

Review

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[Fabiano de Abreu Agrela Rodrigues](#) ^{*}, [Adriel Pereira da Silva](#) ^{*}, Francisco Kaiut ^{*}, Ravi Kaiut

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Review

Neurobiological Architecture of Early Alzheimer's Failure: A Structural and Biochemical Perspective

Fabiano de Abreu Agrela Rodrigues ^{1,*}, Adriel Pereira da Silva ^{2,*}, Francisco Kaiut ^{3,*} and Ravi Kaiut ³

¹ Centro de Pesquisa e Análises Heráclito (CPAH), Department of Neuroscience and Genomics, Brazil & Portugal

² Centro de Pesquisa e Análises Heráclito (CPAH), Department of Physics, Brazil & Portugal

³ Instituto Kaiut Yoga, Centro de Pesquisa e Análises Heráclito (CPAH) Departamento de Neurociências e Genômica

* Correspondence: contato@cpah.com.br (F.d.A.A.R.); adrielpsilv@gmail.com (A.P.d.S.); contato@cpah.com.br (F.K.)

Abstract

Alzheimer's disease is manifested by a pattern of asymmetric neurofunctional decline, with initial impairment in the consolidation of recent memories and relative preservation of remote information. This dissociation is related to the topography of synaptic degeneration and the biochemical selectivity of structures such as the hippocampus, entorhinal cortex, anterior cingulate cortex and dorsolateral prefrontal cortex. The reduction in the synthesis and transmission of neurotransmitters, especially acetylcholine and dopamine, is associated with loss of efficiency in episodic memory, executive functions and sustained attention. The loss of functional connectivity, measured by diffusion and functional imaging, shows that Alzheimer's failure is not only morphological, but also functional. Understanding this complex dynamic is fundamental for the development of preventive approaches and early interventions based on applied neuroscience.

Keywords: Alzheimer's disease; synaptic degeneration; functional connectivity; neurotransmitters; applied neuroscience

Introduction

Alzheimer's disease is a progressive neurodegenerative disorder characterized by structural and functional alterations in brain regions critical for memory, language, and adaptive behavior. Although traditionally associated with the presence of beta-amyloid plaques and tau neurofibrillary tangles, there is increasing evidence that loss of functional connectivity between neocortical, limbic, and subcortical regions precedes evident clinical signs. In this context, this article aims to analyze the role of synaptic failure, disintegration of the neurotransmission network and loss of efficiency in functional integration as foundations for understanding the pathophysiology of Alzheimer's.

Development

The initial manifestations of Alzheimer's disease show an asymmetric pattern of neurofunctional impairment, characterized by difficulty in acquiring new information, contrasting with the relative preservation of remote memories. This dissociation is directly related to the topography of synaptic degeneration, with typical onset in the entorhinal and hippocampal regions, critical areas for recent memory consolidation (Braak; Braak, 1991; Goriounova; Mansvelder, 2019). The selectivity of the impairment arises from the differential vulnerability between primary and associative cortical circuits, and from the synaptic architecture of these regions, which are more susceptible to the

neurotoxic action of hyperphosphorylated tau protein and β -amyloid plaques (Goriounova; Mansvelder, 2019).

The hippocampus, especially the CA1 and subiculum regions, presents an early reduction in synaptic density, while neocortical associative areas, responsible for storing long-term information, maintain relative functionality in the initial phases of the condition (Gómez - Isla et al., 1996). This pattern is consistent with histopathological findings and functional neuroimaging studies, which indicate an anterograde progression of synaptic failure, temporarily preserving the already consolidated circuits (Serrano-Pozo et al., 2011). Therefore, the initial clinical profile of the disease reflects not a global mnemonic anomaly, but a specific failure in the integration and codification of new experiences, supported by morphofunctional evidence.

In the neuropathological context of Alzheimer's disease, the hippocampus, particularly the CA1 sector and the dentate gyrus, presents a progressive reduction in synaptic density associated with the accumulation of beta-amyloid oligomers and hyperphosphorylated forms of tau protein, compromising the integrity of the trisynaptic circuit (GENGLER et al., 2007; ZHENG et al., 2020). This structural change has a direct impact on the efficiency of adult neurogenesis, especially in the subgranular zone of the dentate gyrus, where synaptic plasticity depends on a stable neurochemical environment and the integrity of cholinergic inputs from the nucleus basalis of Meynert (SCHNEIDER et al., 2009).

With the progressive installation of cholinergic dysfunction, intensified by neuronal loss in the nuclei magnocellular, there is a measurable and steady decline in the encoding of recent episodic memory, a function largely dependent on acetylcholine as a modulator of hippocampal activity (SCHMIDT et al., 2013). Such dynamics highlight the interdependence between the cholinergic and glutamatergic systems in maintaining synaptic homeostasis and the viability of neuroplasticity.

Acetylcholine is synthesized from choline and acetyl-CoA by the action of the enzyme choline acetyltransferase (ChAT), a process that occurs in the presynaptic terminals of cholinergic neurons. (MUSAR Ó et al., 2023). Choline is actively transported into neurons through a sodium-dependent mechanism, coupled to mitochondrial energetic metabolism (MUSAR Ó et al., 2023). In the early stages of Alzheimer's disease, a decrease in ChAT activity is observed, resulting in reduced acetylcholine synthesis (MUSAR Ó et al., 2023). This cholinergic deficiency mainly affects the hippocampus and the entorhinal cortex, crucial areas for memory consolidation (MUSAR Ó et al., 2023). The progressive decrease in the synaptic availability of acetylcholine compromises the efficient integration of contextual and spatial information, contributing to the cognitive deficits characteristic of the disease (MUSARÓ et al., 2023).

In the context of Alzheimer 's disease, the associative cortical regions responsible for storing the consolidated memories, such as the lateral temporal neocortex and parts of the posterior parietal cortex, tend to maintain their functional connections for longer periods (SQUIRE et al., 2004). This structural preservation allows long-term memories, already transferred and stabilized in these areas, to remain accessible, giving the individual the ability to report remote events with apparent clarity (SQUIRE et al., 2004). Consequently, this maintenance of old memories can mask initial cognitive deficits, delaying the clinical recognition of the disease (SQUIRE et al., 2004). Although recent temporal orientation is compromised due to hippocampal dysfunction, the recall of old information no longer depends on the functional integrity of the hippocampus, but rather on preserved neocortical connections (SQUIRE et al., 2004).

In Alzheimer's disease, the dysfunction of the anterior cingulate cortex, especially in layers III and V, compromises its modulating function between executive attention and affective integration, directly affecting the informational relevance filter and logical coherence, which impairs both working memory and the ability to make situational judgments (SILVA et al., 2008).

Simultaneously, the dorsolateral prefrontal cortex, responsible for data integration based on logic and planning, loses functional connectivity with episodic memory systems, which results in early impairment of executive functions, even before the appearance of explicit behavioral manifestations (MOURÃO JÚNIOR; MELO, 2009).

The functional decline observed in Alzheimer's disease does not follow a linear course. It is influenced by variations in secondary neurotransmitter systems, such as dopamine and norepinephrine, which also undergo significant changes throughout the neurodegenerative process (CHO et al., 2004). Dopamine, whose synthesis depends on the conversion of tyrosine into L-DOPA by the action of tyrosine hydroxylase, plays an essential role in motivational regulation and sustained attention (HAAVIK; TOSKA, 1998).

The reduction of dopaminergic transmission, especially in the mesocortical circuit that connects the ventral tegmental area to the prefrontal cortex, compromises the ability to maintain short-term goals and impairs the cognitive flexibility. Such executive disorganization, even in the presence of preserved consolidated memory, contributes to the early intensification of behavioral and motivational deficits associated with the clinical picture (CHO et al., 2004).

Throughout the neurodegenerative process observed in Alzheimer's disease, the integrity of connectivity between brain subregions is as critical as the molecular alterations. Specifically, the communication between the hippocampus and the medial prefrontal cortex, mediated by the uncinate fasciculus, demonstrates a significant reduction in its structural integrity. Studies using diffusion tensor imaging demonstrate this disconnection in the early stages of the disease (MORIKAWA et al., 2010). These findings reinforce the understanding that cognitive failure in Alzheimer's is not only due to neuronal death, but also due to the progressive loss of functional connectivity, the oscillatory synchronicity and biochemical efficiency in synaptic transmission.

The clinical approach to Alzheimer's disease must transcend the simplistic view of a sudden onset of symptoms. The pathology is established as a silent degenerative reorganization, whose roots lie in the molecular levels of synaptic transmission and in the patterns of connectivity between specific brain substructures. Studies indicate that alterations in the synthesis of neurotransmitters, such as acetylcholine, play a crucial role in the progression of the disease, directly affecting the cognitive function (KANDIMALLA; RAO; RANGANATHAN, 2011). Furthermore, the loss of integrity in neural connectivity, especially in the regions responsible for memory and learning, contributes significantly to the cognitive decline observed in patients with Alzheimer's (HE et al., 2024). Superficial interpretation of the initial signs compromises the time of intervention. A deep understanding of these dynamics, which range from neurotransmitter synthesis to interregional communication, is essential for the development of early interventions and preventive strategies based on applied neuroscience.

Methodology

This article adopts a theoretical-analytical design, based on a narrative review of open access scientific literature with verified DOI, including publications indexed in the PubMed, Scopus and ScienceDirect databases, in addition to original documents by Dr. Fabiano de Abreu Agrela Rodrigues. The selection criteria involved articles published between 1991 and 2024 that address synaptic mechanisms, cholinergic and dopaminergic failures, functional imaging and connectivity in Alzheimer's.

Discussion

Analysis of vulnerable cortical regions in Alzheimer's reveals a pattern of selective impairment, with early synaptic degradation in the hippocampal region, entorhinal cortex, anterior cingulate cortex and dorsolateral prefrontal cortex. The decrease in the availability of acetylcholine and dopamine compromises the efficiency of information integration, affecting the working memory, attention and executive function. The dysfunction between the hippocampal and frontal networks, via fasciculus uncinate, compromises the narrative coherence and temporal anchoring. The loss of oscillatory synchrony between these regions is an early marker of cognitive decline, identifiable by diffusion tensor and fMRI techniques. The nonlinearity of the decline is modulated by secondary

systems, such as dopamine and norepinephrine, whose decline impacts motivational and attentional regulation.

Final Considerations

It is concluded that Alzheimer's disease should be understood as a systemic degenerative process, which affects not only the brain morphology, but also the functional connectivity, the interregional integration and the neurochemical efficiency. The dissociation between recent and remote memory, the lack of coordination between cognitive networks and the decline in neurotransmission indicate the need for a multidimensional diagnostic approach. Prevention and early intervention depend on the recognition of these signs in their subclinical stages and the incorporation of applied neuroscience as a structuring axis of cognitive medicine.

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