what we would call "the vector paradigm." We present a neural modeling approach to our "memory gate" and describe its component neural modules together with their properties. Finally, we analyze the impact of this MG on AD.

2 | Memory systems

Memory types are operationally classified as short-term memory, lasting briefly, and long-term memory that stores information for a good part of a person's life. This old distinction is still used today [10].

Short-term memory includes memories of recently experienced events and WM. Long-term memory includes so-called declarative memories and procedural memories. Procedural memories store sequences of automatic and usually unconscious procedures (such as the actions of an expert car driver). Declarative memories, generally conscious, involve access to the conceptual world and encompass semantic memory (language and meanings) and episodic memory (temporal structures of events experienced by people) [11].

Schacter and Tulving [12] recognize five MSs: episodic, semantic, procedural, working, and the perceptual representation system. The latter is a MS that identifies sensory inputs and maps them into a conceptual memory associated with these percepts. WM [13] is a MS that is strongly involved in multiple aspects of our cognitive function. However, perhaps these five MSs do not exhaust the possible alternatives that future research will reveal [14].

The cerebral location of the different MSs is a difficult topic, but important advances have been made with functional brain imaging techniques. An updated review can be found in [15].

A powerful experimental area linked to the neural basis of memory comes from the discoveries of synaptic plasticity and modifications of synaptic conductivity based on repeated stimuli. This phenomenon, called long-term potentiation, has been found in neurons of the hippocampus and has contributed to highlighting the importance of these brain structures in mnemonic functions.

Clinical evidence from decades ago has demonstrated how the hippocampus, and the brain areas linked to it, affect memories when they are almost completely destroyed during various neurological conditions or traumatic accidents. Following these events, the patient exhibits a virtual inability to install memories of current events (anterograde amnesia) while preserving other forms of memory. Evidence centers on the ability to incorporate new information in the medial temporal lobe (MTL), which may be an essential neural pathway for recent data to be transferred to consolidated memories. This region comprises the hippocampus, the perirhinal cortex, entorhinal cortex, and the parahippocampal cortex. These systems appear to be hierarchically linked, with the perirhinal and parahippocampal cortices operating on the entorhinal cortex and generating inputs to the hippocampus [15]. However, the size of the hippocampus is incompatible with the volume of information stored in semantic and episodic memories, which explains why the network complex establishes connections with the neocortical and subcortical regions. As regards the semantic network, it is worth mentioning the exhaustive research by Huth et al. [16, 17] showing the cortical ubiquity of the areas that support this network. Ullman [18] also proposes a neural model of language that links declarative memories with procedural memories.

Concerning WM, of fundamental importance in the organization of executive functions, its location sits in the prefrontal cortex [19]. WM participates in reentrant loops that link frontal regions with posterior regions of the brain, as well as with subcortical structures [20].

A particularly interesting result supporting the MG hypothesis that we will present here was published by Aminoff et al. [21], showing that the recognition of contexts induces an intense activity in the retrosplenial complex, regions of the lateral parietal cortex, the medial prefrontal cortex, and the occipito-temporal sulcus.

3 | Theory of Neural Networks and the Vector Paradigm

In this research field, memories are viewed in a different way than what we discussed in the previous section. Here, the focus is on extensive neural network models where precise biological details are avoided. A compilation of the fundamental articles on neural network theory was published by MIT Press under the title "Neurocomputing" [22].

What we call the "vector paradigm" assumes that the central basis of information processing by neural modules is an extensive collection of signals traveling along the axons that connect one module to another. The multidimensional vector (an extension of the intuitive idea of 2 and 3-dimensional vectors) is the natural mathematical representation for such collections of neural signals. The foundational papers on the theory of associative memories were published independently by Anderson and Kohonen in 1972 [23, 24]. The idea was to define a memory as a set of associated (input-*f*-output-*g*) pairs:

$$Mem = \{(g_1, f_1),\ \ (g_2, f_2), \ldots, (g_K, f_K)\}$$

This definition leads to a *Mem* mathematical structure that implements these associations in the form of a matrix. The theory also shows that the numerical components of this matrix represent the synaptic connections of the idealized neurons on which memories are built. Moreover, these matrices are capable of learning, that is, of adding up to a certain limit new pairs of associated vectors.

Analyses of these matrix memories reveal three essential properties:

1. They are usually very large matrices: if the inputs and outputs are vectors with thousands of components, the matrix representing synapses has millions of components.
2. The pairs of associated vectors are "split" and dispersed among the different synaptic coefficients. This is why they are called distributed memories. When an input enters the memory, it has the capacity to collect the dispersed information and reconstruct the output. A biologically relevant corollary of this distribution of information is the resistance of stored data to random physical deterioration of memory components, a property known to biologists and physicians but often unexplained until the appearance of distributed memory models. These models suggest an explanation: given the large size of the memory, the deterioration of some synapses or neurons eliminates very small pieces of the stored information but does not prevent recognition of the associated patterns. In Figure 1, we show an extremely elementary example to illustrate the distribution of data and its reconstruction by the inputs.
3. The matrix memories superimpose the distributed segments of their associated vectors on the synaptic coefficients. This means that each coefficient of the matrix stores superimposed components of various stored input-output pairs. A particular input may temporarily weaken or cancel the superimposed patterns that do not correspond to this association and, consequently, strengthen the components of the output. We illustrate this overlaying property with a simple geometric example in Figure 2.

We refer to the mathematical details of these processes in the cited articles [23, 24] or in books by Anderson [25] and Kohonen [26].

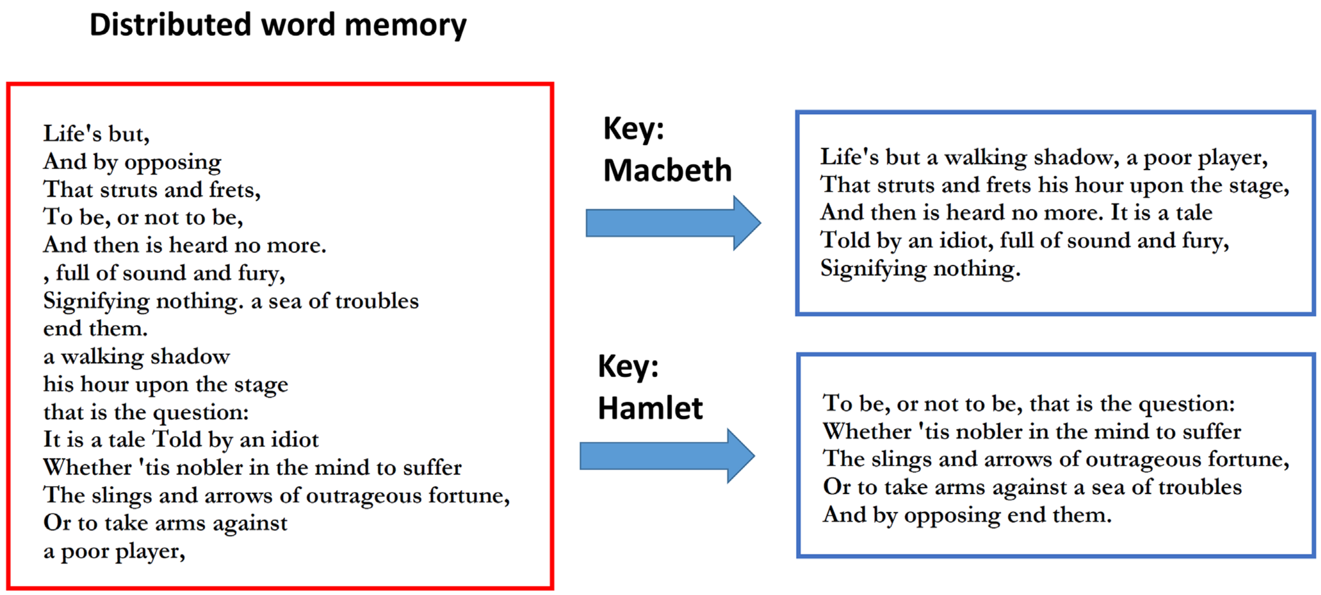
These remarkable properties of distributed memories contributed significantly to the vector paradigm among researchers. Moreover, the neural vectors on which these memories are based were compatible with the various coding modes used by different kinds of neurons (frequency codes, bursts of action potentials, topographic codes, etc.). However, these memories fundamentally have two important limitations, which we proceed to outline.

These ideas about distributed memories were preceded by Denis Gabor's seminal article "Holographic model of temporal recall," published in 1968 [27]. Furthermore, the concept of neural vector and the idea of distributed storage of information were framed in an influential paradigm, that of vector symbolic architectures (VSA) [28]. VSA has extremely versatile applications, such as seeking to solve difficult problems in linguistics [28] and the extension of holographic memories to various domains of biology and computing [29–33]. In this framework, the notion of hyperdimensional computing emerged, which bases computation on large random vectors and distributed representations [30]. Let us mention that a realist model of a biological brain—large but of limited scale—[34] with specific neural modules for information recognition and processing functions, can organize the activity of this brain by means of neural vectors whose components are neuronal signals imitated from real neurobiology.

The storage capacity of these memories is limited. The more associated pairs are stored, the more interferences arise on recall. In fact, the authors who proposed these memories studied the limit at which the signal/noise ratio invalidates the capacity of these matrix memories to be operative. However, the memory's disability limit is protected when the matrix dimension is large. The model also allows for the implementation of forgetting mechanisms that extend the useful lifetime of the memories.

Perhaps the most serious limitation is the inability of these memories to modulate associations through contexts. As an example, let us imagine that a memory is sought to associate the neural image *f* of an animal with the different names that this animal has in two different languages encoded by the context vectors *p* and *p**. If one seeks to associate different pairs (*p, f*) and (*p*, f*) with two different vectors g(*p*) and g(*p**) that represent the name of the animal in languages *p* and *p**, respectively, matrix memories cannot do so. This mathematical failure can be demonstrated in various ways (see Hinton [35]).

In the 1980s, various solutions to the context problem were found. The most influential solution was discovered and rediscovered several times and consisted of creating neural models where, between the layer of neurons that received the input and the layer that generated the output, other connected neural layers were interspersed that transported and processed the input to



Life's but,
And by opposing
That struts and frets,
To be, or not to be,
And then is heard no more.
, full of sound and fury,
Signifying nothing. a sea of troubles
end them.
a walking shadow
his hour upon the stage
that is the question:
It is a tale Told by an idiot
Whether 'tis nobler in the mind to suffer
The slings and arrows of outrageous fortune,
Or to take arms against
a poor player,

Life's but a walking shadow, a poor player,
That struts and frets his hour upon the stage,
And then is heard no more. It is a tale
Told by an idiot, full of sound and fury,
Signifying nothing.

To be, or not to be, that is the question:
Whether 'tis nobler in the mind to suffer
The slings and arrows of outrageous fortune,
Or to take arms against a sea of troubles
And by opposing end them.

FIGURE 1 | On the left, a lexical mix of words and signs that make up parts of two famous Shakespeare monologues is shown. On the right, we show how the appropriate inputs reorganize this scattered information and reconstruct the texts.

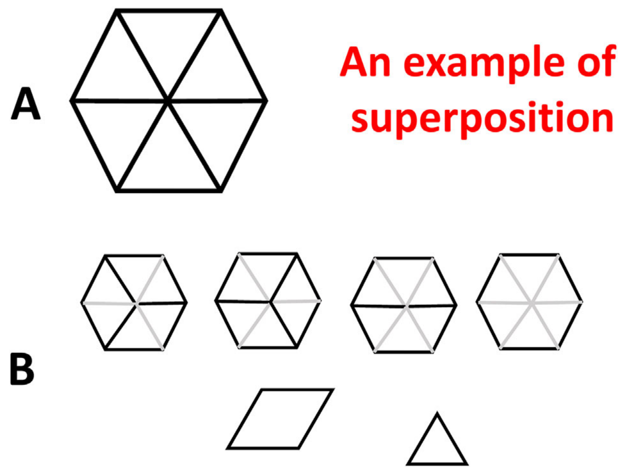


FIGURE 2 | The image shown in (A) includes, superimposed, the various images shown in (B).

the output. These intermediate layers, sometimes called “hidden layers,” significantly expanded the learning capacities of these MSs and solved the context problem. Multi-layer systems were trained by a powerful algorithm that achieved error minimization in associations by backpropagating the adjustments of the synaptic weights of the model (simply called “backpropagation”). A classic reference of this type of multi-layer memory is [36].

The expansion of computational power in recent decades has also allowed us to refine these multi-layered, trainable memory models and generate a process known as “deep learning,” so important in today’s AI algorithms. Recently, McClelland and Botvinick [37] published an outline of deep learning from the perspective of human memory psychology.

However, there is another alternative to solve the context problem. In the second half of the 1980s, three independent investigations converged on the same kind of solution: composing from the context vector p and the input vector f a new vector by means of the tensor product (also called Kronecker product) of both vectors [5, 38, 39]. This multiplicative composition expands the dimension of the input to become the product of the dimensions of p and f. The memory matrix expands in complexity but completely solves the context problem while preserving for the theory all the power of matrix algebra [40].

To show the theoretical power of multiplicative contextualization, let us point out that in one of the papers introducing the method [5], context-dependent memories can associate the image of an object with two different outputs representing its name in two different languages; they can also represent the operations of formal logic and implement procedural memories.

In one of the processes mentioned, multilayer networks or tensor composition, solves the branching problem that we illustrate in Figure 3.

In the next section we present our “memory gate” hypothesis. We have previously carried out a mathematical exploration of the idea to evaluate its formal consistency within the framework of memory models [41]. To do this, we use multiplicative MSs and analyze the interaction of the various modules that make up the gate model.

However, our priority here is to point out that there are empirical indications that suggest the existence of this gate. We will then show a configuration of neural networks that implement the gate, where the important feature is the topology of the model, or equivalently, the set of functional relationships between the modules that compose it. As a corollary, we indicate something obvious: if this MG can be found, the way it operates, whether through multiplicative contexts or via contextualization by multilayer systems or by any other procedure, will depend solely on biological reality and not on the preferences of modelers.

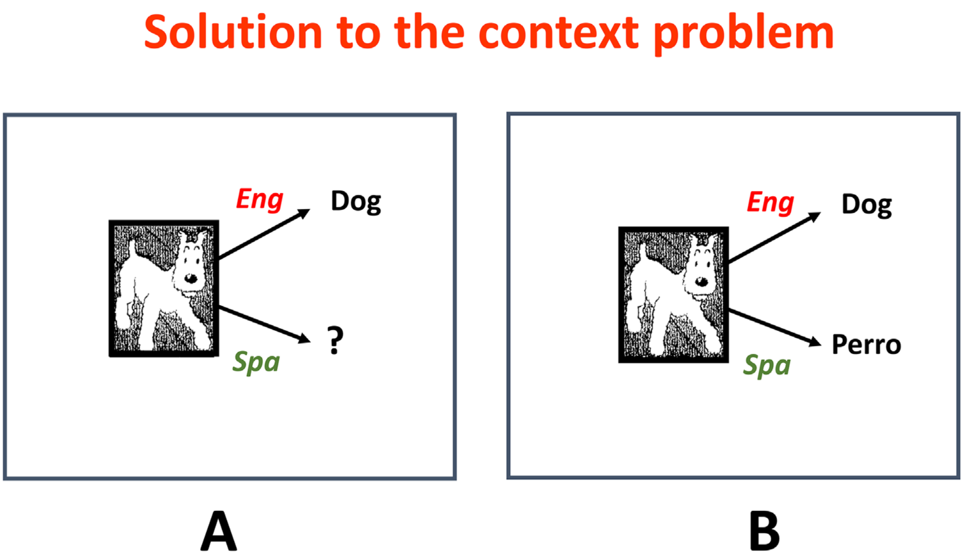


FIGURE 3 | Panel A illustrates a memory that is limited to being trained in an English language context, and where the image of a dog can only be associated with its name in English; in a Spanish language context, it does not give any response (?). Panel B shows a memory that modulates its associations by contexts and can give two different responses to the same image depending on the linguistic context. In this representation we assume that the image of the dog, the linguistic contexts (Eng, Spa) and the two responses (Dog, Perro) are extended vectors with each category (image, context, name) having its own specific dimension. Image of the dog drawn by Cristina Arruti, reproduced with permission.

4 | Memory Gate Hypothesis

We begin the presentation of our model by describing situations that are frequently experienced by almost all people. Each situation below describes transient and minor memory failures.

Situation 1. Let us imagine the following. At a concert a high school teacher observes an elegant gentleman near her. His face appears to be familiar, but she is unable to remember it. Given this situation, we can anticipate three possible scenarios:

A. On returning home she suddenly remembers that this man is a librarian whom she sporadically meets at the National Library.
B. After returning home, she sees a book on a table and immediately remembers him.
C. A long time passes, but when she returns to the library and meets the librarian, she wonders where she saw him in the past.

Case A seems mysterious because the memory arises without the person understanding how it happens. Case B is clearer, since the association of the book with the face at the concert allows her to identify him. Case C indicates another frequent occurrence, which is the fleeting memory of certain unimportant events.

Situation 2. A journalist wants to remember the name of an actress he admires, although he can only recall the first letter of her surname or a few syllables. However, if he manages to conjure up her face in his imagination or see her in a scene of a film, the whole name appears in his mind.

Situation 3. After many decades of not riding a bicycle, a singer rents one during her vacation at the seashore and starts riding it as if time did not pass.

Situation 4. A lawyer watches on the TV that a former classmate has just been appointed minister of Transportation. Immediately, “buried” episodes from his teenage years suddenly come to mind. He recalls that both were spectators in a riotous football match, left the stadium, went to the movies, and ended up chatting in an ice cream parlor. Together with this episode, other forgotten stories emerge in a long chain of memories that occurred during their student days.

In Situation 1 the librarian’s face is associated with events in the context of the library, in Situation 2 the name is associated with the actress’s face, in Situation 3 the presence of the bicycle reactivates a procedural memory that allows her to ride it, and in Situation 4 the mention of a former high school classmate awakens memories of episodes experienced together in their students days.

These contextual triggers lead us to postulate the following assumptions:

(H1) Consolidated MSs store data along with their contexts.

(H2) Access to the MS is filtered by a MG that allows the key pattern and the experienced context to pass through. However, if the MS does not recognize the “key pattern-context” pair, the MG replaces the original context with successive contexts it receives from a contextual network. If the appropriate context for the key pattern is among the latter, the memory identifies the pattern, and the search ends.

Note that in our conception, the search ends when consolidated memory can finally connect the association. The association in

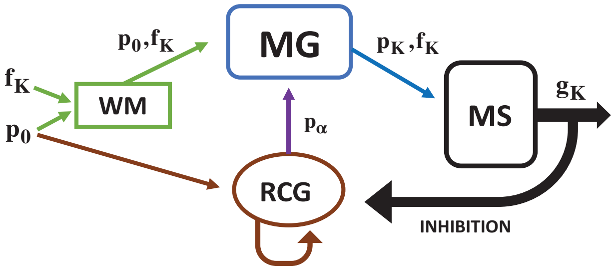


FIGURE 4 | Network of modules that support the memory gate (MG), which receives the f_K (key input) and p_0 (initial context) vectors from a working memory (WM) and sends them to the MG. From here, the contexts not accepted by the memory system (MS) are replaced by a set of contexts p_α cyclically emitted by the random context generator (RCG). If a p_K context appears to fit the input, the MS identifies it and generates a g_K output vector that inhibits the contextual network and ends the process.

memory can be made when the key pattern is accompanied by the appropriate context. Also, this association, whose uncomfortable expectation is followed by subjective satisfaction—possibly linked to the “Aha!” experience [42]—turns off the contextual web.

(H3) Recognition without external “clues,” as in Case A of Situation 1, suggests that there is an endogenous mechanism for storing and emitting contexts, a neural network that we will call random context generator (RCG). This network contains many contexts acquired throughout an individual’s life and has the capacity to emit contexts to the Gate if it is not inhibited. We will assume that it is activated by the incoming context and inhibited by the output of the consolidated memory.

It is important to establish the presence of perceptual patterns so familiar they are never forgotten under physiological conditions, for example, the faces and voices of our parents or children. In these cases, we assume the variety of contexts stored in these patterns is so extensive that it is extremely difficult for identification to fail. We will see in the next section how this is no longer the case in the presence of severe cognitive impairments. We show in Figure 4 the neural modules that sustain the MG.

The hypothesis about the existence of MG and the modules that support it, assumes that the dimensions of the neural vectors are determined by the physical neural systems involved. Here we do not impose any neurocomputational model on the modules participating in Figure 4, except for the adoption of the vector paradigm. In a previous work [41], we modeled these modules using matrix memories and composing key vectors and contexts by tensor products. In the next section we analyze some empirical consequences that can be drawn from the MG hypothesis.

We emphasize that in physiological situations of transient forgetting, recognition will depend on the competition between the retention time of the patterns in the WM and the appearance of the appropriate context. This time depends on the cycles of context replacement in the RCG. The RCG can be an anatomically fixed neural network, whose contexts arise from the person’s experience, but where synaptic connections are modulated by the interplay of inhibitory and activation modulators. Their interplay results in the existence of a wide variety of functional subnetworks that act at different times. In Figure 5, we show a simple drawing to illustrate the model. The technical details were shown in [41].

It is interesting to note the similarity between the impossibility of identifying or naming a person or thing we know through random searching in a contextual network—an everyday experience we describe in the article—and the experience of unconsciously solving a problem we have been meditating intensely until the solution appears by surprise, sometimes in the middle of sleep. Perhaps in this widely known and reported situation in the field of science (particularly in mathematics [43]) and other areas there is also a random and unconscious search in our brain until suddenly all the pieces fit together and the solution appears as if by magic.

If the modules shown in Figure 4 were to exist in the true anatomical-functional organization of the human brain, they may be distributed among several regions of the brain. We have already seen something similar in a previous section with the anatomical location of MSs and with the complexity of context storage in the brain [15, 21]. Perhaps MG is also distributed in several regions of the brain. Also, finding the components of MG may be a very difficult task. However, as we shall see, the various stages of AD would provide a path for establishing the existence and the properties of MG.

5 | Memory Gate and Alzheimer’s Disease

So far, we have postulated the existence of a MG based on observations of banal and transitory difficulties in memory recollection that occur in the lives of all human beings, regardless of age. However, in this section, we want to argue that if this gate hypothesis were consistent with a neurobiological substrate, then it would have consequences for understanding the pathological mechanisms of AD, and eventually for its prevention. Indeed, as will be argued in this section, this MG could be a trigger zone of cascade events that lead to a state of irreversible neurodegeneration, destroying memory structures that in early stages of AD appear to be very little altered. Also, as a corollary, it is a privileged zone to focus on preventive therapies.

Dementia is a highly prevalent condition [44] whose main risk factor is age [4], so the number of affected adults could increase dramatically in countries whose demography trends toward a distribution with a larger weight for older adults. This fact poses a challenge to the availability of health care systems and the cost of social welfare [45].

AD is the most common cause of dementia (about 80% of all cases) and its prevalence for people over 65 years of age has been estimated, for example, between 10% and 19% in the United States, depending on the characteristics of the populations [46] and the diagnostic criteria used in the studies [47].

According to DSM-5 [48], starting from a mild, non-specific cognitive disorder not yet affecting the daily functional life of a person, progression to AD involves meeting the following three

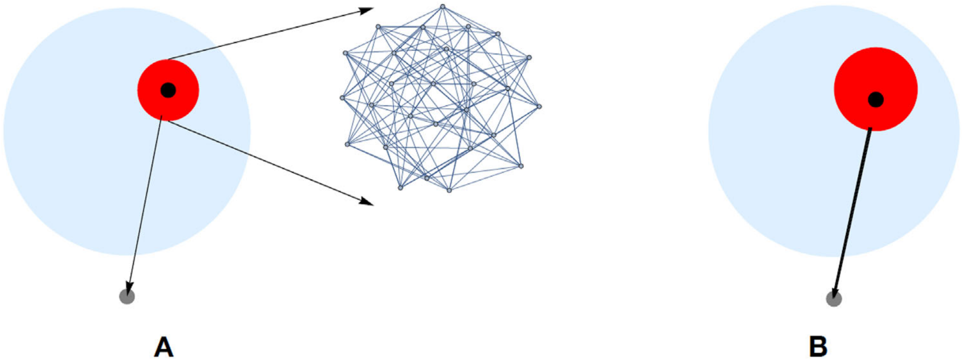


FIGURE 5 | (A) In the large universe of contexts (light blue circle) there is a contextual web, the red circle which we illustrate as a tangled network of nodes (contexts) and lines (transition probabilities) of a Markov chain directly associated with the key input pattern and the final matching context (gray circle). The search starts somewhere (black dot), randomly moves around the transitory red states before arriving at the gray circle. The arrow is a condensed way to express those nodes within the red circle transitioning to the final context, which is an absorbing state—once the final context is recognized, the search ends. We estimate the search time t_S as a mean first passage time (MFPT)—the average of a distribution of random first arrival times from the initial state to the final context. If t_S is smaller or larger than the holding time T the search is successful or unsuccessful. (B) If the subject is tenacious and capable, now or later, to expand the cluster of contexts (larger red circle) or to increase the strength of certain critical transitions into the final state, a search, previously unsuccessful, may now succeed. As more channels become available (slightly thicker arrow) the MFPT decreases, and the probability of success would be higher. Simulations of simplified models and the calculation of MFPT's are given in [41].

criteria: (1) clear evidence of decline in memory and learning, (2) steadily progressive and gradual decline in cognition without extended plateaus, and (3) absence of other neurological or systemic disease, or condition likely contributing to cognitive decline. The predominant clinical presentation is the episodic memory deficit characterized by impaired free recall that is not normalized by cueing [49].

But the definitive diagnosis of AD is still brain autopsy [50] with recognition of cortical atrophy, the presence of amyloid-predominant neuritic plaques, and of tau-predominant neurofibrillary tangles in patients who have suffered progressive and ultimately disabling neurocognitive deterioration [48]. There are also cases related to genetic and familial origin, typically of early onset, which can be diagnosed by the presence of specific mutations.

The development of in vivo measures of AD pathology via positron emission tomography (PET) imaging has opened new possibilities for the study of pathological mechanisms and diagnosis of the disease. PET imaging has allowed visualization of the spatial distribution of β-amyloid plaques since the mid-2000s [51], but it was not until a decade later that neurofibrillary tangle pathology became selectively detected [52].

Although the possibility of visualizing tau protein deposits is very recent, some conclusions suggest a correlation between the progression of clinical symptoms and certain neurohistological findings. The pathological substrate of AD is a widespread dissemination of intracellular deposition of tau neurofibrillary tangles departing from the MTL and the presence of pathological intercellular cortical deposition of amyloid-β neuritic plaques [53]. Amyloid-ß alone does affect cognition, but these may be relatively weak and take years to develop [54, 55]. Cognitively normal individuals with amyloid-β deposits have higher levels of tau in the MTL and inferior temporal cortex compared to those with no or low levels of amyloid [56–59].

The initial stages of AD development reflect a necessary interaction between cortical intercellular deposition of amyloid-β and the presence of tau in the medial temporal lobe. The process most probably begins with a slow deposition of amyloid-β in the cortex—this preclinical process unfolds decades before clear neurodegeneration and clinical symptoms of dementia are present—leading to an elevated tau, which in turn provokes neurodegeneration and finally, to cognitive decline [60]. There is extensive evidence for this model from human imaging data [61].

It has also been found that the accumulation of MTL tau, which may not be linked to AD, usually precedes the deposition of cortical amyloid-β in cognitively healthy older people [61]. The relationship between these two proteins is associated with spread of tau out of the MTL into the medial parietal, lateral parietal and temporal cortices. This condition displays neurodegeneration with a similar topography to tau deposition, and is followed by cognitive decline and eventually, dementia [61]. Necroptosis, a programmed cellular death that in contrast to apoptosis activates inflammation, has recently been attributed to the neurodegeneration mechanism responsible for the extensive synaptic and neuronal loss observed in AD brains. It has also been linked to the appearance of tau pathology and the presence of granulovacuolar neurodegeneration vesicles [62].

Early diagnosis is important because the rate of cognitive decline can be slowed down with medication. Besides, types of dementia other than AD involve different and specific treatment approaches. However, the insidious onset of AD and the gradual progression of behavioral-cognitive symptoms renders diagnosis of the early stages **of AD** problematic. Predicting which cases with mild cognitive impairment will ultimately progress to Alzheimer's would be very helpful.

In this scenario, delayed recall in episodic memory has been found to be a robust predictor of progression toward AD [63–65]. Much current research is focused on the development of biomarkers, capable of detecting early signs of the disease or accurately predicting the risk of developing it. Biomarkers, such as tau in cerebrospinal fluid and especially amyloid levels in conjunction with neuroimaging findings, for example, hippocampal atrophy, have been integrated with cognitive assessments to enhance predictive accuracy [66–68]. Recent advances in AI-based neural networks promises increased predictive accuracy of the onset of AD [69, 70] and may suggest new disease mechanisms, such as disruption of complex patterns in brain connectivity [71]. Let us mention in passing that, regarding neuroimaging, some researchers have expressed serious doubts about the significance of the information provided by functional brain images. These doubts arise from the fact that these images, with current techniques, are captured under conditions that seriously decontextualize the cognitive activities they are intended to explore [72, 73].

Of particular importance in support of our hypothesis are two facts that we present below. First, the observation that in early stages, Alzheimer's patients have "good" and "bad days" in their cognitive functioning and access to semantic and episodic memory. This is a well-known clinical observation: patients with mild/moderate disease experience daily fluctuations in recognition and memory access to well-installed memories [74]. Why does a mother with moderate AD does not recognize her daughter on a given day? From the network of modules in Figure 4 we may recognize that the mother's memory of her daughter is associated with a wide variety of contexts and perhaps days later she will be recognized again. What did happen that day? If the MG fails, the image of her daughter, no matter the clothes she wears or the words she speaks, does not pass the MG and cannot access the semantic memory. In the absence of neural damage, the context network activity is not noticed because her daughter is always accompanied by the "good contexts". This suggests that in early stages of AD, where there is only mild neuronal damage, the hypothetical MG shows functional fluctuations that explain the "good and bad days" [74]. However, if the MG is eventually destroyed, fluctuations will no longer exist, memory recollection becomes impossible, and the trophic neuronal actions of the gate itself may trigger subsequent degeneration.

Second, recent experiments with animal models have shown that in early stages of AD, neurons that store information of a memory trace (memory engram) can be activated with optogenetic techniques, suggesting that the memory storage process is preserved in early stages of the disease [75]. There was a long-standing debate among researchers about whether memory impairment was caused by a degradation or a failure to access the information from the semantic network. These experiments suggest that memory disorders in early stages of the disease would rest almost solely on the recall process [75]. Similar mechanisms appear to be present in other amnesic conditions [76, 77].

Although the speed of cognitive decline varies among individuals and can be slowed with medication, there are currently no known treatments to prevent or stop the progression of dementia. The hardship to individuals and the socioeconomic burdens for caregivers and society will increase enormously with the rising population of elderly people unless effective interventions and programs are developed [78]. The gate hypothesis for access to memories we propose could provide another way of attacking the development and progression of the disease. In effect, if there were a localized gate with an anterograde neurotrophic function, acting on this neuronal module could improve access to memory or, in the best of cases, prevent the progression of AD. Also, if the gate were a mechanism of contextualization carried out on the dendrosomatic tree of neurons that support consolidated memories spread across various regions of the cortex, its investigation and description would help us understand the pathophysiological processes of the disease and eventually, guide us to develop new therapeutic targets.

6 | Concluding Remarks

The existence of a gateway to access memory could explain many experiences of daily life and the fluctuating symptomatology in the early stages of AD. The everyday experience of being blocked when recognizing or accessing a known name together with the clinical and experimental data indicating that in early stages of AD memories are correctly installed while there exists an alteration in their retrieval, point to an underlying neural mechanism that facilitates or prevents access to information. The MG hypothesis offers explanations for transient blockades to memory access and would suggest these impediments as probable evidence of an unknown and fundamental neural structure.

Our main goal was to postulate the existence of a neural gate that allows entry to an established memory and to propose a plausible neurocomputational mechanism for this gate. As we have argued, the existence of this gate could have important implications for understanding and developing therapeutic approaches to AD. If the neurons of the hypothetical MG play a trophic role downstream in the neural pathway, the deterioration of the gate may explain the origin of the chain of events that lead to severe forms of AD, and it may suggest ways of preventing the cascade of events that guide this neurodegenerative process.

Our second goal is therefore to draw attention to the experimental community to the possibility of searching, locating and identifying this gate. Thanks to the advanced state of brain exploration techniques, the latter is possible today. Various functional neural imaging or electrophysiological techniques, both in situations of fleeting memory alterations in cognitively normal people and in people going through early stages of AD, can explore the existence of the gate. The experiments mentioned by Aminoff, Schacter and Bar [21] on the neural localization of context processing, as well as the work of Huth et al. [17] elucidating the structure of the semantic network, show the power of current techniques to "dissect" fine aspects of neural processing.

We cannot rule out that the neural structures involved in the gate may already be known and probably are. What would be necessary is to test, with attention now focused on the concept of the existence of a gate to memory, the role of the gate in one of these already known structures and its functioning. Recent works point to the existence of a developmental hierarchy within the brain [79, 80], giving rise to functional coordination and pointing to the mediofrontal cortex and the hippocampus as the critical network controller regions [81, 82]. These structures may be capable of exercising a controlling gating function.

Meta-analysis techniques applied to neuroimaging of early AD may also be a method for searching the gate [83]. For example, a very exciting possibility arises from the fact that early tau deposits in the MTL (which correlate with early cognitive impairments [53, 60, 61]) occur in an orderly fashion, starting from the entorhinal cortex and continuing through CA1 [53]. These areas are some of the first candidates to explore. In this regard, we note that perhaps the natural variability of functional regionalization in the brain [72], a consequence (obviously self-limiting) of neural plasticity, has resulted in a remarkable prevalence of publications containing meta-analyses of articles related to neuroimaging. As a very schematic measure, consider that Google Scholar lists between 18 000 and 20 000 papers, depending on the search terms, on brain imaging meta-analysis since 2024.

Another interesting observation is that patients with AD show, in addition to an early impairment of episodic memory, a deterioration of the neural "navigation system," causing some of them to feel strange in the familiar streets near their homes and become disoriented [84]. These situations could indicate that the notion of "memory gate" may be plural and have specificities for different types of memory. An alternative explanation could be that an alteration of navigation system would show that some of the neural structures that support navigation are also part of the access gate to episodic and semantic memories. This would provide further clues as to where to look for the gate.

Throughout this work, we have emphasized the importance of contexts. As early as 1952, psychiatrist W. Ross Ashby postulated that contexts (which he called "parameters") played a crucial role in generating adaptive processes by which living beings depended for survival [85]. The human brain is surely the most refined adaptive system created by Nature, and its memories store the basic strategies for survival apart from the physiological regulatory and instinctual schemes. Consequently, it is natural to envision that contexts in memories have a leading role in the adaptation to new and unexpected eventualities [40] (Figure 3 illustrates an elementary adaptation).

In summary, we hope that the MG hypothesis will inspire new ideas to identify the neural bases of access to MSs and suggest approaches to understand both, our common everyday experience as well as the severe processes that lead to irreversible neurodegeneration of AD.

Author Contributions

Eduardo Mizraji, Juan Lin and Andrés Pomi contributed to the writing of the manuscript.

Acknowledgments

A.P. acknowledges partial support from CSIC, Universidad de la República, and Agencia Nacional de Investigación e Innovación (ANII). We would like to thank both reviewers for their helpful comments and insights.

Data Availability Statement

Data sharing not applicable—no new data generated, or the article describes entirely theoretical research.

References

1. M. J. Kahana and A. D. Wagner, eds., *The Oxford Handbook of Human Memory* (Oxford University Press, 2024).

2. L. Nyberg, "Functional Brain Imaging of Episodic Memory Decline in Ageing," *Journal of Internal Medicine* 281 (2017): 65–74.

3. J. Krüger, M. Aaltonen, K. Aho, et al., "Incidence and Prevalence of Early-Onset Dementia in Finland," *Neurology* 103 (2024): 209654.

4. M. Prince, G. C. Ali, M. Guerchet, et al., "Recent Global Trends in the Prevalence and Incidence of Dementia, and Survival With Dementia," *Alzheimer's Research & Therapy* 8 (2016): 23.

5. E. Mizraji, "Context-Dependent Associations in Linear Distributed Memories," *Bulletin of Mathematical Biology* 51 (1989): 195–205.

6. C. H. Chatham and D. Badre, "Multiple Gates on Working Memory," *Current Opinion in Behavioral Sciences* 1 (2015): 23–31.

7. S. Verschooren, Y. Kessler, and T. Egner, "Evidence for a Single Mechanism Gating Perceptual and Long-Term Memory Information into Working Memory," *Cognition* 212 (2021): 104668.

8. C. A. O. Coelho, A. J. Mocle, A. D. Jacob, et al., "Dentate Gyrus Ensembles Gate Context-Dependent Neural States and Memory Retrieval," *Science Advances* 10, no. 31 (2024): adn9815.

9. Y. Liu, Z. Wang, C. Qiao, and Z. Xu, "GATE: Adaptive Learning With Working Memory by Information Gating in Multi-Lamellar Hippocampal Formation," *arXiv preprint* (2025), https://arxiv.org/pdf/2501.12615v1.

10. D. Norris, "Short-Term Memory and Long-Term Memory Are Still Different," *Psychological Bulletin* 143 (2017): 992–1009.

11. H. L. Roediger and O. Uner, "Critical Concepts in the Study of Learning and Memory," in *The Oxford Handbook of Human Memory*, ed. M. J. Kahana and A. D. Wagner. (Oxford University Press, 2024): 3–28.

12. D. L. Schacter and E. Tulving, "What Are the Memory Systems of 1994?," in *Memory Systems*, ed. D. L. Schacter and E. Tulving. (MIT Press, 1994): 1–38.

13. A. D. Baddeley and G. J. Hitch, "Working Memory," in *The Psychology of Learning and Motivation*, vol. 8, ed. G. H. Bower. (Academic Press, 1974): 47–89.

14. E. Tulving, "Are There 256 Different Kinds of Memory?," in *The Foundations of Remembering: Essays in Honor of Henry L. Roediger*, ed. J. S. Nairne, 3rd ed. (Psychology Press, 2007): 39–52.

15. T. Amer and L. Davachi, "Neural Mechanisms of Memory," in *The Oxford Handbook of Human Memory*, ed. M. J. Kahana and A. D. Wagner (Oxford University Press, 2024): 94–112.

16. A. G. Huth, S. Nishimoto, A. T. Vu, and J. L. Gallant, "A Continuous Semantic Space Describes the Representation of Thousands of Object and Action Categories across the human Brain," *Neuron* 76 (2012): 1210–1224.

17. A. G. Huth, W. A. De Heer, T. L. Griffiths, F. E. Theunissen, and J. L. Gallant, "Natural Speech Reveals the Semantic Maps That Tile human Cerebral Cortex," *Nature* 532 (2016): 453–458.

18. M. T. Ullman, "Contributions of Memory Circuits to Language: The Declarative/Procedural Model," *Cognition* 92 (2004): 231–270.

19. A. H. Lara and J. D. Wallis, "The Role of Prefrontal Cortex in Working Memory: A Mini Review," *Frontiers in Systems Neuroscience* 9 (2015): 173.

20. J. Eriksson, E. K. Vogel, A. Lansner, et al., "Neurocognitive Architecture of Working Memory," *Neuron* 88 (2015): 33–46.

21. E. Aminoff, D. L. Schacter, and M. Bar, "The Cortical Underpinnings of Context-Based Memory Distortion," *Journal of Cognitive Neuroscience* 20 (2008): 2226–2237.

22. E. Rosenfeld and J. A. Anderson, *Neurocomputing. Foundations of Research* (MIT Press, 1989).

23. J. A. Anderson, "A Simple Neural Network Generating an Interactive Memory," *Mathematical Biosciences* 14 (1972): 197–220.

24. T. Kohonen, “Correlation Matrix Memories,” *IEEE Transactions on Computers* 100 (1972): 353–359.

25. J. A. Anderson, *An Introduction to Neural Networks* (MIT Press, 1995).

26. T. Kohonen, *Associative Memory. A System-Theoretical Approach* (Springer-Verlag, 1977).

27. D. Gabor, “Holographic Model of Temporal Recall,” *Nature* 217 (1968): 584.

28. R. W. Gayler, “Vector Symbolic Architectures Are a Viable Alternative for Jackendoff’s Challenges,” *Behavioral and Brain Sciences* 29 (2006): 78–79.

29. D. Kleyko, M. Davies, E. P. Frady, et al., “Vector Symbolic Architectures as a Computing Framework for Emerging Hardware,” *Proceedings of the IEEE* 110 (2022): 1538–1571.

30. P. Kanerva, “Hyperdimensional Computing: An Introduction to Computing in Distributed Representation With High-Dimensional Random Vectors,” *Cognitive Computation* 1 (2009): 139–159.

31. T. A. Plate, “Holographic Reduced Representations,” *IEEE Transactions on Neural Networks* 6 (1995): 623–641.

32. D. Aerts, M. Czachor, and B. D. Moor, “Geometric Analogue of Holographic Reduced Representation,” *Journal of Mathematical Psychology* 53 (2009): 389–398.

33. D. Kleyko, E. Osipov, A. Senior, A. I. Khan, and Y. A. Sekerciogglu, “Holographic Graph Neuron: A Bioinspired Architecture for Pattern Processing,” *IEEE Transactions on Neural Networks and Learning Systems* 28 (2017): 1250–1262.

34. C. Eliasmith, T. C. Stewart, X. Choo, et al., “A Large-Scale Model of the Functioning Brain,” *Science* 338 (2012): 1202–1205.

35. G. E. Hinton, “Implementing Semantic Networks in Parallel Hardware,” in *Parallel Models of Associative Memories* ed. G. E. Hinton, and J. A. Anderson (Lawrence Erlbaum Associates, 1989), 191–217.

36. D. E. Rumelhart, G. E. Hinton, and R. J. Williams, “Learning Representations by Back-Propagating Errors,” *Nature* 323 (1986): 533–536.

37. J. L. McClelland and M. M. Botvinick, “Deep Learning: Implications for Human Learning and Memory,” in *The Oxford Handbook of Human Memory* ed. M. J. Kahana and A. D. Wagner (Oxford University Press, 2024), 215–243.

38. M. S. Humphreys, J. D. Bain, and R. Pike, “Different Ways to Cue a Coherent Memory System: A Theory for Episodic, Semantic, and Procedural Tasks,” *Psychological Review* 96 (1989): 208–233.

39. P. Smolensky, “Tensor Product Variable Binding and the Representation of Symbolic Structures in Connectionist Systems,” *Artificial Intelligence* 46 (1990): 159–216.

40. J. C. Valle-Lisboa, A. Pomi, and E. Mizraji, “Multiplicative Processing in the Modeling of Cognitive Activities in Large Neural Networks,” *Biophysical Reviews* 15 (2023): 767–785.

41. A. Pomi, J. Lin, and E. Mizraji, “A Memory Access Gate Controlled by Dynamic Contexts,” *Bio Systems* 241 (2024): 105232.

42. M. Becker and R. Cabeza, “The Neural Basis of the Insight Memory Advantage,” *Trends in Cognitive Sciences* 29(3) (2005): 255–268.

43. J. Hadamard, *An Essay on the Psychology of Invention in the Mathematical Field* (Dover Publications, 1954).

44. J. J. Manly, R. N. Jones, K. M. Langa, et al., “Estimating the Prevalence of Dementia and Mild Cognitive Impairment in the US,” *JAMA Neurology* 79 (2022): 1242–1249.

45. GBD 2019 Dementia Forecasting Collaborators., “Estimation of the Global Prevalence of Dementia in 2019 and Forecasted Prevalence in 2050: An Analysis for the Global Burden of Disease Study 2019,” *Lancet Public Health* 7 (2022): e105–e125.

46. Alzheimer’s Association., “2024 Alzheimer’s Disease Facts and Figures,” *Alzheimer’s & Dementia* 20 (2024): 3708–3821.

47. R. S. Wilson, D. R. Weir, S. E. Leurgans, et al., “Sources of Variability in Estimates of the Prevalence of Alzheimer’s Disease in the United States,” *Alzheimer’s & Dementia* 7 (2011): 74–79.

48. American Psychiatric Association., *Diagnostic and Statistical Manual of Mental Disorders, DSM-5*, 5th ed. (American Psychiatric Publishing, 2013), 611–614.

49. A. Tsiakiri, C. Bakirtzis, S. Plakias, et al., “Predictive Models for the Transition From Mild Neurocognitive Disorder to Major Neurocognitive Disorder: Insights From Clinical, Demographic, and Neuropsychological Data,” *Biomedicines* 12 (2024): 1232.

50. T. G. Beach, S. E. Monsell, L. E. Phillips, and W. Kukull, “Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010,” *Journal of Neuropathology & Experimental Neurology* 71 (2012): 266–273.

51. W. E. Klunk, H. Engler, A. Nordberg, et al., “Imaging Brain Amyloid in Alzheimer’s Disease With Pittsburgh Compound-B,” *Annals of Neurology* 55 (2004): 306–319.

52. D. T. Chien, S. Bahri, A. K. Szardenings, et al., “Early Clinical PET Imaging Results With the Novel PHF-Tau Radioligand [F-18]-T807,” *Journal of Alzheimer’s Disease* 34 (2013): 457–468.

53. E. C. Mormino and W. J. Jagust, “Cognitive Aging and the Transition to Early Alzheimer’s Disease,” in *The Oxford Handbook of Human Memory*, ed. M. J. Kahana and A. D. Wagner (Oxford University Press, 2024), 1727–1754.

54. M. C. Donohue, R. A. Sperling, R. Petersen, et al., “Association Between Elevated Brain Amyloid and Subsequent Cognitive Decline among Cognitively Normal Persons,” *JAMA* 317 (2017): 2305–2316.

55. W. J. Jansen, R. Ossenkoppele, B. M. Tijms, et al., “Association of Cerebral Amyloid-β Aggregation With Cognitive Functioning in Persons Without Dementia,” *JAMA Psychiatry* 75 (2018): 84–95.

56. S. N. Lockhart, M. Scholl, S. L. Baker, et al., “Amyloid and Tau PET Demonstrate Region-Specific Associations in Normal Older People,” *Neuroimage* 150 (2017): 191–199.

57. A. Maass, S. N. Lockhart, T. M. Harrison, et al., “Entorhinal Tau Pathology, Episodic Memory Decline, and Neurodegeneration in Aging,” *Journal of Neuroscience* 38 (2018): 530–543.

58. R. A. Sperling, E. C. Mormino, A. P. Schultz, et al., “The Impact of Amyloid-Beta and Tau on Prospective Cognitive Decline in Older Individuals,” *Annals of Neurology* 85 (2019): 181–193.

59. P. Vemuri, V. J. Lowe, D. S. Knopman, et al., “Tau-PET Uptake: Regional Variation in Average SUVR and Impact of Amyloid Deposition,” *Alzheimer’s & Dementia* 6 (2017): 21–30.

60. C. R. Jack, D. S. Knopman, W. J. Jagust, et al., “Tracking Pathophysiological Processes in Alzheimer’s Disease: An Updated Hypothetical Model of Dynamic Biomarkers,” *Lancet Neurology* 12 (2013): 207–216.

61. W. Jagust, “Imaging the Evolution and Pathophysiology of Alzheimer Disease,” *Nature Reviews Neuroscience* 19 (2018): 687–700.

62. S. Balusu and B. De Strooper, “The Necroptosis Cell Death Pathway Drives Neurodegeneration in Alzheimer’s Disease,” *Acta Neuropathologica* 147 (2024): 96.

63. J. J. Gomar, M. T. Bobes-Bascaran, C. Conejero-Goldberg, et al., “Utility of Combinations of Biomarkers, Cognitive Markers, and Risk Factors to Predict Conversion From Mild Cognitive Impairment to Alzheimer Disease in Patients in the Alzheimer’s Disease Neuroimaging Initiative,” *Archives of General Psychiatry* 68 (2011): 961–969.

64. J. S. Lee, S.-K. Cho, H. J. Kim, et al., “Prediction Models of Cognitive Trajectories in Patients With Nonamnestic Mild Cognitive Impairment,” *Scientific Reports* 8 (2018): 10468.

65. D. Gallagher, A. N. Mhaolain, R. Coen, et al., “Detecting Prodromal Alzheimer’s Disease in Mild Cognitive Impairment: Utility of the CAMCOG and Other Neuropsychological Predictors,” *International Journal of Geriatric Psychiatry* 25 (2010): 1280–1287.

66. T. Pereira, L. Lemos, S. Cardoso, et al., “Predicting Progression of Mild Cognitive Impairment to Dementia Using Neuropsychological Data: A Supervised Learning Approach Using Time Windows,” *BMC Medical Informatics and Decision Making* 17 (2017): 110.

67. S. Palmqvist, J. Hertze, L. Minthon, et al., “Comparison of Brief Cognitive Tests and CSF Biomarkers in Predicting Alzheimer’s Disease in Mild Cognitive Impairment: Six-Year Follow-Up Study,” *PLoS One* 7 (2012): 38639.

68. L. Yue, D. Hu, H. Zhang, et al., “Prediction of 7-Year’s Conversion From Subjective Cognitive Decline to Mild Cognitive Impairment,” *Human Brain Mapping* 42 (2021): 192–203.

69. A. Javeed, A. L. Dallora, J. S. Berglund, et al., “Early Prediction of Dementia Using Feature Extraction Battery (FEB) and Optimized Support Vector Machine (SVM) for Classification,” *Biomedicines* 11 (2023): 439.

70. A. Wolf, K. Ravienna, and E. Salobrar-Garcia, “Editorial: Early Indicators of Cognitive Decline, Editorial: Early Indicators of Cognitive Decline, Alzheimer’s Disease, and Related Dementias Captured by Neurophysiological Tools,” *Frontiers in Psychology* 15 (2024): 1393724.

71. C. Hohenfeld, C. J. Werner, and K. Reetz, “Resting-State Connectivity in Neurodegenerative Disorders: Is There Potential for an Imaging Biomarker?,” *NeuroImage: Clinical* 18 (2018): 849–870.

72. S. Frisch, “How Cognitive Neuroscience Could be More Biological and What It Might Learn From Clinical Neuropsychology,” *Frontiers in Human Neuroscience* 8 (2014):1–13.

73. A. Métraux and S. Frisch, “Some Critical Remarks on the Epistemology of Functional Magnetic Resonance Imaging,” *Science and Philosophy* 8 (2020): 63–74.

74. K. Rockwood, S. Fay, L. Hamilton, et al., “Good Days and Bad Days in Dementia: A Qualitative Chart Review of Variable Symptom Expression,” *International Psychogeriatrics* 26 (2014): 1239–1246.

75. D. S. Roy, A. Arons, T. I. Mitchell, et al., “Memory Retrieval by Activating Engram Cells in Mouse Models of Early Alzheimer’s Disease,” *Nature* 531 (2016): 508–512.

76. D. S. Roy, S. Muralidhar, L. M. Smith, and S. Tonegawa, “Silent Memory Engrams as the Basis for Retrograde Amnesia,” *Proceedings of the National Academy of Sciences USA* 114 (2017): E9972–E9979.

77. S. Poll, M. Mittag, F. Musacchio, et al., “Memory Trace Interference Impairs Recall in a Mouse Model of Alzheimer’s Disease,” *Nature Neuroscience* 23 (2020): 952–958.

78. N. I. H. National Institute of Neurological Disorders and Stroke., “Focus on Alzheimer’s Disease and Related Dementias,” Retrieved February 5, 2025, from https://www.ninds.nih.gov/current-research/focus-disorders/focus-alzheimers-disease-and-related-dementias.

79. J. Wright and P. Bourke, “Cortical Development in the Structural Model and Free Energy Minimization,” *Cerebral Cortex* 34(10) (2024): bhae416.

80. J. J. Wright and P. D. Bourke, “The Mesoanatomy of the Cortex, Minimization of Free Energy, and Generative Cognition,” *Frontiers in Computational Neuroscience* 17 (2023): 1169772.

81. P. Luu, D. M. Tucker, and K. Friston, “From Active Affordance to Active Inference: Vertical Integration of Cognition in the Cerebral Cortex through Dual Subcortical Control Systems,” *Cerebral Cortex* 34(1) (2024): 1–30.

82. D. M. Tucker and P. Luu, “Adaptive Control of Functional Connectivity: Dorsal and Ventral Limbic Divisions Regulate the Dorsal and Ventral Neocortical Networks,” *Cerebral Cortex* 34 (2023): 7870–7895.

83. V. I. Müllera, E. C. Cieslika, A. R. Laird, et al., “Ten Simple Rules for Neuroimaging Meta-Analysis,” *Neuroscience and Biobehavioral Reviews* 84 (2018): 151–161.

84. G. G. Tangen, M. H. Nilsson, E. Stomrud, et al., “Spatial Navigation and Its Association With Biomarkers and Future Dementia in Memory Clinic Patients Without Dementia,” *Neurology* 99 (2022): e2081–e2091.

85. W. R. Ashby, *Design for a Brain: The Origin of Adaptive Behavior* (Chapman & Hall, 1952).