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Neurobiological mechanism in cognitive decline: from synaptic dysfunction to large-scale neural network disruption

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Abstract:

Neurodegenerative diseases are characterised by progressive cognitive decline, traditionally attributed to the accumulation of beta-amyloid (Aβ) and tau pathology. However, growing evidence indicates that the diseases are not only caused by synaptic dysfunction but also a syndrome of large-scale network dysconnectivity. This review synthesised current findings on how synaptic dysfunction scales up to disrupt functional connectivity across brain networks. At the microscopic level, impaired long-term potentiation, enhanced long-term depression, and AMPA receptor dysregulation compromise synaptic plasticity. These local defects extend to macroscopic network breakdown, particularly within the default mode network (DMN) and hippocampal-prefrontal circuits. Neuroimaging techniques such as resting-state fMRI and positron emission tomography (PET) reveal consistent patterns of weakened connectivity and altered synchrony that closely correlate with deficits in episodic memory, executive function, and language. Importantly, effective connectivity within DMN has been shown to predict both the incidence and timing of neurrodegenerative diseases, even years before diagnosis, underscoring its value as biomarker. Furthermore, Aβ and tau accumulation preferentially disrupt DMN, linking molecular pathology with network-level dysfunction. Together, these findings support a synapse-network model of neurodegenarative diseases such as Alzheimer's disease, where local and global disruptions interact to drive cognitive decline. This framework highlights novel diagnostic opportunities and suggests that interventions preserving both synaptic and network integrity may hold promise for delaying disease progression.

Keywords: Neurodegenerative Disease; Synaptic Dysfunction; Default Mode Network.

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1. Introduction

Cognitive decline is the key characteristic of normal aging and neurodegenerative diseases, which is mainly manifested in loss of memory, executive function, language ability, attention, orientation and slower learning and processing speed. In general, people with neurodegenerative diseases have faster rate of cognitive decline due to synaptic dysfunction and large-scale neural network disruption. The aging population is steadily growing because of enhanced nutrition, advanced health care service and decreasing birth rate, which poses great challenges such as increasing demand for health and social care, higher economic burden to public health. Synaptic dysfunction and large-scale neural network disruption have been identified as the key processes in triggering the core pathology of neurodegenerative diseases. Their relation understanding is crucial for the discovery of early intervention and diagnosis, as well as offering a plausible route for targeted therapy.

Synapses are the connections of neurones and they are essential for neuronal signal transmission. Synaptic dysfunction is another important pathological hallmark of neurodegenerative diseases, and it is the main reason for cognitive decline. This emerging pathophysiological target is manifested by neuronal loss, and it is the major driver and significant early event of Alzheimers disease (AD) affecting memory, leaning and other cognitive functions. Soluble Aβ in neurodegenerative diseases such as AD, disrupt the normal function of synapses such as neuronal impulses transmission and plasticity and contribute to cognitive impairment [1]. Tau pathology is another key player of synaptic dysfunction, which is influenced by the beta-amyloid, but it is even more closely link to neurodegeneration and cognitive impairment [2]. Pathological Tau detaches and move into presynaptic and postsynaptic region with different effects by these two regions. Overall, pathological tau disrupts synapses by impairing vesicle release, reducing glutamatergic receptors, blocking dendritic spine maturation, disturbing mitochondrial function and promoting microglial synapse elimination, thus driving cognitive decline [3].

As the consequence of synaptic dysfunction, large-scale system exhibits impaired connectivity, correlating with cognitive decline. DMN is composed core regions such as the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobe, and it is highly vulnerable in AD. Once considered a task-negative network, the DMN is now recognised as crucial for high-order cognition, including memory, social processing, and self-referential thought. Numerous studies reports altered DMN connectivity in AD, supporting the view that dementia represents a syndrome of dysconnectivity. Emerging approaches focusing on effective connectivity, which models causal excitatory and inhibitory interactions, provide deeper insights into how synaptic dysfunction scales up to disrupt large-scale neural network and drive cognitive decline [4]. Amyloid pathology in 5XFAD mice disrupts hippocampal-prefrontal connectivity, leading to impaired adaptive decision-making. In naturalistic foraging tasks, mice exhibit rigid hippocampal CA1 coding, reduced sharp wave ripple (SWR) activity, and decreased behavioural flexibility under threat. These findings link amyloid-induced circuit dysfunction to cognitive decline, emphasising the role of hippocampal-prefrontal dynamics in supporting flexible memory-guided behaviour. The study highlights SWR disruption and corticolimbic network breakdown as key mechanisms and potential intervention targets in AD [5].

This review aims to systematically summarises the pathological mechanisms of cognitive decline from molecular and cellular levels, with particular emphasis on the causal relationship between synaptic pathology and alterations in neural network function. Clarifying the neurobiological mechanism in cognitive decline will not only advance our knowledge and the relationship, but also inform the development of novel therapeutic interventions targeting both early synaptic alterations and widespread network abnormalities. This review therefore emphasises the need to connect molecular mechanisms with network-level changes to inform targeted therapy.

2. Synaptic Pathology and Cognitive Impairment in Neurodegenerative Disease

2.1 Synaptic Dysfunction and Cognitive Decline

Synapses are the key component for neural information transmission and the connections of neurones. It is also an integral unit for learning, memory, and other cognitive functions. In the neurodegenerative diseases like AD and Parkinson's disease, the dysfunction of synapse is the significant characteristics for diagnosis at the early stage. Understanding the molecular mechanism and functional consequence is important for developing a new therapeutic approach, then eliminate the incidence of neurodegenerative disease.

2.1.1 Synaptic Dysfunction and Aβ

In neurodegenerative diseases, the accumulation of Aβ disrupts the normal function of synapses, result in deficiency of neural information transmission, neuronal plasticity, and the synaptic toxicity. Beta amyloid oligomers

exert neurotoxic effects by directly activating NMDA receptors (NMDARs), leading to intracellular Ca^{2+}overload and neuronal death. In xenopus oocyte, Aβ induced inward non-desensitising currents that were blocked by antagonists such as memantine, APV, and MK-801, with stronger responses in NR1/NR2A receptors than in NR1/NR2B. In cortical neurons, Aβ-induced Ca^{2+}overload was abolished by AP5 but only slightly reduced by the NR2B-selective blocker ifenprodil, suggesting preferential involvement of NR2A containing receptors. These findings highlight a subunit-specific mechanism through which Aβ disrupts Ca^{2+}homeostasis and synaptic signalling, ultimately contributing to toxicity and cognitive decline [6]. Therefore, the balance of long-term potentiation and depression (LTP/LTD) is disturbed, within impaired synaptic plasticity. These changes compromise the molecular substrates of learning and memory, linking beta amyloid accumulation directly to synaptic dysfunction and cognitive decline [7]. Therefore, targeting NR2A-mediated receptor activity may therefore represent a promising therapeutic strategy in AD.

2.1.2 Synaptic Dysfunction and Tau

Apart from that, Tau pathology leads to the synaptic dysfunction. Neurofibrillary tangles are found in the brains of people with AD, and the tau protein is the key component of them. Tau is normally a soluble protein that stabilises microtubule and cytoskeletal integrity. In AD, tau becomes abnormally phosphorylated, less soluble, and prone to aggregation into filamentous structures. Hyperphosphorylated tau reduces its affinity for microtubules, leading to microtubule destabilisation and the mislocalisation of tau, which sets the stage for synaptic dysfunction and neurodegeneration [8]. Pathological Tau detaches from axonal microtubules and moves into pre- and postsynaptic compartments. At presynaptic terminals, it reduces vesicle mobility and release, which weakens the neurotransmission. At postsynaptic sites, it lowers the number of glutamatergic receptors and blocks the proper maturation of dendritic spines [3]. Tau pathology also interferes with mitochondria with three aspects, which are mitochondrial transport, dynamics and bioenergetics. For mitochondrial transport, hyperphosphorylated tau disrupts axonal mitochondrial transport by trapping Kinesin motor complex JIP1 and impairing Kinesin-dynein trafficking. This results in mitochondrial mislocalisation, energy deficits, axonal dysfunction, and progressive synapse degeneration in AD. Pathological tau disrupts mitochondrial dynamics by aberrantly interacting with Drp1, enhancing fission and reducing fusion proteins such as OPA-1 and Mfn1/2. This imbalance causes mitochondrial fragmentation, impaired distribution, and synaptic degeneration in AD. Mitochondria is defined as the main source of reactive oxidative species (ROS), the damage in mitochondria affects the energy supply and significantly associated with AD [9]. In addition, tau promotes microglia to engulf and eliminate synaptic structures. Microglia regulates synaptic pruning via activity-dependent mechanisms involving receptors such as CX3CR1 and P2RY12, and complement proteins including C1q, C3, and C4. While essential for normal circuit maturation, dysregulation contributes to pathological synapse loss in neurodegenerative and psychiatric disorders [10]. In AD brains, numerous activated microglia are present, releasing cytokines such as TNF-α, IL-6, and IL-10. These cytokines inhibit the synaptic plasticity to cause cognitive decline [11]. These combined effects gradually damage synaptic integrity and lead to cognitive decline in neurodegenerative diseases like AD. These tau-related mechanisms collectively accelerate synaptic impairment, providing potential molecular targets for early intervention.

2.1.3 Functional Consequence of Synaptic Dysfunction

There are several functional consequences of synaptic dysfunction. Impaired synaptic plasticity is one of the consequences that causes cognitive decline. LTP and LTD are critical for learning and memory, and their disruption is a hallmark of AD. Both animal models and clinical samples consistently show impaired synaptic plasticity, with LTP attenuation and LTD enhancement. Studies in APPswe; PS1ΔE9 transgenic mice reveal that young animals initially exhibit enhanced LTP at the expense of LTD, while adults show the opposite pattern, reflecting a failure in developmental metaplasticity [12].

These changes are associated with altered AMPA receptor phosphorylation and the presence of Ca^{2+}-permeable AMPA receptors, indicating a molecular basis for synaptic deficits. The inability to adjust the LTP/LTD induction threshold across development compromises synaptic efficacy and contributes directly to cognitive decline [12]. Neural dyssynchronisation is the other functional consequences. AD is characterized not only by neuronal loss but also by impaired neural synchrony, which contributes to cognitive deficits. Resting-state EEG studies show increased θ and Δ activity with decreased α-, β-, and γ-band oscillations, reflecting reduced local and long-range synchronization. Task-based studies indicate that AD patients exhibit lower α- and β-band synchronization during working memory maintenance. The fMRI and DTI studies reveal disrupted functional connectivity between hippocampus, prefrontal cortex, and other cortical regions, consistent with a neocortical disconnection syndrome. Mechanistically, degeneration of cholinergic projections and alterations in glutamatergic neurotransmission, including

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NMDA-receptor dysfunction, impair high-frequency oscillations and spike timing, further reducing neural synchrony [13].

Synaptic dysfunction represents one of the earliest and most critical pathological events underlying cognitive decline. It establishes a fundamental basis for the progressive breakdown of brain function by impairing synaptic plasticity, disrupting neural communication, and initiating local circuit. These molecular and cellular alterations not only compromise cognition at the microcircuit level but also lay the groundwork for large-scale neural network disruption. In the following section, we will explore how cumulative synaptic impairments propagate across distributed brain systems, ultimately manifesting as widespread network dysconnectivity that further exacerbates cognitive decline.

2.2 Large-Scale Neural Network Disruption

Synapses are the elementary units of brain networks, and their integrity is essential for efficient information transfer across neural systems. In AD, early pathological events such as Aβ oligomer accumulation, tau hyperphosphorylation, and progressive synaptic loss compromise neurotransmission and plasticity at the local level. These microcircuit impairments gradually scale up,disrupting the coordinated activity of distributed neural populations. Over time, alterations in excitatory-inhibition balance, impaired LTP, and structural disconnection converge to destabilise large-scale network organisation. This hierarchical progression underscores a central principle: dysfunction at the synaptic level does not remain confined to individual's neurones but propagates to the system levels, undermining the brain's capacity to sustain coherent connectivity. Thus, AD is not only a disease of synapses but also a syndrome of network dysconnectivity, where the collapse of micro-level mechanisms culminates in impaired large-scale communication and cognitive decline.

2.2.1 Large-Scale Neural Network Disruption and DMN

The DMN, with core nodes in the medial prefrontal cortex, posterior cingulate cortex/precuneus, and inferior parietal lobes, is particularly vulnerable to AD pathology. Supplementary regions include the medial temporal lobes and temporal poles. Initially described as a task-negative network active during rest, the DMN is now understood as crucial for autobiographical memory, social cognition, and mental time-travel, collectively supporting an individual's narrative sense of self. Altered DMN connectivity has therefore become a major focus in undertaking AD-associated cognitive decline. The study examined whether effective connectivity changes in the DMN can predict dementia incidence and prognosis using the UK Biobank cohort. A nested case-control design compared individuals who later developed dementia with matched controls, focusing on all-cause dementia to capture population-level pathology. Resting-state fMRI (rs-fMRI) data were analyzed with spectral dynamic causal modeling (DCM), which estimates causal excitatory and inhibitory influences among brain regions. The study predicted that altered DMN effective connectivity would be detectable years before diagnosis and robust enough to predict dementia incidence out-of-sample. The results shows that DMN effective connectivity can accurately predict whether and when an individual may develop dementia by different aspects. Bayesian medel reduction and averaging were used to estimate the difference of effective connectivity between dementia cases and control. A shows baseline effective connectivity in controls, with gray indicating inhibitory and purple indicating excitatory connections, including auto-inhibition on the diagonal; b presents case-control differences, where gray reflects toward inhibition and purple toward excitation; c visualises these differnces in MNI space, with solid tubes indicating strengthened connections, dashed tubes showing attenuated ones, tube thickness indicaitng effect size, and colours marking the originating regions. These suggests the most prominent connectivity alterations in dementia were stronger inhibition from vmPFC to IPHF and from IIPC to IPHF, along with reduced inhibition from rPHF to dmPFC [4].

The Bayesian model reduction and averaging were used to predicts time until dementia diagnosis under effective connectivity. A suggests that dementia cases show distinct excitatory and inhibitory connectivity patterns with only highly reliable connections displayed; b presents connectivity changes linked to a longer time until clinical diagnosis reveal shifts towards increased inhibition and reduced excitation (gray); c showed effective connectivity changes. There was very strong evidence that connectivity parameters were associated with the time until diagnosis [4].

After we understand the change of DMN effective connectivity can predict whether and when will develop dementia, it is important to understand the mechanism. Aβ accumulation in preclinical AD begins in core DMN regions, including the precuneus, medial orbitofrontal cortex, and posterior cingulate. This early deposition occurs even in individuals with normal cerespinal fluid Aβ42 and positron emission tomography (PET) measures but who later progress to abnormal profiles. Importantly, initial Aβ accumulation is linked to reduced connectivity within the DMN and between the DMN and the frontoparietal network, rather than structural atrophy or metabolic decline. These findings highlight DMN vulnerability as an early

marker of AD-associated network dysfunction [14]. For early diagnosis and risk evaluation of neurodegenerative diseases, we can use the rs-fMRI for providing potential biomarkers and early intervention.

2.2.2 Large-Scale Neural Network Disruption and Hippocampal-Prefrontal Circuits

The hippocampal-prefrontal network dysfunction is also the cause of cognitive decline. The hippocampal-prefrontal network is a critical circuit for working memory, episodic recall, flexible decision-making, and goal-directed behaviour [15]. In the healthy brain, hippocampal SWRs synchronize with prefrontal activity, enabling the integration of past experiences to guide adaptive choices. This dynamic coordination ensures that memory representations remain flexible and context sensitive [5]. In AD, this network becomes selectively vulnerable to amyloid and tau pathology. Evidence from transgenic models such as 5XFAD mice shows that hippocampal–prefrontal connectivity is markedly reduced, accompanied by decreased SWR activity and rigid CA1 coding. These disruptions impair the flexible use of memory during naturalistic tasks such as foraging under threat, where affected animals display reduced behavioral adaptability and decision-making rigidity. Such findings illustrate how local synaptic dysfunction in hippocampal circuits scales up to disturb long-range corticolimbic communication [5]. The breakdown of hippocampal–prefrontal interactions thus represent a key mechanism linking molecular pathology to cognitive decline. Beyond its diagnostic value, this vulnerability also highlights potential therapeutic strategies. Interventions designed to restore SWR activity, strengthen hippocampal–prefrontal synchrony, or modulate network excitability through closed-loop stimulation may provide novel avenues for preserving flexible memory-guided behaviour in AD.

Large-scale neural network dysfunction represents a system-level hallmark of AD, bridging molecular pathology with cognitive decline. Core brain networks such as the DMN and hippocampal-prefrontal circuits show disrupted functional connectivity, as revealed by rs-fMRI or PET. These disruptions reflect the cumulative impact of Aβ and tau pathology on synapse as we discussed in the first part, which scales up to impaired interregional communication.

3. Conclusion

This review highlights that synaptic pathology and large-scale network disruption act as reciprocal drivers of cognitive decline in AD. At the microscopic level, Aβ and tau pathology impair LTP and synaptic plasticity, weakening the fundamental units of neuronal communication. These local deficits scale up to macroscopic disconnection across core brain systems, including the DMN and hippocampal-prefrontal circuits, shown by rs-fMRI and PET. The resulting dysconnection manifests as memory loss, executive dysfunction, and language impairment, reflecting the network-level basis of AD symptoms. Importantly, effective connectivity studies demonstrate that alterations within the DMN can predict not only who whether develop dementia but also when, offering valuable biomarkers for early detection.

The significance of this framework lies in linking molecular pathology with systems neuroscience, moving beyond isolated mechanisms to an integrated synapse-network model of AD. Recognising this dual pathway provides new opportunities for intervention. Beyond pharmacological approaches, lifestyle strategies such as exercise, cognitive training, and social engagement may help preserve synaptic integrity and sustain network connectivity, thereby delaying clinical progression. Future research should explore how targeted therapies can protect both synaptic and network health, offering a more holistic approach to prevention of neurodegeneration diseases.

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