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Review

Synaptic and synchronic impairments in subcortical brain regions associated with early non-cognitive dysfunction in Alzheimer's disease

Nicolás Riffo-Lepe[1, #], Juliana González-Sanmiguel[1, #], Lorena Armijo-Weingart[2], Paulina Saavedra-Sieyes[1], David Hernandez[1], Gerson Ramos[1], Loreto S. San Martín[1, 3, *], Luis G. Aguayo[1, 3, *]

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From the Contents

Abstract

For many decades, Alzheimer's disease research has primarily focused on impairments within cortical and hippocampal regions, which are thought to be related to cognitive dysfunctions such as memory and language deficits. The exact cause of Alzheimer's disease is still under debate, making it challenging to establish an effective therapy or early diagnosis. It is widely accepted that the accumulation of amyloid-beta peptide in the brain parenchyma leads to synaptic dysfunction, a critical step in Alzheimer's disease development. The traditional amyloid cascade model is initiated by accumulating extracellular amyloid-beta in brain areas essential for memory and language. However, while it is possible to reduce the presence of amyloid-beta plaques in the brain with newer immunotherapies, cognitive symptoms do not necessarily improve. Interestingly, recent studies support the notion that early alterations in subcortical brain regions also contribute to brain damage and precognitive decline in Alzheimer's disease. A body of recent evidence suggests that early Alzheimer's disease is associated with alterations (e.g., motivation, anxiety, and motor impairment) in subcortical areas, such as the striatum and amygdala, in both human and animal models. Also, recent data indicate that intracellular amyloid-beta appears early in subcortical regions such as the nucleus accumbens, locus coeruleus, and raphe nucleus, even without extracellular amyloid plaques. The reported effects are mainly excitatory, increasing glutamatergic transmission and neuronal excitability. In agreement, data in Alzheimer's disease patients and animal models show an increase in neuronal synchronization that leads to electroencephalogram disturbances and epilepsy. The data indicate that early subcortical brain dysfunctions might be associated with non-cognitive symptoms such as anxiety, irritability, and motivation deficits, which precede memory loss and language alterations. Overall, the evidence reviewed suggests that subcortical brain regions could explain early dysfunctions and perhaps be targets for therapies to slow disease progression. Future research should focus on these non-traditional brain regions to reveal early pathological alterations and underlying mechanisms to advance our understanding of Alzheimer's disease beyond the traditionally studied hippocampal and cortical circuits.

Key Words: Alzheimer's disease; AMPA receptors; amygdala; epilepsy; gamma-aminobutyric acid; glutamate; hippocampus; neurodegeneration; neuronal excitability; N-methyl-D-aspartate receptors; non-cognitive; nucleus accumbens

Introduction

The nervous system is the most complex human organ and comprises billions of neurons and glial cells forming both diffuse and specific circuits. As such, it receives, processes, and sends electrochemical information reaching diverse brain regions and also sends neural messages to the rest of the body. Due to its neuroplasticity, the nervous system can undergo structural and functional changes during aging, including memory formation, neuronal loss, and dysregulations in synaptic activity (Bennett and Madden, 2014). These alterations, when potentiated by genetic and environmental factors, can increase the risk of developing neurodegenerative diseases and dementia (Peters, 2006; Bennett and Madden, 2014).

From a public health view of the aging brain, a particular concern is the global rise in life expectancy over the past few decades, which has led to a higher prevalence of dementia, such as Alzheimer's disease (AD). AD is the leading cause of dementia among elderly adults and accounts for nearly 70% of all cases. For example, projections indicate that the global prevalence of AD will increase from 55 million cases reported in 2019 to almost 139 million by 2050 (Knopman et al., 2021; Gauthier S., 2022). This significant rise underscores the urgent need to understand the neurobiological basis of this disorder. AD manifests itself through both cognitive and non-cognitive alterations (de Jong et al., 2012; Nobili et al., 2017; De Marco and Venneri, 2018), and its neuropathological hallmarks are characterized by the extracellular and intracellular accumulation of amyloid beta peptide (extracellular amyloid beta, eAβ and intracellular amyloid beta, iAβ, respectively) and intracellular neurofibrillary tangles composed of abnormally phosphorylated Tau as well as oxidative stress and neuroinflammation (Ittner and Gotz, 2011).

For several decades, AD research has primarily focused on impairment within cortical and hippocampal regions, which appear to be related to cognitive dysfunction such as memory and language deficits (Kälin et al., 2017; Li et al., 2023). However, recent studies support the notion that early neurodegenerative processes involving subcortical brain regions also contribute to brain damage and cognitive decline in AD. In line with

[1]Laboratorio de Neurofisiología, Departamento de Fisiología, Universidad de Concepción, Concepción, Chile; [2]Facultad de Odontología y Ciencias de la Rehabilitación, Universidad San Sebastián, Concepción, Chile; [3]Programa de Neurociencia, Psiquiatría y Salud Mental (NEPSAM), Universidad de Concepción, Concepción, Chile
*Correspondence to: Luis G. Aguayo, PhD, laguayo@udec.cl; Loreto S. San Martín, PhD, loresanmartin@udec.cl.
https://orcid.org/0000-0003-3160-1522 (Luis G. Aguayo); https://orcid.org/0000-0003-0793-217X (Loreto S. San Martín)
#Both authors contributed equally to this work and share first authorship.

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this data, an increasing body of evidence indicates that early AD includes alterations in non-cognitive functions (e.g., motivation, anxiety, and motor impairment) mediated by subcortical areas, such as the striatum and amygdala, in human and animal models (Masters et al., 2015b; Nobili et al., 2017; De Marco and Venneri, 2018; Serra et al., 2018; Fernández-Pérez et al., 2020; Gloria et al., 2021; Armijo-Weingart et al., 2024). Interestingly, the pathological synaptic signature in these areas appears to be more closely associated with the early accumulation of iAβ rather than amyloid plaques, also known as "tombstones" (Fernández-Pérez et al., 2020).

Furthermore, numerous studies have revealed a higher prevalence of neuronal circuit synchronization and epilepsy among individuals with mild cognitive impairment (MCI), attributed to increased brain excitability early in AD (Born, 2015; Vossel et al., 2017; Giorgi et al., 2020). Similar changes appear to occur in animal models of the disease. For instance, in a commonly used AD mouse model (APP/PS1) that harbors a chimeric mouse/human APP with the Swedish mutation (K670N, M671L) and the human exon-9-deleted variant of presenilin 1 (PS1-dE9) which is characterized by memory deficits, synapse loss, and widespread Aβ deposits (Jankowsky et al., 2004; Garcia-Alloza et al., 2006; Huang et al., 2016), seizures have been reported starting at four months of age, preceding the formation of Aβ plaques (Minkeviciene et al., 2009). Additionally, recent evidence in APP/PS1 AD models found that accumbal neurons exhibit increased excitability (Fernández-Pérez et al., 2020). The present review will focus on the synaptic mechanisms associated with Aβ accumulation in the brain, beginning with the amyloid cascade hypothesis and comparing synaptic alterations not only in the hippocampus and cortex but also across other brain regions. This broader approach recognizes that AD involves multiple circuits and is not localized. Additionally, we highlight the significance of iAβ in various brain regions, including subcortical nuclei, and its potential link to early excitability changes and non-cognitive symptoms in the initial stages of AD.

Retrieval Strategy

An online search was conducted using the PubMed and Web of Science databases to identify relevant publications. The search employed a combination of keywords: "Alzheimer's disease," "extracellular amyloid beta," "intracellular amyloid beta," "subcortical regions," "synaptic transmission," "neural plasticity," "nucleus accumbens," "amygdala," "raphe nucleus," "locus coeruleus," "non-cognitive behaviors," and "neuropsychiatric symptoms." Articles were screened by title and abstract, with selections based on the relevance of the data to eAβ and iAβ effects and their presence in subcortical regions, as opposed to cortical and hippocampal areas, during the early stages of AD. The search included publications up to August 2024. When appropriate, differences between them will be discussed.

Physiopathology of Alzheimer's Disease

The exact cause of AD is still under debate. Still, it is widely accepted that the generation of the neurotoxic Aβ peptide from the transmembrane amyloid precursor protein (APP) is a critical step in AD development (Cline et al., 2018). Aβ, a peptide consisting of 39–42 amino acids, is generated by the sequential cleavage of APP mediated by β-secretase, which cleaves APP at the N-terminus, and γ-secretase, responsible for the processing of its C-terminus. In contrast, α-secretase cleaves APP within the Aβ domain, preventing the formation of Aβ (Turner et al., 2003; Bai et al., 2021). Significantly, Aβ peptides with longer C-termini dictated by cleavage by γ-secretase have higher levels of aggregation and toxicity. Therefore, a higher ratio of $A\beta_{42}/A\beta_{40}$ is associated with increased neurotoxicity and AD progression (Selkoe and Hardy, 2016; Chai et al., 2021).

While the precise mechanisms of Aβ peptide neurotoxicity remain debated, it is widely accepted that Aβ oligomers interact with neuronal membranes and form oligomeric pores, causing cellular leakage (Österlund et al., 2019; Gonzalez-Sanmiguel et al., 2020). These non-selective pores allow the passage of calcium, sodium, ATP, and other large molecules critical for ionic and metabolic homeostasis (Arispe et al., 1993; Parodi et al., 2010; Sepulveda et al., 2014). This process, primarily located in cellular membranes, triggers a neuropathological cascade that leads to plaque formation in advanced stages of the disease, along with an increase in neurofibrillary tangles and, ultimately, neuronal death (Katsnelson et al., 2016). Additionally, in early disease stages, where non-cognitive alterations are reported, similar neurotoxic mechanisms may occur within intracellular organelle membranes, where iAβ may exert an impact due to its presence in these compartments.

Tau, a microtubule-associated protein, is vital in stabilizing microtubules in adult neurons (Black et al., 1996; Biswas and Kalil, 2018). In AD, Tau proteins become hyperphosphorylated and abnormally folded, impairing their ability to bind to microtubules. This leads to its aggregation into bundles of filaments, contributing to the formation of neurofibrillary tangles (Nestor et al., 2008; Jouanne et al., 2017; DeTure and Dickson, 2019). Substantial evidence supports the idea that Aβ accumulation induces early toxic stress in neurons, with Tau hyperphosphorylation ultimately leading to neuronal death (Ittner and Gotz, 2011; Martin et al., 2013; Liu et al., 2020; Dong et al., 2022).

Although most AD cases occur sporadically, there are also inherited forms of this disorder that cause early-onset AD and follow an autosomal dominant fashion. The early form of AD displays clinical and pathological features similar to those of sporadic cases (Elder et al., 2010; Bai et al., 2021). For instance, the "Swedish" mutation, which involves amino acid variations near the cleavage site in APP, results in increased production of Aβ (Mullan et al., 1992; Elder et al., 2010). Additionally, mutations in presenilin 1 (PS1), a component of the γ-secretase multiprotein complex, have also been implicated in familial AD and are associated with elevated Aβ production (Jankowsky et al., 2001, 2004). Despite the varying molecular effects of different presenilin mutations, they generally decrease the activity of C to N-terminal cleavage and increase the production of longer, self-aggregating Aβ peptides, thus raising the $A\beta_{42}/A\beta_{40}$ ratio (Selkoe and Hardy, 2016).

Furthermore, several genetic factors unrelated to Aβ production and metabolism increase the risk of developing late-onset AD. Notably, the APOE4 isoform of the apolipoprotein E (*APOE*) gene confers the most significant risk of developing AD (Mayeux et al., 1993). The precise mechanisms by which *APOE* alleles differentially affect Aβ accumulation in the brain in sporadic AD are not fully understood and remain controversial. However, emerging evidence suggests that APOE contributes to AD risk by affecting Aβ synthesis, aggregation, clearance, and degradation (Castellano et al., 2011; Selkoe and Hardy, 2016; Chai et al., 2021). Additionally, other risk factors for late-onset AD involve cholesterol metabolism, endocytosis, and immune response (Karch and Goate, 2015; Feringa and van der Kant, 2021). Understanding the role of these risk factors in AD might provide new insights into the neurobiological mechanism involved in the disease (DeTure and Dickson, 2019). Some important macroscopic features of AD include cortical and subcortical atrophy, decreased brain volume, and expansion of ventricles. However, none of these characteristics are specific to AD (Nestor et al., 2008; DeTure and Dickson, 2019).

Additionally, the presence of reactive microglia and astrocytes, along with synaptic loss, are also hallmark features of AD pathology (Selkoe and Hardy, 2016; DeTure and Dickson, 2019). Recent studies have revealed the critical involvement of reactive glial cells, including astrocytes and microglia, as they respond to injury and inflammation by undergoing reactive changes that can either mitigate or exacerbate neuronal damage (Valles et al., 2019; Wu and Eisel, 2023). The transformation of these glial cells can lead to protective effects, such as the clearance of amyloid plaques, but can also have detrimental consequences, including the release of neurotoxic mediators and pro-inflammatory factors, which may contribute to neurodegeneration over time (Birch, 2014; Nirzhor et al., 2018; Uddin and Lim, 2022).

Amyloidogenic Pathway

The most extensively examined hypothesis used to explain the neurotoxicity associated with AD is the "amyloid hypothesis," which postulates that Aβ is the main component of amyloid plaques and the initial triggering cause of the neuropathological cascade that leads to the formation of plaques and neurofibrillary tangles of Tau protein (Hardy and Higgins, 1992; Hampel et al., 2021). APP travels through the secretory pathway through membrane complexes in the endoplasmic reticulum and Golgi before reaching the plasma membrane. It typically remains at the cell surface for only a few minutes before being internalized and transported to endosomes, a key source of iAβ (Koo and Squazzo, 1994; Choy et al., 2012). The extracellular matrix is not the sole source of Aβ since APP has been detected in various intracellular locations, including the mitochondrial membrane, trans-Golgi network, endoplasmic reticulum, endosomes, and lysosomes (Koo and Squazzo, 1994; Cook et al., 1997; Pasternak et al., 2003; Vetrivel and Thinakaran, 2006). Additionally,

APP appears to be processed by enzymatic activity in these secretory pathway organelles because β- and γ-secretases have been traced in these subcellular compartments (Pasternak et al., 2003; Hansson et al., 2004; Maesako et al., 2022).

Moreover, it was reported that all familial AD mutations linked to presenilins 1 and 2 can cause an increase in the extracellular concentration of $A\beta_{42}$ (Suzuki et al., 1994; De Jonghe et al., 2001). In this context, a previous study demonstrated that APP internalization from the plasma membrane to the endosomes can occur via endocytosis and that blocking this process results in a reduction in iAβ levels (Tang, 2009). Preferential cleavage of APP has also been reported. For example, the late Golgi is implicated in the generation of iAβ, primarily due to the high γ-secretase activity in this compartment, where the C99 precursor is cleaved, leading to Aβ production within the Golgi network (Grimm et al., 2003). Another example is the Swedish mutation of APP, which has a preferential cleavage at the Golgi apparatus different from the wild type (WT) (Wang et al., 2024). It is important to note that Aβ generation is directly linked to γ-secretase activity across various organelles, highlighting its role as a potential neurotoxic element in AD (**Figure 1**).

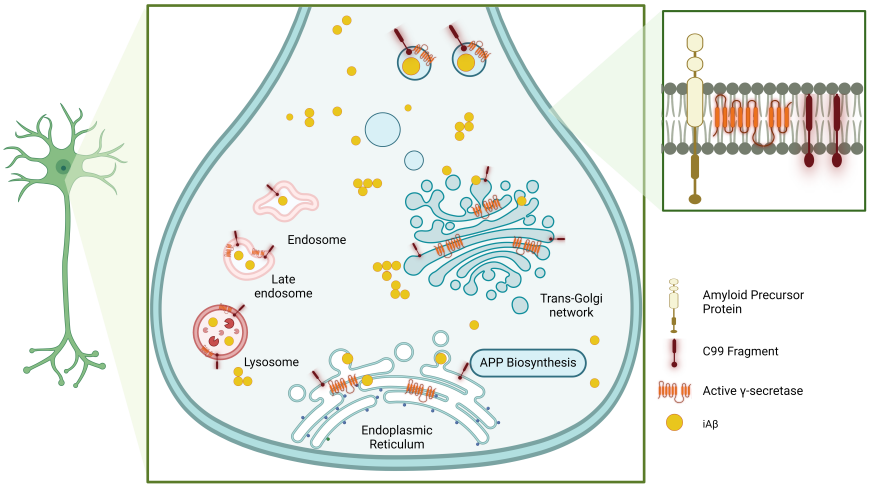

Figure 1 | **Different sources of intracellular Aβ generation.**
The scheme shows the cellular sites where Aβ is produced. It is highlighted that during the amyloidogenic APP processing, the activity of the γ-secretase enzyme generates Aβ from the C99 fragment. Several sites are sources of Aβ generation, mainly related to APP synthesis and recycling. Components of the secretory pathway, such as the endoplasmic reticulum, Golgi apparatus, and secretory vesicles, are crucial elements in Aβ production. Additionally, early and late endosomes, as well as lysosomes, are involved in Aβ generation, with γ-secretase activity playing a crucial role in Aβ biosynthesis in these compartments. Created with BioRender.com. APP: Amyloid precursor protein; Aβ: amyloid-beta; C99: 99 amino-acid fragment; iAβ: intracellular amyloid beta.

Synaptic Effects of Extracellular Amyloid-Beta in Cortical and Subcortical Brain Regions

Extracellular amyloid beta causes synaptic failure in the cortex and hippocampus

Since the initial description of AD, the scientific community has primarily focused on elucidating the cellular and molecular underpinnings of cognitive symptoms, such as memory and language impairments observed in late-stage patients (Hardy and Selkoe, 2002; Blennow et al., 2006; Selkoe and Hardy, 2016). These cognitive deficits have prompted extensive investigations of brain regions associated with higher executive functions. Therefore, postmortem brain tissue analysis has revealed a progressive accumulation of Aβ from cortical to subcortical areas (Thal et al., 2002; Klunk et al., 2004; Dubois et al., 2010). However, these anatomical studies predominantly identified macroscopic eAβ plaques, a histopathological hallmark appearing considerably later than iAβ accumulation. This notion might significantly impact our understanding of early disease onset and affected brain regions. Nevertheless, a substantial portion of AD research has been centered on characterizing the presence and toxic effects of eAβ aggregates on hippocampal and cortical neurons, which gave rise to the amyloid cascade hypothesis, a prevailing theory for over three decades (Hardy and Selkoe, 2002; Cline et al., 2018). This hypothesis proposes that eAβ oligomers disrupt synaptic function, damage neurites, and impair neural ionic homeostasis, ultimately leading to brain dysfunction and neuronal death (Karran et al., 2011; Selkoe and Hardy, 2016; **Figure 2**). However, this original hypothesis does not consider the presence of iAβ as an initial factor in the disease and has primarily focused on hippocampal and cortical dysfunction. We will now examine the classical paradigm of Aβ in AD, describing recent evidence on hippocampal and cortical dysfunction associated with eAβ across human and animal models, with a focus on synaptic impairment and its underlying mechanisms, before progressing to eAβ-induced synaptic alterations in subcortical regions. Subsequently, we present recent evidence on the early presence of iAβ in the AD brain and its effects in both classical and subcortical brain regions.

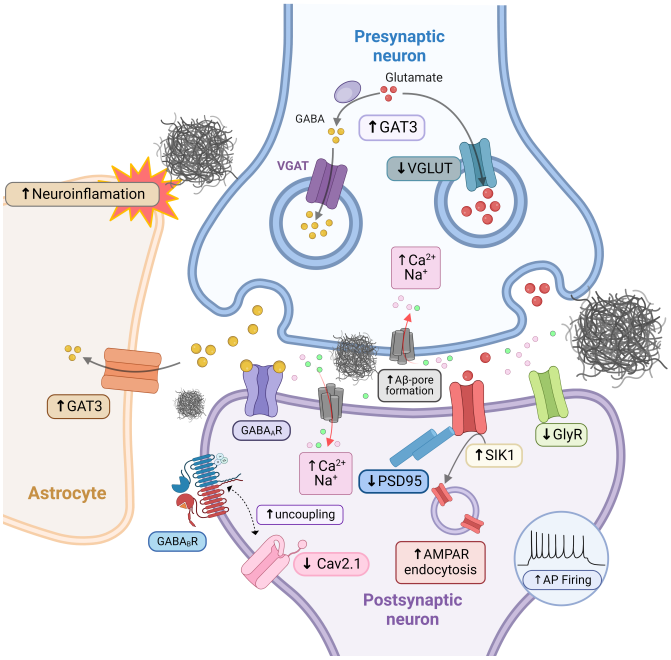

Figure 2 | **Extracellular Aβ effects in synaptic transmission.**
The scheme illustrates a synapse, where the presynaptic compartment, once activated, releases synaptic vesicles containing neurotransmitters that interact with their receptors on the postsynaptic neuron membrane. Additionally, astrocytes release and reuptake neurotransmitters, modulating synaptic transmission. Early during the neurotoxicity process, Aβ oligomers can insert into the membrane leading to pore formation and a dysregulated entry of extracellular calcium, increasing the release of glutamate. At advanced stages of Alzheimer's disease progression, the formation of amyloid plaques induces synaptic failure through various mechanisms. Aβ also causes $GABA_BRs$ to uncouple from $Ca_v2.1$ channels, impairing their function and increasing neuronal excitability. In addition, reduction in AMPARs and GlyRs enhances synaptic dysfunction, which in turn increases action potential firing. Created with BioRender.com. Aβ: Amyloid-beta; AMPAR: AMPA receptor; AP: action potential; $Ca_v2.1$: voltage-gated calcium channel type 2.1; $GABA_AR$: GABA-A receptor; $GABA_BR$: GABA-B receptor; GAT3: GABA transporter 3; GlyR: glycine receptor; PSD95: postsynaptic density protein 95; SIK1: salt-inducible kinase 1; VGAT: vesicular GABA transporter; VGLUT: vesicular glutamate transporter.

A critical event in the amyloid cascade and disease development is the imbalance in the synaptic excitation-inhibition (E/I) ratio, which likely occurs decades before clinical symptoms manifest, increasing the brain's energy demands to compensate for these synaptic alterations (Palop and Mucke, 2010, 2016; Bezzina et al., 2015). Homeostatic synaptic plasticity, manifested as a stable E/I balance, regulates neural network activity within a restricted temporal window by adjusting the strength of excitatory and inhibitory neurotransmission in response to external stimuli (Hyman et al., 2006; Froemke, 2015; Wen and Turrigiano, 2024). Alterations of this E/I balance will carry consequences. For instance, it was reported that carriers of *APOE* ε4 show significantly increased brain activity in the neocortex and the hippocampus at preclinical stages (Bookheimer et al., 2000; Sperling et al., 2010; Tran et al., 2017). Additionally, compared to healthy aged controls, a significant increase in seizure prevalence has been reported in patients with mild to moderate symptoms of AD, which suggests a loss of neural network stability in the AD brain (Amatniek et al., 2006; Vossel et al., 2017). Interestingly, brain regions with network functional abnormalities strongly coincide with vulnerable regions displaying AD pathological hallmarks, such as the temporal lobe and hippocampus (Vossel et al., 2017; Bi et al., 2020). Recent studies used synaptosome-enriched samples from the parietal cortex, hippocampus, and temporal cortex of non-demented controls, individuals with MCI, and AD patients. The synaptosomes were transplanted into *Xenopus* oocytes for electrophysiological recordings (Lauterborn et al., 2021; Scaduto et al., 2023). Oocytes with synaptosomes from AD patients and aged control donors revealed an increased electrophysiological E/I ratio (Lauterborn et al., 2021). Additionally, it was found that oocytes microtransplanted with membranes from AD donors exhibited a more depolarized resting membrane potential than those injected with membranes from MCI donors, while a similar trend was seen in control membranes. Interestingly, electrophysiological E/I ratio was significantly increased in the temporal cortex of AD donors compared to controls. Moreover, the greater the amount of APP and Tau measured by proteomics, the higher the electrophysiological E/I ratio (Scaduto et al., 2023). Understanding the mechanisms underlying this neural imbalance is crucial, as it could offer insights into the cellular processes driving synaptic dysfunction. By exploring these mechanisms, potential molecular targets could be identified, enabling the development of therapies aimed at restoring network homeostasis and mitigating the early and silent neurodegenerative processes in AD (Targa Dias Anastacio et al., 2022).

Recent studies in animal and cellular models of AD have been focused on analyzing the synaptic mechanisms associated with the presence of Aβ, revealing multiple molecular targets in both the hippocampus and cortex. For instance, it was reported that vesicular glutamate transporter 1 (VGLUT1) and postsynaptic density protein 95 (PSD-95) immunoreactivity was reduced in the neighborhood of Aβ plaques in the neocortex and hippocampus of APP-KI ($APP^{NL-G-F/NL-G-F}$) mice, indicating the loss of glutamatergic synapsis (Sakakibara et al., 2021). The $APP^{NL-G-F/NL-G-F}$ AD mice had normal APP levels but increased Aβ production. These mice carry three specific mutations: the Swedish mutation (K670N, M671L) in exon 16, the Beyreuther/Iberian mutation (I716F), and the Arctic mutation (E693G) in exon 17 (Sakakibara et al., 2021). Additionally, a recent study developed a real-time assay based on fluorescence lifetime imaging, where glutamate AMPA receptors (AMPAR) are tagged with a pH-sensitive GFP (SEP), enabling *in vivo* measurements of AMPAR trafficking (Kopec et al., 2006; Fujii et al., 2018; Prinkey et al., 2024). The results showed that the fluorescence intensity for SEP-GluA1, SEP-GluA2, and SEP-GluA3 AMPAR subunits in hippocampal cultures from APP/PS1 mice was significantly reduced, indicating a lower presence of AMPARs associated with increased eAβ production (Prinkey et al., 2024). Additionally, fluorescence lifetime for SEP-GluA1 and SEP-GluA2 in spines and dendrites was significantly decreased, which is consistent with increased levels of GluA1/2 receptors in endocytic vesicles and eAβ levels in APP/PS1 compared with WT neurons (Prinkey et al., 2024). In agreement, another study found that incubating hippocampal neurons with synthetic $Aβ_{42}$ oligomers for 24 hours caused a decrease in GluA1 expression dependent on the redistribution of the AMPK-related protein SIK1, a salt-inducible kinase (Hou et al., 2024). Interestingly, SIK1 expression was increased in the hippocampus and prefrontal cortex in postmortem AD human brains. In contrast, knockdown of SIK1 in a triple transgenic mice model (3×Tg) of AD expressing the APP Swedish, the PS1 M146V familial AD mutation, and Tau MAPT P301L frontotemporal dementia mutation, leads to restoration of AMPAR expression and rescue of the cognitive deficits (Hou et al., 2024; **Table 1**).

Although excitatory synaptic transmission is significantly affected in AD, abnormalities of the inhibitory synaptic system in AD have also been reported. Initial studies in humans using magnetic resonance spectroscopy have shown that gamma-aminobutyric acid (GABA) levels decrease significantly in the parietal cortex of AD patients relative to age-matched controls (Bai et al., 2015). Using a magnetic resonance spectroscopy technique to quantify GABA levels in the brain (Harris et al., 2017), recent evidence shows that the levels of GABA normalized to creatine GABA are significantly decreased in the anterior cingulate cortex and posterior cingulate cortex in MCI patients compared to healthy controls (Fu et al., 2023). Also, quantitative polymerase chain reaction analysis of the mRNA expression of the main subunits of the GABA ionotropic receptor ($GABA_AR$) in the human temporal cortex revealed a significant reduction in the expression of α1, β2, β3, β5, γ2, and δ subunits (Limon et al., 2012). Consequently, western blot analysis showed a significant decrease in the $GABA_AR$α1 and γ2 subunit expression, and electrophysiological recordings of GABA-evoked currents in microtransplanted oocytes with purified $GABA_ARs$ derived from AD patients displayed a reduction in current amplitude approximately 70% smaller than that of aged controls (Limon et al., 2012).

In animal models of AD, growing evidence supports the idea that inhibitory transmission is also affected by Aβ (Verret et al., 2012; Palop and Mucke, 2016). For instance, a recent study evaluated the nanoscale organization, density, and function of voltage-gated Ca^{2+} 2.1 channels ($Ca_v2.1$) in association with metabotropic $GABA_BR$ in the hippocampus and cortex of 12-month-old APP/PS1 mice, an age associated with advanced disease stages and characterized by abundant eAβ plaques, revealing a significant decrease in Cav2.1 density in the hippocampus, as assessed by histoblot experiments using an anti-α1A subunit antibody (Martin-Belmonte et al., 2024). Additionally, electrophysiological analysis of miniature inhibitory postsynaptic currents showed a significant reduction in frequency, but not in amplitude, indicating impaired GABAergic neurotransmission (Martin-Belmonte et al., 2024). Additionally, in the same AD mice model, protein expression analysis showed an increase in $GABA_AR$-associated proteins in the hippocampus at 6 but not 4 months of age (Salazar et al., 2021). Moreover, using the double-labeling SDS-digested freeze-fracture replica labeling technique in 12-month-old WT animals, it was found that $GABA_B1R$ clustered with $Ca_v2.1$ within the active zones of axon terminals in the hippocampus. In contrast, 12-month-old APP/PS1 mice displayed scattered and segregated immunoparticles for $GABA_B1R$ and Cav2.1 along the plasma membrane of active zones (Martin-Belmonte et al., 2024).

Furthermore, a recent study examined protein levels and subcellular localization of glycine receptor (GlyR) subunits α2 and α3 in the hippocampus of $APPswe/PS1_{L166P}$ transgenic mice at early (3-month-old) and late (12-month-old) stages of AD progression and found that GlyR expression is decreased only in late stages of AD in the APP/PS1 compared to WT (Kuhse et al., 2023). GABA is the primary inhibitory neurotransmitter in the brain, playing a critical role in maintaining the balance between neuronal excitation and inhibition. Seizures, particularly in conditions like epilepsy, are often linked to an imbalance in this E/I balance (Palop and Mucke, 2010; Mao et al., 2024).

In summary, the synaptic imbalance between excitation and inhibition appears to be a crucial characteristic of AD, driving compensatory mechanisms that destabilize neural circuits. Particularly, the recent evidence reviewed suggests that hippocampal GABAergic interneurons are a vulnerable target in AD, potentially contributing to network dysfunctions and epileptiform activity. Although it is widely accepted that eAβ is associated with a significant synaptic imbalance in the hippocampus and cortex, most studies using animal models of AD are conducted at advanced disease stages, where memory loss is reported. Additionally, not all studies characterize Aβ presence, making it challenging to establish specific associations between eAβ accumulation and these synaptic changes. Furthermore, despite the extensive focus on AMPAergic and GABAergic systems in the hippocampus and cortex, the role of glycinergic neurotransmission in AD remains an underexplored area of study that could reveal new therapeutic targets (Armijo-Weingart et al., 2024).

Table 1 | **Summary of experimental models and principal findings on extracellular amyloid accumulation**

AD models	Mutation(s) /Treatments	Ages	Brain regions	Principal findings	References
APP/PS1 mice	Chimeric mouse/human APP Swedish (K670N, M671L); Human exon-9-deleted variant of PS1 (PS1dE9)	6–7 mon	Hippocampus	Increase expression of GABAAR-associated proteins GAD65 and GAT3.	Salazar et al., 2021
		7.5 mon	Locus coeruleus	AβOs at nanomolar concentrations bind to the allosteric site of the α2A adrenergic receptor, leading to the activation of GSK3β, which subsequently induces tau hyperphosphorylation.	Zhang et al., 2020
		12 mon	Hippocampus	Reduction of CaV2.1 (P/Q-type) calcium channels, uncoupling of CaV2.1 channels from GABAB receptors.	Martin-Belmonte et al., 2024
		12–14 mon	Amygdala	Changes in dendritic structure and a significant decrease in large spines, even in plaque-free neurons. Reduced freezing behavior during auditory fear conditioning.	Knafo et al., 2009
		16 mon	Locus coeruleus	Reduction of over 20% in tyrosine hydroxylase-positive neurons.	Liu et al., 2013
APP-KI mice	APP Swedish (K670N, M671L), Beyreuther/Iberian (I716F), Artic (E693G)	2 mon	Hippocampus	Aggressive Aβ pathology, including subcortical depositions. Increased inflammatory response, by the activation of astrocytes and microglia.	Nilsson et al., 2014
		12 mon	Hippocampus, cortex, locus coeruleus	Degeneration and structural atrophy of axonal noradrenergic afferents.	Sakakibara et al, 2021
3×Tg mice	APP Swedish (K670N, M671L), PS1 (M146V)	8 mon	Hippocampus, prefrontal cortex	Knockdown of SIK1 led to the rescue of synaptic proteins, including AMPA receptor subunits GluA1 and GluA2. Knockdown of SIK1 rescued memory deficits.	Hou et al., 2024
		12 mon	Hippocampus	Protein levels of GlyR α2 and α3 subunits were significantly decreased.	Kuhse et al., 2023
		24 mon	Hippocampus, cortex, locus coeruleus	Reduction in the density of norepinephrine transporter (NET)-positive fibers. Pronounced reduction of VGLUT1 and PSD95 immunoreactivity near Aβ plaques.	Hou et al., 2024
hAPP-J20 mice	APP Swedish (K670N, M671L), Indiana (V717F)	6 mon	Parietal cortex	Reduction in the expression of the Nav1.1 in PV+ Ins.	Verret et al., 2012
		8–9 mon	Hippocampus	Increased firing frequency and decreased rheobase, which are indicative of heightened excitability.	Wang et al., 2023
Tg2576 mice	APP Swedish (K670N, M671L)	1.5 mon	Hippocampus	Increased susceptibility to pharmacologically induced seizures. Ectopic expression of neuropeptide Y.	Bezzina et al., 2015
5×FAD mice	Human APP Swe (K670N, M671L), Florida (I716V), and London (V717I), PS1 (M146L) (L286V)	3 mon	Dorsal raphe nucleus, hippocampus	Reduction in the excitability of 5HT neurons and its projections to hippocampal dCA1 region. Long-term potentiation was decreased and overexpression of TPH2 in the DRN restored LTP.	Wang et al., 2023
APP/PS1-mice derived primary culture	Chimeric mouse/human APPswe (K670N, M671L); Human exon-9-deleted variant of PS1 (PS1dE9)	8–12 DIV	Hippocampal neurons	Aβ accumulation increases endocytosis of AMPARs.	Prinkey et al., 2024
Primary culture from WT Sprague-Dawley rats	24-h incubation with AβOs 1–42	14 DIV	Hippocampal neurons	AβOs induce a reduction in GluA1 expression dependent on SIK1 redistribution.	Hou et al., 2024
Wistar WT rats	Unilateral cannula-delivery of 4 μM Aβ oligomers	2–3 mon	Nucleus accumbens	Increased norepinephrine concentration and iNOS mRNA after 2 hours of AβOs.	Morgese et al., 2015
	Acute *in vivo* brain infusion of AβOs	2–3 mon	Nucleus accumbens	Reduced ability of cholinergic stimulation to enhance DA release.	Grilli et al., 2010
C57BL/6J WT mice	Injection of 20 μM $A\beta_{1-42}$ oligomers (91 ng/μL)	3 mon	Nucleus accumbens	Decrease in GluA1 expression not as significant as that of GluA2 in synaptosomes. Insertion of CP-AMPARs in MSNs. Decrease in dendritic spines correlated with reduced motivation to take sucrose pellets.	Guo et al., 2022

APP/PS1: Amyloid precursor protein/presenilin 1; APP: amyloid precursor protein; Aβ: amyloid-beta; AβOs: amyloid-beta oligomers; CaV2.1: voltage-gated calcium channel type 2.1; DIV: days in vitro; GABAAR: gamma-aminobutyric acid type A receptor; GABAB: gamma-aminobutyric acid type B receptor; GluA1: glutamate receptor 1 (AMPA receptor subunit); GluA2: glutamate receptor 2 (AMPA receptor subunit); GlyR: glycine receptor; GSK3β: glycogen synthase kinase 3 beta; iNOS: inducible nitric oxide synthase; LTP: long-term potentiation; MSNs: medium spiny neurons; Nav1.1: sodium channel protein type 1 subunit alpha; NET: norepinephrine transporter; PSD95: postsynaptic density protein 95; PV: parvalbumin; SIK1: salt-inducible kinase 1; TH: tyrosine hydroxylase; VGLUT1: vesicular glutamate transporter 1; α1A: alpha-1A subunit of P/Q-type calcium channels; α2A: alpha-2A adrenergic receptor.

Extracellular amyloid-beta impairs subcortical brain regions associated with non-cognitive features

In contrast to the classical physiopathological paradigm of AD, where cortical and hippocampal brain regions are first affected, additional evidence shows that subcortical brain regions are also significantly affected in the early stages of the disease progression, both in postmortem human brain tissue and transgenic mice models, showing Aβ deposits in striatum, nucleus accumbens (nAc), caudate nucleus, putamen, amygdala, ventral tegmental area (VTA), and locus coeruleus (LC), illustrating its extensive nature (Knafo, 2012).

Nucleus accumbens

Recent evidence shows that the early neurodegenerative processes leading to brain atrophy and cognitive impairment in AD also involve the limbic system, where the nAc is a critical center (Russo and Nestler, 2013; Cordella et al., 2018; D'Amelio et al., 2018). The nAc, or ventral striatum, operates as an integration hub within the mesolimbic system, receiving glutamatergic inputs from the subiculum, amygdala, hippocampus, thalamus, prelimbic, and prefrontal cortex (Salgado and Kaplitt, 2015). It also integrates dopaminergic projections from the VTA and substantia nigra, playing a pivotal role in emotional behaviors such as aggression and social interaction (Nieoullon, 2002; Russo and Nestler, 2013). Moreover, the nAc is involved in memory consolidation, reward, and addiction, driving action selection that underlies goal-directed behaviors (Gleichgerrcht et al., 2010; Floresco, 2015).

A previous study in AD postmortem brain tissue reported the early presence of neuritic plaques in the striatum (Wolf et al., 1999). Another independent study evaluated the presence of Aβ and Tau in postmortem AD and healthy patients revealing that the nAc and dorsal striatum showed Aβ deposits and neuritic plaques in AD patients, but it was absent in healthy aged controls (Suenaga et al., 1990). Additionally, using positron emission tomography-PIB signal to measure Aβ levels in patients with AD and to compare to healthy aged controls, a study found extensive Aβ deposition in the striatum of AD patients (Klunk et al., 2004). Interestingly, volumetric and vertex-based analysis of deep gray matter structures in AD and MCI patients showed subregional atrophy in the nAc and hippocampus, which correlated with worse global clinical scores (Nie et al., 2017).

Functional studies have reported that after 2 hours of unilateral cannula-delivery of 4 μM Aβ oligomers (AβOs) into the nAc of WT Wistar rats, the norepinephrine concentration in the nAc was significantly increased (Morgese et al., 2015). Additionally, a significant increase in inducible nitric oxide synthase mRNA was also increased in the nAc after AβOs delivery, suggesting that the

noradrenergic system seems to be activated in the nAc as a compensatory mechanism following increased eAβ levels (Morgese et al., 2015). Similarly, a study conducted in WT rats reported that a brain infusion of AβOs inhibited dopamine release, as measured by microdialysis in the nAc (Grilli et al., 2010). Additionally, it has been reported that acute administration of AβOs in the nAc of 3-month-old *C57BL/6J* WT mice induced a significant decrease in glutamate receptor subunit GluA2 but not GluA1, suggesting an increase in calcium-permeable AMPA receptors. These results were confirmed through electrophysiological recordings that showed inward rectification at positive potential and significant inhibition of electrically evoked excitatory postsynaptic currents with the calcium-permeable AMPA receptor antagonist NASPM (Guo et al., 2022).

These studies highlight the role of the nAc in the pathogenesis of AD. However, the mechanisms by which the nAc is affected by Aβ deposits have not been extensively investigated. Additionally, recent evidence in 6-month-old mice models of AD suggests an iAβ pathology in the nAc rather than plaque-dependent dysfunction (Fernández-Pérez et al., 2020). In line with this, recent studies using a double transgenic mouse model of AD suggest that the nAc is affected at pre-plaque stages showing early iAβ pathology associated with changes in non-cognitive behaviors (e.g., motivation and anxiety) (Krashia et al., 2019; La Barbera et al., 2022; Armijo-Weingart et al., 2024).

Amygdala

The amygdala is a brain region critically involved in the processing of emotional information. It has widespread reciprocal connections with cognitive areas, such as memory-related regions (hippocampus) and perceptual pathways (primary visual cortex and inferior temporal cortex) (Tye et al., 2011; Choi et al., 2021). In AD, the amygdala has been reported to be affected by the deposition of extracellular amyloid plaques and neurofibrillary tangles in post-mortem human samples (Scott et al., 1991). AD patients (≈75 years old) showed significant shrinkage and neuronal death as well as widespread gliosis (Scott et al., 1991; Vereecken et al., 1994). Using magnetic resonance imaging (MRI), volumetric analysis showed that the atrophy of the amygdala and hippocampus are comparable at early clinical stages of the disease (Poulin et al., 2011; Contador et al., 2021).

In addition to examining the amygdala through brain imaging and post-mortem analysis in AD patients, this region has also been analyzed in murine AD models to elucidate the progression of histopathological hallmarks such as Aβ accumulation (Spires-Jones and Knafo, 2011). For instance, in APP/PS1 transgenic AD mice, analysis of Aβ accumulation in the lateral amygdala revealed abundant senile plaques at 12 months of age (Knafo et al., 2009). Moreover, morphological analyses showed altered neuronal projections in the lateral amygdala of APP/PS1 mice, reflected in reduced dendritic complexity and a decrease in large spines (Knafo et al., 2009). Another study showed reduced neuronal function in the amygdala of 10-week-old APPswe/$PS1_{L166P}$ AD mice (Wu et al., 2024). When tested in the elevated plus maze, a paradigm that allows the evaluation of anxiety-like behaviors, c-fos positive neurons were decreased in the basolateral amygdala (BLA) of APPswe/$PS1_{L166P}$ mice after elevated plus maze exposure. Additionally, BLA pyramidal neurons also exhibited increased excitatory postsynaptic currents and a higher resting membrane potential (Wu et al., 2024). The serotonin receptors 5-HT_{1A}R and 5-HT_{2A}R appeared upregulated, and their downregulation improved emotional and cognitive function by restoring normal synaptic E/I balance, increasing the number of c-fos positive cells, indicating a reduction in Aβ neurotoxicity in 24-week-old APPswe/$PS1_{L166P}$ mice (Wu et al., 2024). Additionally, the study did characterize the extracellular presence of Aβ plaques in 24-week-old AD mice, which agreed with previous reports that demonstrated that APPswe/PS1L166P develops plaques from 2 months of age in the hippocampus, entorhinal cortex, and motor cortex (Montarolo et al., 2013).

Furthermore, Zn^{2+} ion dyshomeostasis has been related to cognitive decline in AD (Xie et al., 2020). For instance, intracranial injection of $A\beta_{42}$ into the BLA of WT Wistar rats shows a significant increase in intraneuronal Zn^{2+} together with a reduction in long-term potentiation (LTP) (Ishikawa et al., 2022). These data suggest that morphological and functional impairments of amygdala neurons may contribute to the early non-cognitive symptoms observed in AD patients, contributing to the progression and worsening of the disease in later stages.

Locus coeruleus

LC is a noradrenergic nucleus located in the posterior region of the pons, playing a crucial role in regulating attention, alertness, stress response, pain modulation, cognition, emotion, and the sleep-wake cycle (Berridge and Waterhouse, 2003; Aston-Jones and Cohen, 2005). A study performed on postmortem AD brains showed that LC volume diminished in parallel to pathology progression (Theofilas et al., 2017). It has been previously reported that patients with AD-related senile dementia exhibit a significant reduction in the number of noradrenergic neurons in the LC, along with structural changes in the somata and dendritic branching of these neurons (Chan-Palay and Asan, 1989; Chan-Palay, 1991). Recently, the degeneration and structural atrophy of axonal LC afferents into the neocortex and hippocampus in 12 and 24-month-old APP-KI ($APP^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$) have been demonstrated, suggesting that Aβ plaques in the LC lead to a noradrenergic deficit (Sakakibara et al., 2021). This mouse develops Aβ pathology, including subcortical Aβ plaque deposition from 4 months of age, synaptic impairment, and memory loss (Nilsson et al., 2014). Also, the number of tyrosine hydroxylase-positive neurons was reduced in the LC of 16-month-old APP/PS1 mice (Liu et al., 2013). Additionally, degeneration of aminergic LC neurons with noradrenergic neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine increased the presence of eAβ deposition in the hippocampus and frontal cortex, and augmented $A\beta_{42}$ levels in 6-month-old APP/PS1 mice in norepinephrine-depleted regions (Heneka et al., 2010). Interestingly, it has been shown that nanomolar concentrations of AβOs bind to the allosteric site of the α_{2A} adrenergic receptor, which is expressed in LC in both noradrenergic and non-noradrenergic neurons, redirecting the receptor signaling to activate the glycogen synthase kinase 3β and the subsequent induction of tauopathy (Zhang et al., 2020). Altogether, these studies indicate that AD amyloidopathy alters subcortical nuclei, contributing to the onset of neuropsychiatric manifestations of the disease and cognitive decline.

Raphe nucleus

The dorsal raphe nucleus (RN) is the primary source of serotonin or 5-hydroxytryptamine (5-HT), which because of its release in extensive regions of the brain, participates in many biological processes, including sleep-wake cycles, emesis, appetite, mood, and memory (Abela et al., 2020). It projects efferent fibers to crucial regions implicated in AD, including the hippocampus, amygdala, entorhinal cortex, prefrontal cortex, basal forebrain, and hypothalamus (Lyness et al., 2003; Braun and Van Eldik, 2018). Significantly, postmortem analyses of AD brains have demonstrated that the loss of serotonergic neurons in the RN is an early event in disease progression, occurring even in the absence of cognitive decline (Yamamoto and Hirano, 1985; Hendricksen et al., 2004; Simic et al., 2009). Using positron emission tomography to measure the expression of the serotonin transporter in the dorsal RN of patients with MCI indicated a significant reduction of the marker associated with lower levels of functional connectivity in the hippocampus (Barrett et al., 2017). Interestingly, a recent study utilizing the 5×FAD transgenic mouse model, Interestingly, a recent study using the 5×FAD transgenic mouse model, which overexpresses human APP with the Swedish, Florida (I716V), and London (V717I) mutations, along with human PS1 carrying the M146L and L286V mutations, has reported the accumulation of Aβ plaques in the hippocampus and cortex as early as 2–4 months of age (Jawhar et al., 2012; Forner et al., 2021), reported a significant reduction in the excitability of dorsal RN 5-HT neurons and a corresponding decrease in their projections to the dorsal CA1 region at 3 months of age, along with impaired LTP (Chen et al., 2024a). Optogenetic or chemogenetic activation of the specific dorsal RN–hippocampus circuit (comprising 5-HT projection neurons targeting hippocampal CA1 pyramidal CAMKII-positive neurons) ameliorated depressive behaviors at early stages (3 months of age) and cognitive impairments at later stages (6 months of age) (Chen et al., 2024a). Additionally, a recent study reported the presence of eAβ deposits and a significant reduction in 5-HT3A serotonin receptor levels in the medial RN of 8- to 9-month-old hAPP-J20 AD mice. Fiber photometry experiments measuring calcium dynamics further demonstrated a significant increase in the CA1 hippocampus region innervated by medial RN 5-HT neurons in 8-month-old J20 mice (Wang et al., 2023). Overall, significant changes in the RN occur in AD associated with eAβ, impairing the serotonergic pathway. These alterations would enhance synaptic dysfunction in the hippocampus, driving cognitive decline.

Presence of Intracellular Amyloid-Beta and Synaptic Alterations in Alzheimer's Disease

In contrast with the presence of eAβ plaques in advanced stages of AD, not only in cortical but also sub-cortical brain regions, experimental evidence has demonstrated that the accumulation of iAβ, which contributes to neuronal dysfunction in both human and animal models, appears early in AD, preceding the accumulation of extracellular amyloid plaques (Tseng et al., 2004; Cuello et al., 2012; Wilson et al., 2017; Gallego Villarejo et al., 2022). Despite limited knowledge regarding the specific pathways involved in the excessive and toxic aggregation of iAβ, its accumulation is believed to result from the imbalance between intracellular production of Aβ, Aβ import within cells, and its clearance (LaFerla et al., 2007; Gallego Villarejo et al., 2022). We will now describe recent evidence on the presence of iAβ in cortical and sub-cortical brain regions and its synaptic effects.

Cortical and hippocampal regions are affected by intracellular amyloid-beta

It is reported that accumulation of iAβ in AD brains can cause cell death in cortical pyramidal neurons, with cell lysis being an essential source of amyloid plaques (D'Andrea et al., 2001). Although numerous studies report iAβ aggregation in the neocortex of aged AD brains (Thal et al., 2002; Klunk et al., 2004; Dubois et al., 2010), other studies have shown that iAβ also accumulates in the neocortex of healthy aging brains (Blair et al., 2014; Welikovitch et al., 2018).

Notably, multiple studies in animal models of AD have confirmed the presence of iAβ preceding extracellular deposition, regardless of the specific mutation they carry (Tomiyama et al., 2010; Iulita et al., 2014; Esquerda-Canals et al., 2017; Wilson et al., 2017; Fernández-Pérez et al., 2020, 2021). For instance, immunostaining studies using specific antibodies for Aβ showed iAβ at pre-plaque stages in the hippocampus, neocortex, and amygdala at 1 to 3 months of age in McGill-Thy1-APP rats, which express hAPP Swedish and Indiana mutations (Ferretti et al., 2011; Iulita et al., 2014). Interestingly, the presence of iAβ was correlated with impairment of fear-conditioning and novel object recognition in 3-month-old transgenic rats with AD (Iulita et al., 2014). Additionally, iAβ was detected in the hippocampus and cortex as early as 3 months of age in ArcAβ mice (expressing hAPP with the combined Swedish and Artic APP FAD mutations), while amyloid plaque deposits started to appear at 7 months (Knobloch et al., 2007). These mice exhibited cognitive impairment starting at 6 months of age and increased basal locomotor activity at 3 months (Knobloch et al., 2007). Additionally, a recent study suggested that deletion of Cathepsin D, a lysosomal protease involved in Aβ and Tau degradation, increases Aβ in Tg2576 mice at 3 weeks of age evidenced by an intense signal of Aβ aggregates within the somata, indicating an active role of Cathepsin D in AD proteinopathy (Terron et al., 2024). In agreement, the early presence of iAβ in humans was reported in the hippocampus of patients with MCI (Gouras et al., 2000), supporting its involvement in the early stages of AD development.

Although the early events driving AD progression are not fully understood, much less the molecular mechanisms, synaptic loss has been identified as a critical early process leading to cognitive decline (Bayer and Wirths, 2010). For instance, it was reported that patients with MCI have fewer synapses in the hippocampus compared to controls (Scheff et al., 2007). Notably, early Aβ accumulation disrupts synaptic plasticity by inhibiting LTP in the hippocampus of McGill-Thy1-APP rats as early as 3 months of age (Qi et al., 2014; Wilson et al., 2017). Additionally, the McGill AD rats exhibited impairments in learning visual stimulus–reward associations and showed reduced levels of transcripts associated with synaptic plasticity, including *Arc*, *c-fos*, *Egr1*, and brain-derived neurotrophic factor. Notably, these alterations were observed at early AD stages, prior to plaque formation, at 6 months of age (Wilson et al., 2017). Moreover, using a transgenic mice model expressing a fusion protein of human $A\beta_{42}$-GFP that forms oligomers intracellularly, it was demonstrated that both short-term plasticity and LTP were impaired in AD mice from 3 months of age. In addition, synaptic protein analysis showed a significant decrease in the expression level of postsynaptic proteins such as the GluN2B subunit of the N-methyl-D-aspartate receptor, the GluA2 AMPAR subunit, and neuroligin, an anchor protein that connects pre and postsynaptic components (Ochiishi et al., 2019). Furthermore, the acute application of nanomolar concentrations of intracellular human AβOs to hippocampal neurons in WT mice increased excitatory synaptic transmission and neuronal excitability both *in vitro* and *in vivo* (Fernandez-Perez et al., 2021). Whole-cell electrophysiological recordings revealed that iAβ differentially impacted excitatory and inhibitory synaptic currents; both AMPAR- and $GABA_A$R-mediated miniature synaptic currents exhibited increased frequency, while only AMPAR-mediated currents showed a significant amplitude increase. This effect extended to evoked postsynaptic AMPA currents, but not GABAergic currents, suggesting that iAβ affects AMPAergic transmission through both pre and postsynaptic mechanisms, whereas GABAergic transmission is primarily impaired by enhanced presynaptic release (Fernandez-Perez et al., 2021). iAβ also increased nitric oxide levels, a retrograde messenger involved in neurotransmitter release, dependent on protein kinase C activation, suggesting that iAβ induces functional spreading and hyperexcitability in the hippocampus, potentially contributing to the development of early neuropathological alterations in AD (Fernandez-Perez et al., 2021). Additionally, another study demonstrated that intrinsic membrane properties of CA1 pyramidal neurons showed a significant increase in firing frequency and diminished rheobase in hAPP-J20 mice at pre-plaque stages, consistently indicating that these neurons are more excitable in AD mice (Wang et al., 2023). Additionally, calcium responses were significantly elevated in CA1 pyramidal neurons, indicating hyperactivation of these cells in pre-plaque AD (Wang et al., 2023). The study also demonstrated a decreased relative expression of the 5-HT3 serotonin receptor in the hippocampus at both pre-plaque and plaque stages in AD mice. Blocking the 5-HT3 receptor mitigated CA1 pyramidal neuron activation, suggesting that this receptor mediates serotonergic activation within the hippocampus (Wang et al., 2023).

Although our understanding of how iAβ oligomers influence brain neuron function remains limited, some in-vitro studies on hippocampal primary cultures suggest that Aβ can interact with phospholipids and disrupt the plasma membrane by forming pore-like structures permeable to cations, anions, and other small molecules, leading to synaptic failure in the nervous system (Fernández-Pérez et al., 2017, 2018). Additionally, iAβ can disrupt the activity of cellular components such as the endoplasmic reticulum, mitochondria, endosomes, lysosomes, and trans-Golgi network (Tomiyama et al., 2010; Lee et al., 2017; Oren et al., 2020; Gallego Villarejo et al., 2022). Despite significant progress in elucidating the pathogenesis of AD, our understanding of how iAβ influences brain function in the early stages of AD progression remains insufficiently explored (**Figure 3**).

Intracellular amyloid beta also accumulates in subcortical brain regions

In addition to previously described cortical and hippocampal regions, subcortical regions such as the striatum, amygdala, LC, and RN have also been identified as vulnerable brain structures in the early stages of AD. Studies have revealed increased excitability in the nAc, reduced fiber density in LC, and increased hyperactivity in the RN even before eAβ accumulation (Fernández-Pérez et al., 2020; Sakurai et al., 2020; Chen et al., 2022; **Table 2**).

Nucleus accumbens

Non-cognitive behaviors such as reward, aggression, and social interaction, which are regulated by the nAc, are affected early in the progression of AD, even before amyloid plaque deposition and memory loss, suggesting a critical role of nAc in the pathogenesis of AD (Masters et al., 2015a, b; D'Amelio et al., 2018; Chen et al., 2021). As we mentioned earlier, studies in humans have shown atrophy in the nAc of patients with MCI and AD (Wolf et al., 1999; Klunk et al., 2004; Annus et al., 2016; Nie et al., 2017; Contreras et al., 2020), and postmortem AD brain tissue analysis showed amyloid plaque accumulation and hyperphosphorylated Tau in the late stages of the disease (Suenaga et al., 1990; Kawakami et al., 2014). Nevertheless, it is important to consider the presence of iAβ at early stages of AD, where non-cognitive symptoms are observed. Interestingly, the presence of Aβ in the nAc was characterized in transgenic Tg2576 mice with AD (Nobili et al., 2017). Immunofluorescence experiments using the 6E10 antibody to detect Aβ showed the absence of amyloid plaques but increased cytosolic and intracellular expression levels of APPswe and Aβ in both the nAc core and shell of 6-month-old Tg2576 mice (Nobili et al., 2017). Furthermore, a recent study reported the early presence of iAβ in the absence of extracellular amyloid plaque in the nAc of 6-month-old Mo/Hu APP/PS1 transgenic mice (Fernández-Pérez et al., 2020). Detection of iAβ was done through immunohistochemistry using the MOAβ2 antibody, which recognizes the C-terminal region of Aβ, excluding APP detection (Fernández-Pérez et al., 2020). Interestingly, iAβ accumulation in the nAc was associated with

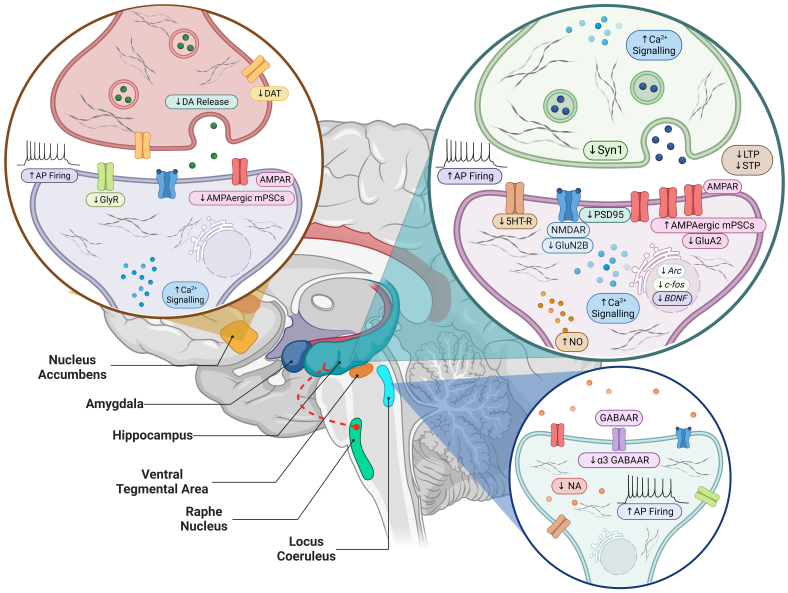

Figure 3 | **Synaptic alterations by intracellular amyloid-beta (iAβ) accumulation in vulnerable brain regions.**
The scheme illustrates the intracellular accumulation of amyloid-beta (Aβ) in several brain regions such as the hippocampus, prefrontal cortex, nucleus accumbens (nAc), amygdala, locus coeruleus (LC), and raphe nucleus. In classical regions such as the hippocampus, Aβ causes increased neuronal excitability, with an enhancement in AMPAergic postsynaptic currents, firing rate, nitric oxide (NO) levels, and calcium signaling. Decreases in synaptic proteins Synapsin 1 and postsynaptic density protein 95 (PSD95), serotonin receptors (5HT-R), and long-term and short-term potentiation (LTP and STP) were also observed. In subcortical regions, such as the nAc, Aβ leads to increases in neuronal excitability but also to a reduction in excitatory postsynaptic currents, glycine receptors (GlyR), dopamine transporter (DAT), and dopamine (DA) levels. LC exhibits an increase in neuronal excitability and spontaneous firing rate, while norepinephrine levels, $GABA_A$-evoked current, and $GABA_A$ receptor subunits are reduced. Raphe nucleus efferent projections to the hippocampus show signs of degeneration. Created with BioRender.com.

functional changes in medium spiny neurons, showing a significant increase in excitability and reduced frequency of AMPA-mediated miniature postsynaptic currents (Fernández-Pérez et al., 2020). Additionally, GlyR protein levels, mRNA expression, and function were significantly reduced in these mice during the early stages of disease progression (Fernández-Pérez et al., 2020; Armijo-Weingart et al., 2024). This reduction in GlyR function was further confirmed by GCaMP6s-calcium analysis, which showed a marked decrease in GlyR-mediated inhibition of calcium homeostasis in the nAc of APP/PS1 mice at pre-plaque stages, where iAβ is present (Armijo-Weingart et al., 2024). Moreover, despite the well-established role of ethanol in modulating GlyR function (Yevenes et al., 2010; Burgos et al., 2015; Forstera et al., 2017), GlyRs in medium spiny neurons of 6-month-old APP/PS1 mice exhibited insensitivity to ethanol (Armijo-Weingart et al., 2024). Overall, these data provide evidence of iAβ accumulation in the nAc in the early stages of AD, associated with alterations in excitatory and inhibitory neurotransmission, reflecting an early E/I imbalance.

The medium spiny neurons in the nAc are GABAergic projection neurons that innervate the VTA, modulating dopamine (DA) activity in the brain (Russo and Nestler, 2013). A recent study suggests that DA loss is critical to AD pathogenesis (D'Amelio et al., 2018; Krashia et al., 2019). In line with this, amperometric recordings in brain slices from the Tg2576 AD mouse revealed decreased dopaminergic input in both the nAc core and shell, but not in the dorsal striatum, during pre-plaque stages of AD at 4 months of age (Cordella et al., 2018). Consequently, the expression of the dopamine transporter in the nAc was significantly reduced in Tg2576 mice (Nobili et al., 2017; La Barbera et al., 2022). Interestingly, the alteration in the tonic control of DA release was manifested as a deficit in reward-associated behaviors (Nobili et al., 2017) (for more details see the section "Early Non-Cognitive Alterations in Alzheimer's disease").

This evidence suggests the early involvement of the nAc in AD pathogenesis, preceding amyloid plaque deposition and memory loss. It is associated with iAβ pathology and E/I imbalance, which, in turn, could impair reward processing within the mesolimbic system. This underscores the need for further research into the mechanisms underlying nAc dysfunction in the early stages of disease progression.

Amygdala

Immunohistochemical experiments using postmortem brain tissue of AD patients revealed intraneuronal accumulation of Aβ in the amygdala, evidenced by an increase in the number of iAβ positive neurons (España et al., 2010). In AD animal models, immunohistochemical analysis using the 6E10 antibody showed abundant accumulation of iAβ and APP in the BLA nucleus of 5-month-old 3×Tg AD (Esquerda-Canals et al., 2017). Moreover, the detrimental role of iAβ on amygdala-dependent emotional responses was demonstrated by its effects on the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) signaling pathway (España et al., 2010). Using 6-month-old AD transgenic mice expressing the APP Indiana mutation, another expressing both APP Swedish and Indiana mutations (APPswe/Ind), and the 3×Tg model that expresses APPswe, PS1 M146V, and Tau P301L mutations, the intracellular accumulation of Aβ was observed in the BLA of the three mice models (España et al., 2010). Data also showed that conditioned fear behaviors were increased in these AD models (España et al., 2010). Additionally, iAβ was differentially accumulated in glutamatergic and GABAergic neurons of 3×Tg and APPswe/Ind mice, respectively, which was evidenced in the signal of the 6E10 antibody co-localized with the neuronal glutamatergic marker pCaMKIIα and GABAergic neuron marker VGAT (Vesicular GABA Transporter) (España et al., 2010). Furthermore, ERK signaling in the basolateral amygdala of APPInd mice showed increased levels of pERK/ERK ratio and in the number of positive pERK neurons in the BLA. Overall, these data suggest that Aβ is involved in enhancing amygdala-dependent emotional responses in AD transgenic mice, and these effects would be mediated by ERK signaling (España et al., 2010).

While morphological and structural changes associated with Aβ in the amygdala have been documented in both AD brains and transgenic animal models, along with amygdala-dependent non-cognitive manifestations, the synaptic effects of iAβ in this brain region remain underexplored.

Locus coeruleus

Recent studies have demonstrated that LC might be altered in the early stages of AD (Kelly et al., 2021; Chen et al., 2022). For instance, a recent study showed the presence of iAβ in the LC of both AD patients and in 2- to 4-month-old APP/PS1 mice (Kelly et al., 2021). Notably, the oligomeric form of Aβ was also detected in intraneuronal organelles, such as mitochondria, evidenced by the co-distribution of Aβ Os signal and citrate synthase enzyme located in the mitochondrial matrix, as well as with superoxide dismutase 2, which showed diminished immunoreactivity in the LC of AD mice. Additionally, intraneuronal AβOs were located in the proximity of synaptic vesicle 2, VGAT, and VGLUT2 synaptic markers and colocalized with α3 $GABA_A$R (Kelly et al., 2021). Supporting the notion that iAβ enhances neuronal excitability, electrophysiological recordings in LC brain slices showed that noradrenergic neurons from AD mice exhibited a significant increase in the spontaneous firing rate and reduced noradrenaline levels compared to WT (Kelly et al., 2021). Also, noradrenergic neuron hyperexcitability was associated with GABAA receptor dysfunction and a reduced inhibitory synaptic influence, supported by electrophysiological experiments showing a significant decrease of GABA-evoked response on firing rate and decreased levels of α3 $GABA_A$R subunit in this brain region in AD mice. These results suggest that Aβ oligomers affect the function of α3 containing $GABA_A$R in the LC, thus impairing the noradrenergic system, whose role is to enhance brain connectivity and situational awareness, which are reported to be decreased in early AD (Kelly et al., 2021). Additionally, *in vitro* studies have shown that the Cath.a-differentiated (CAD) cell line, a catecholaminergic cell line derived from brain stem neurons, had a large number of intracellular AβOs accumulated at terminal processes of neurons, proposing a cell culture model for iAβ mechanisms in catecholaminergic cells (Muresan and Muresan, 2006).

Table 2 | **Significant actions of intracellular Aβ on AD models**

AD models	Mutation(s) /Treatments	Ages	Brain regions	Principal findings	References
APP/PS1 mice	Chimeric mouse/human APP Swedish (K670N, M671L), Human exon-9-deleted variant of PS1 (PS1dE9)	2–4 mon	Locus coeruleus	Spontaneous firing rates in noradrenergic neurons. Reduced intensity of TH-immunopositively somata. Increased IBA1 immunoreactivity associated with microglial activation.	Kelly et al., 2021
		4 mon	–	Increase in seizure incidence compared to controls.	Minkeviciene et al., 2009
			Hippocampus	Susceptibility to chemical seizure-induced cognitive impairment. Increased hyperexcitability and decreased GABAergic neurotransmission. Decreased number of PV^+ Ins	Mao et al., 2024
		6 mon	Nucleus accumbens	Increased excitability and reduced frequency of AMPA-mediated miniature postsynaptic currents.	Fernández-Pérez et al., 2020
				GlyR protein levels, mRNA expression and function significantly reduced. Decreased GlyR-mediated inhibition of calcium homeostasis	Fernández-Pérez et al., 2020; Armijo-Weingart et al., 2024
3×Tg mice	APP Swedish (K670N, M671L), PS1 (M146V), MAPT (P301L)	2 mon	Hippocampus, amygdala	Impaired spatial memory	España et al., 2010
		6 mon	–	Increased fear and anxiety behaviors. No changes in fear conditioning. Impaired spatial memory.	España et al., 2010
APP Ind	APP Indiana (V717F)	6 mon	Amygdala	Phosphorylated ERK1 and ERK2 levels after cued fear conditioning	España et al., 2010
Tg2576 mice	APP Swedish (K670N, M671L)	4 mon	Nucleus accumbens	Decreased dopaminergic input in both the nAc core and shell, but not in the dorsal striatum. Reduction in dopamine transporter immunoreactivity.	Cordella et al., 2018
APPswe/PS1-L166P mice	APP Swedish (K670N, M671L), human PS1 (L166P)	3 mon	Amygdala	Increase in neuronal excitability. Increased 5-HT1A and 5-HT2A expression. Heightened anxiety-like behavior	Wu et al., 2024
		6 mon	Amygdala	Increased neuronal excitability. Increased C-fos expression. Impaired spatial memory. Downregulation of 5-HT1AR and 5-HT2AR improved emotional and cognitive function.	Wu et al., 2024
McGill-Thy1-APP rats	APP Swedish (K670N, M671L) and Indiana (V717F)	3 mon	–	Decreased auditory fear conditioning. Deficits in novel object recognition and location task.	Iulita et al., 2014
		3–4 mon	Hippocampus	Short-term potentiation and long-term potentiation showed a marked decrease.	Qi et al., 2014
		6 mon	Hippocampus	Impaired learning visual stimulus reward association. Reduction in synaptic plasticity associated transcripts such as Arc, c-fos, Egr1 and brain-derived neurotrophic factor.	Wilson et al., 2017
ArcAβ mice	APP Swedish (K670N, M671L) and Artic (E693G)	3 mon	Hippocampus, cortex	Increased basal locomotor activity.	Knobloch et al., 2007
huAPP/CatD-KO	APP Swedish (K670N, M671L) and CatD-knock down	3 wk	Hippocampus, cortex	Deletion of CatD specifically increases intracellular Aβ levels without promoting plaque formation.	Terron et al., 2024
Aβ-Gfp Tg	Expresses a fusion protein of human $Aβ_{1–42}$ and Green Fluorescent Protein (GFP)	2–3 mon	Hippocampus	Reduction in long-term potentiation. Decreased dendritic spines and more filopodia. Increased levels of phosphorylated tau.	Ochiishi et al., 2019
hAPP-J20 mice	APP Swedish (K670N, M671L), Indiana (V717F)	4–5 mon	Hippocampus	Increased hyperexcitability, characterized by increased action potential firing frequency and decreased rheobase. Elevated calcium responses. Photometry recordings showed depressed serotonergic signaling.	Wang et al,. 2023
Primary cultures from C57BL/6J WT mice	Acute intracellular infusion of $Aβ_{1–42}$ oligomers (50–1000 nM)	10–12 DIV	Hippocampus	Increased excitability and excitatory over inhibitory synaptic transmission. Increase of nitric oxide levels dependent on PKC activation.	Fernandez-Perez et al., 2021

5-HT1A: 5-Hydroxytryptamine receptor 1A; 5-HT2AR: 5-hydroxytryptamine receptor 2A; APP/PS1: amyloid precursor protein/presenilin 1; APP: amyloid precursor protein; Aβ: amyloid-beta; CatD: cathepsin D; DIV: days *in vitro*; ERK1/2: extracellular signal-regulated kinases 1 and 2; GABA: gamma-aminobutyric acid; GFP: green fluorescent protein; GluA1: glutamate receptor 1 (AMPA receptor subunit); GluA2: glutamate receptor 2 (AMPA receptor subunit); GlyR: glycine receptor; IBA1: ionized calcium binding adaptor molecule 1; nAc: nucleus accumbens; PKC: protein kinase C; PS1ΔE9: presenilin 1 exon-9-deleted variant; PV^+: parvalbumin-positive; TH: tyrosine hydroxylase.

These findings underscore the possibility that AD may originate in subcortical regions, such as the LC, where early accumulation of iAβO disrupts neuronal function (Kelly et al., 2021). These alterations in noradrenergic neurons may lead to E/I imbalance and impaired neurotransmitter systems, contributing to the broader pathological progression of the disease as it spreads to cortical and hippocampal areas.

Raphe nucleus

A recent study investigated the impact of RN serotoninergic signaling impairment on the neural function of pyramidal neurons in the CA1 region of the hippocampus in 4- to 5-month-old hAPP-J20 AD mice at pre-plaque stages (Wang et al., 2023). Serotonergic neurons from the medial RN projecting to the hippocampus exhibited increased axonal arborization in hAPP-J20 mice. Despite this increase in serotonergic projections, fiber photometry detected lower serotonin levels in the CA1 region of 4- to 5-month-old AD mice. Furthermore, DREAAD activation of 5-HT-expressing neurons in the medial RN reduced the excitability of pyramidal neurons in the hippocampus. Stimulation of 5-HT neurons in the medial RN increased the frequency of spontaneous inhibitory postsynaptic currents in hippocampal pyramidal neurons in both AD and WT mice, supporting functional connectivity between medial raphe nucleus neurons and hippocampal GABAergic interneurons (Varga et al., 2009; Wang et al., 2023). This study suggests that the impairment of serotoninergic signaling mediated by the 5-HT3 receptor in the medial RN enhances hippocampal hyperexcitability in AD, favoring its progressive neurodegeneration evidenced by cognitive decline.

Early Non-Cognitive Alterations in Alzheimer's Disease

Non-cognitive manifestations in Alzheimer's disease patients

In previous sections, we reviewed evidence indicating the presence of Aβ in subcortical regions such as the nAc and amygdala, with an emphasis on animal models. These findings suggest that, beyond memory and language, other brain functions may also be affected in the early stages of AD. Consequently, we will now discuss studies in both human and animal models that focus on non-cognitive alterations associated with the pathology of the disease (**Table 3**).

Recently, it has become increasingly recognized that, in addition to cognitive symptoms (e.g., memory, learning, and language decline), AD also manifests with non-cognitive behaviors, which can emerge in the early stages of the disease (Gallagher et al., 2011; Zhao et al., 2016; Victoroff et al., 2018; Zufferey et al., 2020). At a clinical level, over 80% of patients with AD exhibit at least one non-cognitive symptom from the onset of cognitive decline. These non-cognitive manifestations include behavioral and psychological symptoms (such as apathy, agitation, anxiety, impaired social

Table 3 | **Non-cognitive symptoms in human and animal models of AD**

Human/animal models	Findings	References
Humans	Follow-up study showed that depression and irritability were the most common non cognitive symptoms before diagnosis of MCI or dementia.	Wise, 2019
	Depression was identified as the first comorbidity 2–10 years before AD diagnosis, followed by anxiety, constipation, and abnormal weight loss.	Nedelec, 2022
	Abnormal AD-related CSF biomarkers (lower $A\beta_{42}$ levels and higher t-tau/$A\beta_{42}$ and p-tau/$A\beta_{42}$ ratios) are linked to increased symptoms of depression, anxiety, apathy, and nighttime behavior disturbances in older, non-demented adults.	Krell-Roesch et al., 2023
	Higher levels of AD-related CSF biomarkers ($A\beta_{42}/A\beta_{40}$, t-tau/$A\beta_{42}$, p-tau/$A\beta_{42}$) are associated with more anger, anxiety, and fatigue over time in cognitively normal older adults.	Babulal et al., 2022
	VTA size is significantly linked with hippocampal size and memory performance, and its functional connectivity with the hippocampus is decreased in AD patients.	De Marco and Venneri, 2018
	Early-onset AD patients experience a faster decline in the volume of the caudate, putamen, and thalamus compared to late-onset AD patients.	Cho et al., 2013
	Amygdala atrophy is comparable to hippocampal atrophy in early AD and correlates with aberrant motor behavior, anxiety, and irritability.	Poulin et al., 2011; Contador et al., 2021
6×Tg mice	Increased motor activity, anxiety-like behavior, and depression-like behavior observed at 9–11 months.	Tag et al., 2022
Tg2576/PS1 (M146L) mice	Circadian disruptions have been identified in AD models, including decreased nocturnal activity and increased daytime activity, alongside alterations in circadian clock gene expression in the hypothalamus, cerebral cortex, and hippocampus observed in 6-month-old mice.	Chauhan et al., 2017; Carrero et al., 2023
Tg2576 mice	Reduced chocolate consumption and failure in conditioned place preference task observed in 6-month-old mice.	Nobili et al., 2017
APP/PS1 mice	Reduction in alcohol consumption correlated with decreased glycine receptor-mediated calcium signalling in the nAc of 6-month-old mice	Armijo-Weingart et al., 2024
3×Tg mice	Motor impairments related to the deep cerebellar nuclei in 6-month-old mice, with progression noted at advanced stages.	Castillo-Mariqueo et al., 2021; Castillo-Mariqueo and Giménez-Llort, 2022

6×Tg: 6×Tg transgenic mice; AD: Alzheimer's disease; Aβ: amyloid-beta; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; nAc: nucleus accumbens; PS1 (M146L): presenilin 1 with M146L mutation; p-tau: phosphorylated tau; Tg2576: Tg2576 transgenic mice; t-tau: total tau; VTA: ventral tegmental area.

cognition, irritability, and depression), circadian rhythm disruptions, sensory impairments, and physical changes (such as altered gait speed and weight fluctuations) (Kaufer et al., 1998; Lyketsos et al., 2002; Masters et al., 2015b; Chen et al., 2024b). The most common psychological symptoms before cognitive decline (MCI or dementia) are depression and irritability (Wise et al., 2019). A recent study examined the association of several mental health states and increased risk of AD, identifying that depression was the first comorbidity 2 to 10 years before its diagnosis, followed by anxiety, constipation, and abnormal weight loss (Nedelec et al., 2022). Other studies have suggested that late-life depression may be an early feature of forthcoming AD rather than a contributing risk factor (Singh-Manoux et al., 2017; Wise et al., 2019).

Studies using cerebrospinal fluid (CSF) biomarkers have shown a correlation between AD biomarkers and non-cognitive manifestations. For example, it was found that in older, non-demented adults, abnormal AD-related CSF biomarkers, such as lower $A\beta_{42}$ levels and higher t-Tau/$A\beta_{42}$ and p-Tau/$A\beta_{42}$ ratios, were linked to increased symptoms of depression, anxiety, apathy, and night-time behavior disturbances (Krell-Roesch et al., 2023). Furthermore, another study aimed to predict changes in mood states based on AD-related CSF biomarkers among cognitively normal older adults over an average of three years (Babulal et al., 2022). For instance, it was found that patients with higher levels of CSF biomarkers ($A\beta_{42}/A\beta_{40}$, t-Tau/$A\beta_{42}$, p-Tau/$A\beta_{42}$) developed more anger, anxiety, and fatigue over time compared to those with normal biomarker levels (Babulal et al., 2022). These findings suggest that neuropsychiatric symptoms could be important indicators for individuals with abnormal CSF biomarkers, highlighting their potential clinical relevance.

Several subcortical regions, such as the VTA, nAc, and amygdala have been reported to exhibit physiopathological alterations in AD patients (Knafo, 2012; Pievani et al., 2013; Nie et al., 2017). For example, a structural MRI study showed that VTA size was significantly linked with hippocampal size and memory performance (De Marco and Venneri, 2018). Furthermore, the study revealed that the functional connectivity between the VTA and the hippocampus was significantly decreased and associated with typical clinical markers of AD (De Marco and Venneri, 2018). Regarding striatal regions, a longitudinal study showed that early-onset AD experienced a faster decline in the volume of the caudate, putamen, and thalamus compared to those with late-onset AD (Cho et al., 2013).

Anatomical evidence has revealed that the amygdala is one of the earliest subcortical regions affected in the preclinical stages of AD (Padulo et al., 2023; Stouffer et al., 2024). Mental score data indicated a correlation between amygdala atrophy and aberrant motor behavior, with a potential relationship between anxiety and irritability in early AD progression (Poulin et al., 2011; Contador et al., 2021). Moreover, MRI analysis demonstrated a close relationship between amygdala volume in mild AD, where a higher amygdala volume was associated with lower odds of developing aggressive and agitated behaviors (Jaramillo-Jimenez et al., 2021). Interestingly, a study found abnormal amygdala-prefrontal cortex connectivity in AD patients with depression using resting-state functional magnetic resonance imaging (fMRI). The data showed that depressed AD patients had increased functional connectivity between the amygdala and orbitofrontal cortex and decreased functional connectivity between the amygdala, medial prefrontal cortex, and inferior frontal gyrus compared to non-depressed AD patients (Guo et al., 2018). These findings suggest that an abnormal functional connectivity of the amygdala may be a key feature of depression in AD patients. Interestingly, the cellular and molecular alterations occurring in these brain regions are thought to occur decades before memory loss (Guo et al., 2017). Overall, these morphological changes might explain some of the neuropsychiatric, non-cognitive symptoms manifested at early stages of the disease.

In summary, the neuropathological characteristics of AD in subcortical regions are still largely unknown. Understanding the relationship between non-cognitive manifestations and dementia and its progression is crucial for accurately anticipating and monitoring potential cognitive decline in individuals in the early stages of AD (**Table 2**).

Early impairment of non-cognitive behaviors in Alzheimer's disease animal models

Recent studies have emphasized the importance of understanding the early stages of AD to prevent irreversible neuronal damage (Chen et al., 2024b). Identifying non-cognitive behaviors in prodromal states may serve as a clinical marker to overcome the limitations of current diagnostic methods, which are restricted in accessibility to the global population due to high costs and invasive procedures (Chen et al., 2024b). In preclinical research using various AD transgenic models, non-cognitive behaviors have been identified as indicators of prodromal AD. For example, in a 9- to 11-month-old 6×Tg mouse model, which overexpresses hAPP harboring the Swedish, Florida, and London mutations, as well as human PS1 M146L and L286V mutations, and MAPT P301L mutation, an increase in motor activity and anxiety-like behavior was observed using the light/dark box and elevated plus maze tests (Tag et al., 2022). Furthermore, the forced swimming and tail suspension tests revealed increased depression-like behavior and decreased sensorimotor inhibition in the pre-pulse inhibition test (Tag et al., 2022).

Another aspect that has been extensively studied in AD models is circadian disorders. The circadian clock, a system regulated by the suprachiasmatic nucleus in the hypothalamus, synchronizes the organism with the 24-hour daily cycle through stimuli such as environmental light (Chauhan et al., 2017). Using animal models, abnormalities in sleep, locomotor activity, and body temperature rhythms have been characterized, with reports of decreased nocturnal activity (the equivalent of daytime napping in a nocturnal species) and increased daytime activity (Chauhan et al., 2017). Recent findings have demonstrated that alterations in circadian clock gene expression are present not only in the hypothalamus but also in the cerebral cortex and hippocampus during the early stages of the disease in 6-month-old APP(Tg2576)/PS1(M146L) transgenic mice, a cross between Tg2576 (overexpressing human APP695) and mutant PS1 (M146L) (Carrero et al., 2023).

Additionally, alterations in reward responses have been documented in the early stages of AD, even before the appearance of amyloid plaques (Nobili et al., 2017). For instance, a study conducted on 6-month-old Tg2576 mice demonstrated a significant decrease in chocolate consumption, along with a lack of conditioning in the conditioned place preference test. These behavioral changes were associated with a loss of dopaminergic neurons in the VTA (Nobili et al., 2017). A similar study investigated the effect of AβOs injected into the nAc of 3-month-old WT mice. The intra-nAc administration of AβOs resulted in a decreased motivation index, as measured by a sucrose preference test (Guo et al., 2022). Mice treated with AβOs exhibited a significant reduction in breakpoint values for sucrose pellets under a progressive ratio schedule compared to control mice. Furthermore, unlike control mice, where a 1-hour pre-feeding with sucrose pellets reduced breakpoint values, AβOs-treated mice showed no such pre-feeding effect, indicating a diminished motivational component in sucrose-seeking behavior (Guo et al., 2022). Additionally, a study employing 6-month-old APP/PS1 mice documented a significant decrease in alcohol consumption on the final day of the drinking in the dark test, a widely used essay for evaluating voluntary alcohol intake (Armijo-Weingart et al., 2024).

Collectively, these studies demonstrate an evident impairment in both motivation and reward processing in the early stages of AD. The evidence points to the involvement of the mesolimbic system as a critical region of early dysfunction. Specifically, the results underscore the importance of exploring early signs of apathy, a symptom commonly reported in early clinical AD populations (Zhao et al., 2016; Victoroff et al., 2018).

Lastly, recent evidence has highlighted motor impairments—including changes in movement, muscle weakness, coordination, and gait scores—associated with the deep cerebellar nuclei at early stages of AD in 6-month-old 3×Tg AD mice (Castillo-Mariqueo et al., 2021; Castillo-Mariqueo and Giménez-Llort, 2022). These impairments were found to be exacerbated in the advanced stages of the disease at 16 months of age (Castillo-Mariqueo and Giménez-Llort, 2022). Similarly, this genotype exhibited more clasping regardless of the disease stage (Castillo-Mariqueo et al., 2021; Castillo-Mariqueo and Giménez-Llort, 2022).

Although research on non-cognitive manifestations in AD is still limited, evidence consistently shows that these symptoms are present in both human and murine models. These symptoms and signs are associated with neurobiological changes in the mesocorticolimbic system, hypothalamus, and cerebellum during the early stages of AD. This research direction offers considerable potential for identifying non-cognitive behaviors, such as depression, apathy, anxiety, and motor impairments, as potential biomarkers for the early diagnosis of AD.

Early alterations in brain synchronization leading to epilepsy

Neuronal hyperexcitability can be defined as the increased likelihood that a neuron fires an action potential when activated by a stimulus that can reach the threshold for firing. In a more complex setting, neuronal circuit hyperexcitability can be observed with extracellular electroencephalographic recordings or fMRI when AD patients are at rest or performing a memory-encoding task (Celone et al., 2006; Targa Dias Anastacio et al., 2022; Kopčanová et al., 2024).

Evidence suggests that seizures and epilepsy are significantly more prevalent in patients with AD (DiFrancesco et al., 2017; Horvath et al., 2018). While earlier research linked this higher prevalence primarily to the late stages of AD (Romanelli, 1990), more recent studies have shown that these conditions can also manifest in the early stages of the disease (Amatniek et al., 2006; Irizarry et al., 2012; Vossel et al., 2013). Indeed, patients diagnosed with AD at the prodromal stage (MCI) have shown increased levels of hippocampal and cortical brain activity in functional MRI studies (Dickerson et al., 2005; Huijbers et al., 2015). Additionally, a follow-up analysis of AD patients with higher levels of CSF biomarkers showed that 40% presented electroencephalograms denoting epileptic activity, suggesting shared cellular and molecular mechanisms (Haoudy et al., 2022).

Like AD, a percentage of epilepsy cases also present genetic causes. Recent bioinformatic analysis of gene expression from both AD and epilepsy patients, sequenced from post-mortem brain tissue samples, identified three differentially expressed genes in both pathologies: *SCN2A* (voltage-dependent sodium channel subunit 1), *GRIA1* (AMPAR subunit 1), and *KCNJ9* (inward rectifier potassium channel) (Tang et al., 2024). In agreement, familial lineages with mutations in APP, PS1, and PS2, associated with early-onset autosomal dominant AD, showed a higher incidence of early seizures (Marcon et al., 2004; Snider et al., 2005; Cabrejo et al., 2006). Also, the striking feature in a human study was the presence of iAβ40 accumulation in granular and pyramidal cells (Cabrejo et al., 2006). Other studies have examined the age-specific incidence of a first unprovoked seizure in AD patients relative to controls of the same age, finding a higher incidence of convulsions (Amatniek et al., 2006; Hommet et al., 2008; Born, 2015). Observational studies showed that seizures were present in 10%–20% of patients diagnosed with sporadic AD and that this symptom was concurrent with the onset of cognitive decline (Mendez and Lim, 2003; Lozsadi and Larner, 2006). Globally, these studies have indicated that changes in the excitability of cortical and hippocampal regions are a feature shared by patients in the early stages of the disease, progressing to hypoactivity during the later stages of neurodegeneration (Targa Dias Anastacio et al., 2022). This idea agrees with the notion of synaptic dysfunction driven by synaptic vesicle depletion, a consequence of hyperexcitability induced by the presence of Aβ (Parodi et al., 2010; Fernandez-Perez et al., 2021; **Figure 4**).

The increase in iAβ is likely a causative mechanism for the augmentation in neuronal activity at the initial stage of Aβ pathology, predisposing the development of synaptopathology (Minkeviciene et al., 2009; Targa Dias Anastacio et al., 2022). Possible mechanisms for this phenomenon include alterations in the E/I balance and/or increased intrinsic membrane excitability. For instance, the ongoing and evoked activity of pyramidal neurons in the frontal cortex of APP/PS1 transgenic mice exhibited hyperexcitability, suggesting changes in the intrinsic electrical properties of the neurons (Kellner et al., 2014). In fact, these excitability changes are consistent with *in vitro* studies showing epileptiform activity after brief exposure to eAβ (Cuevas et al., 2011). Also, 10- to 14-month-old APP/PS1 mice showed a higher frequency of spontaneous action potential in the hippocampus (Šišková et al., 2014). Furthermore, increases in intrinsic excitability were also reported in several other animal models overexpressing Aβ, likely reflecting disruptions in the E/I balance (Minkeviciene et al., 2009; Born et al., 2014; Davis et al., 2014; Bezzina et al., 2015). Supporting this notion, a recent study in the hippocampus of Tg2576 mice reported decreased GABAergic drive onto pyramidal neurons and increases in gamma-oscillations and brain excitability (Spoleti et al., 2024). Because GABA is an inhibitory neurotransmitter, its reduction would enhance circuit excitability.

There is abundant evidence suggesting that the presence of iAβ as a neurotoxicity cellular model is associated with pathophysiological increases in neuronal and synaptic activity (Bayer and Wirths, 2010; Ripoli et al., 2014; Tu et al., 2014). Furthermore, as previously indicated, since increased brain excitability has also been documented in patients exhibiting disease symptoms, findings from AD models provide insights into potential underlying molecular mechanisms. For instance, iAβ increased neuronal excitability in the hippocampus and cortex by suppressing large-conductance voltage- and calcium-activated potassium channels and A-type voltage-gated potassium channels (Yamamoto et al., 2011; Scala et al., 2015). Additionally, AβOs intracellularly applied to neurons in hippocampal slices caused a PKA-dependent increase in AMPA-mediated current amplitude (Whitcomb et al., 2015). In the presence of iAβ, electrophysiological recordings of synaptic transmission and nitric oxide-associated fluorescence showed increased neural synchronization in primary cultures of hippocampal neurons, suggesting that iAβ increases network excitability (Fernandez-Perez et al., 2021).

Given the reported presence of iAβ in the Tg2576 mice model at 1.5 months and in the 3×TgAD

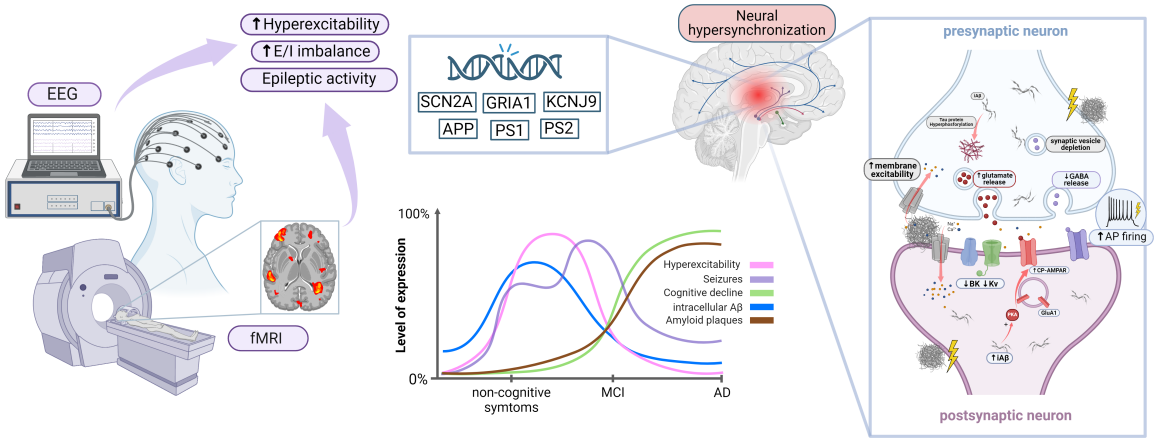

Figure 4 | **Hyperexcitability and Seizures in early AD.**
The figure illustrates neural mechanisms contributing to hyperexcitability, epileptic activity, and neural hypersynchronization during the early stages of AD. Increased neuronal excitability and E/I imbalance are observed through EEG and fMRI, revealing epileptic activity in early AD stages before amyloid plaque deposition and cognitive impairment. Gene expression and mutations also contribute to a higher incidence of seizure, inducing neural hypersynchronization. Cellular mechanisms associated with hyperexcitability include synaptic vesicle depletion, reduced GABA release, reduced large-conductance calcium-activated potassium (BK), and A-type voltage-gated potassium (Kv) channel activity, further amplifying AP firing. On the postsynaptic side, Aβ impairs calcium-permeable AMPA receptors (CP-AMPARs) through PKA activation, increasing receptor surface expression and promoting synaptic dysfunction. These events contribute to hyperexcitability, seizures, and cognitive decline in early AD. Created with BioRender.com. AD: Alzheimer's disease; AP firing: action potential firing; Aβ: amyloid-beta; BK: large-conductance calcium-activated potassium channel; CP-AMPAR: calcium permeable AMPA receptor; E/I: excitation/inhibition; EEG: electroencephalogram; fMRI: functional magnetic resonance imaging; $GABA_AR$: GABA-A receptor; Kv: A-type voltage-gated potassium channel; MCI: mild cognitive impairment; PKA: protein kinase A.

mice model at 3 weeks, along with its association with increased neuronal excitability before the formation of Aβ plaques and the onset of significant cognitive decline (Bezzina et al., 2015; Kazim et al., 2017; Zott et al., 2019), it is plausible to suggest that iAβ contributes to the development of seizures and epilepsy. In fact, a recent study examined the effect of $Aβ_{1–42}$ oligomers intracerebrally injected in the dentate gyrus of the hippocampus of WT mice (Vande Vyver et al., 2023). The results showed that extracellular oligomers did not increase susceptibility to developing seizures even after 3 weeks post-injection (Vande Vyver et al., 2023). In addition to iAβ, other mechanisms could contribute to the increase in excitability reported in humans and transgenic animal models, such as calcium dyshomeostasis, glutamate dysregulation, and tau hyperphosphorylation (Targa Dias Anastacio et al., 2022).

Emerging techniques to study non-cognitive alterations in Alzheimer's disease

As previously noted, recent data implied subcortical areas as the early sites of the disease, so it seems reasonable to develop sensitive assays to examine multiple emotional behaviors such as fear conditioning, anxiety, social interaction, and reward behaviors, which are controlled by the mesolimbic system and affected early on AD (Seoane et al., 2024).

Several behavioral tests have long been used in Alzheimer's research, including the Open Field, elevated plus maze, Conditioned Place Preference (Perry and Kramer, 2015), and Water Maze tests. These allow researchers to gather quantitative data, depending on the nature of data acquisition or measurement parameters. Visual processing software tracks variables such as total distance traveled, movement speed, time spent in specific zones, and the number of transitions between these zones. Recent advancements in machine learning have reduced human bias and software-related errors in data analysis (Kraeuter et al., 2019). Additionally, the Drinking in the Dark paradigm was initially developed to assess alcohol consumption over four days, primarily to study addictive behaviors (Thiele et al., 2014). However, recent studies have analyzed reward behaviors in AD, where 6-month-old APP/PS1 mice showed decreased sucrose and ethanol consumption (Armijo-Weingart et al., 2024). It is common to observe that Drinking in the Dark experiments only consider the change in weight of the bottles containing the liquid before and after each test. For instance, it is necessary to analyze the microstructure of the consumption using a lickometer (Wall et al., 1972; Davis, 1989) to obtain insights into consumption characteristics, enabling their connection to physiological events occurring before, during, and after liquid intake. These events include the potency of orosensory stimulation based on the substance's palatability before and during intake, as well as the inhibition of the stimulus by gastrointestinal regulation after consumption (Smith, 2001; Johnson, 2018). In agreement, it was reported that APP/PS1 mice 12 to 14 months of age exhibited reduced aversion to the consumption of quinine, an aversive substance, evidenced by a higher lick rate when the microstructure of consumption was evaluated (Wood et al., 2020). Moreover, other studies using 12-month-old APP/PS1 mice showed that the number of licks required to obtain a single reward was higher than WT mice, indicating high levels of impulsivity (Sakurai et al., 2020). Furthermore, it would be necessary to examine the microstructure of reward substance consumption in younger AD animals, where cognitive changes are still not observed.

The study of subcortical areas involved in AD and its progression to advanced stages has also been significantly facilitated by imaging techniques and biomarkers applied in both human and animal models (Johnson et al., 2012; Jullienne et al., 2022). Among the most used techniques, structural MRI, fMRI, and positron emission tomography have enabled a more detailed understanding of the structural and functional changes in deep brain regions, including the thalamus, amygdala, and LC (Engels-Domínguez et al., 2023; Seoane et al., 2024). Due to their small size, these structures present significant challenges for precise visualization, as high-resolution techniques are required to delineate their anatomical boundaries. Although advanced imaging techniques provide valuable data, they do not always achieve the resolution necessary for clear anatomical identification (Engels-Domínguez et al., 2023). To overcome these limitations, machine learning-based techniques have emerged, allowing for the processing and analysis of large volumes of data, optimization of experimental designs, and the prediction of outcomes with high precision (Bazarbekov et al., 2024). These machine-learning tools are becoming a promising resource for improving accuracy in the study of early neurological changes associated with AD.

Open-source and data sharing to improve reproducibility in Alzheimer's disease

Technological advancements in the field of neuroscience have been significantly driven by the development of open-source projects (White et al., 2019). These projects share the source code, components, construction instructions, validation methods, and other relevant information regarding sensitive and low-cost software or electronic devices (Pearce, 2020). This openness facilitates analysis and monitoring in studies involving humans and laboratory animal models. Thus, various projects have been developed for studying behavior in animal models that could be useful in evaluating rewarding motor activity in AD models using open-source technologies. For example, minimally invasive lickometers and operant food devices adapted for use in standard cages have been developed, and some of these can be integrated with *in vivo* photometric methods (Amarante et al., 2019; Godynyuk et al., 2019; Matikainen-Ankney et al., 2021; Petersen et al., 2023). Additionally, machine learning has gained importance in preclinical research due to

its ability to handle and analyze large volumes of data, optimize experimental designs, and predict outcomes with high accuracy, which has some advantages in AD diagnosis in humans and animal models (Bazarbekov et al., 2024). A notable study used deep neural networks to classify $APP^{NL-G-F/NL-G-F}$ and WT animal models aged 8 to 12 months at risk of AD, based solely on their compulsive and learning behaviors, achieving 90% accuracy (Sutoko et al., 2021). However, as research progresses, the need for new techniques with higher resolution and reproducibility becomes evident to distinguish early, subtle differences in behavior that might translate into clinical research to diagnose the early stages of the disease. For example, inconsistencies in motor activity have been reported in APP/PS1 mice, with some studies observing increased movement and hyperactivity, while others report normal or even decreased activity at different ages or under varying conditions (Ferguson et al., 2013; O'Leary et al., 2018; Wang et al., 2022). This variability may stem from differences in experimental methods, the age of the mice, or the specific paradigms used. Implementing more robust, potentially mandatory data-sharing practices from preclinical to clinical stages could facilitate the exchange of information regarding environmental conditions, helping to standardize results, reduce variability, and improve the chances of advancing our understanding and treatment of AD (Ashish et al., 2016; Travaglia and Hoffmann, 2024; **Figure 5**).

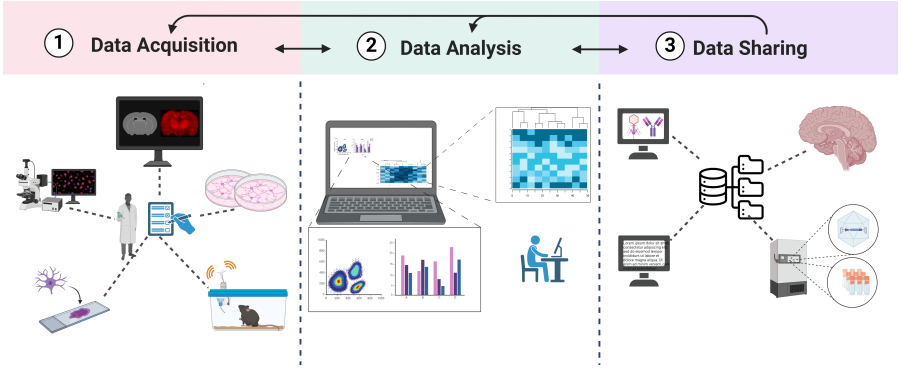

Figure 5 | Scheme depicting data acquisition, management, and sharing for advancing reproducibility in Alzheimer's disease preclinical and clinical science.
The image illustrates the three main stages in the research process: (1) Data acquisition, which includes the collection of raw data through experimentation, observation, or measurement; (2) data analysis, where raw data are processed and evaluated to extract meaningful information and interpretable results; and (3) data repository, where both data and research materials are shared on accessible platforms. This workflow highlights the importance of data sharing to enhance transparency in scientific research, allowing others to validate results and promoting reproducibility in neuroscience research. Created with BioRender.com.

Conclusions

The traditional amyloid cascade model posits that the accumulation and deposition of eAβ in brain regions critical for memory and language serves as the initial trigger leading to neurodegeneration and other classic symptoms of AD. A significant number of studies have shown that synaptic transmission is deteriorated by Aβ in brain regions such as the hippocampus and cortex, suggesting that the disease is primarily synaptic. While it is possible to reduce the presence of Aβ in the brain, cognitive symptoms do not necessarily improve. The data reviewed here shows that basal brain structures are also affected, particularly during the early stages of the disease. Intracellular Aβ appears early in regions such as the nAc, LC, and RN in the absence of amyloid plaques, whose effects are mainly excitatory, increasing glutamatergic transmission and reducing inhibition. AD patients and animal models show an increase in neuronal synchronization that leads to epilepsy. At the same time, subcortical brain dysfunctions appear to be associated with non-cognitive symptoms such as anxiety, irritability, and motivation deficits, which precede memory loss and language alterations. Although there is increasing evidence supporting the idea that sub-cortical regions are critical for early manifestations of AD, there are still questions that remain to be examined, such as the neural circuits implicated in non-cognitive symptoms in AD and how iAβ alters specific cellular mechanisms that lead to hyperexcitability in sub-cortical neurons.

Overall, the evidence reviewed suggests that examining these brain regions could offer promising targets for early therapeutic interventions in AD. By addressing these early changes before a significant cognitive decline occurs, it may be possible to slow disease progression. Future research should focus on these non-traditional brain regions to reveal early pathological alterations and underlying mechanisms to advance our understanding of AD beyond the traditionally studied hippocampal and cortical circuits.

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