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Biomarkers of Activity-Dependent Plasticity and Persistent Enhancement of Synaptic Transmission in Alzheimer Disease: A Review of the Current Status

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Alzheimer disease (AD) is a chronic and heterogeneous neurodegenerative disorder characterized by complex pathological processes involving neuroinflammation, neurodegeneration, and synaptic dysfunction. Understanding the exact neurobiological mechanisms underlying AD pathology may help to provide a biomarker for early diagnosis or at least for assessment of vulnerability to dementia development. Neural plasticity is defined as a capability of the brain to respond to alterations including aging, injury, or learning, with a crucial role of synaptic elements. Long-term potentiation (LTP) and long-term depression (LTD) are important in regulating synaptic connections between neural cells in functional plasticity. Synaptic loss and impairment of the brain's plasticity in AD leads to cognitive impairment, and one of important roles of synaptic biomarkers is monitoring synaptic dysfunction, response to treatment, and predicting future development of AD. Synaptic biomarkers are undoubtedly very promising in developing novel approach to AD treatment and control, especially in the era of aging of societies, which is one of the most common risk factor of AD. Implementing a widespread measurement of synaptic biomarkers of AD will probably be crucial in early diagnosis of AD, early therapeutic intervention, monitoring progression of the disease, or response to treatment. One of the most important challenges is finding a biomarker whose blood concentration correlates with its level in the central nervous system (CNS). This review aims to present the current status of biomarkers of activity-dependent plasticity and persistent enhancement of synaptic transmission in Alzheimer disease.

Keywords: Alzheimer Disease • Cognitive Dysfunction • Cerebrospinal Fluid

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Background – Characteristic of Alzheimer Disease

Alzheimer disease (AD) is one of the most common age-related neurodegenerative diseases, clinically characterized by gradual loss of memory and cognitive functions [1]. AD is a heterogeneous disease with composite etiology [2], with a crucial role of disorders of amyloid-beta (aβ) and tau protein [3]. Recent scientific reports suggest that synaptic dysfunction is also involved in the pathogenesis of AD [4]. Progression of AD is likely to occur years prior to the first signs, symptoms, and clinical diagnosis [5]. It can be divided based on age at development of the first symptoms: early-onset AD (EOAD) for people age <65 years old and late-onset AD (LOAD) (most common) for people age >65 years [6]. Currently, the incidence of AD is increasing, probably due to the aging of society [7].

A potential explanation of AD pathogenesis is provided by a number of hypotheses [8]. The amyloid-beta theory [9] focusses on accumulation of excessive amounts of Aβ (particularly $A\beta_{42}$), which results in synapse loss, and neuronal cell death [10]. The role of NMDA receptors in AD is highly probable because of the finding of glutamatergic neurons in AD-affected tissues and their role in mediating synaptic plasticity through long-term potentiation (LTP) [11-13]. Long-standing activation of NMDA receptors results in a process called "excitotoxicity", eventually leading to neurodegeneration [14]. A high concentration of Ca^{2+} ions leads to loss of learning abilities and memory functions in AD because of suppression of synaptic functions, synaptotoxicity, and atrophy [12]. The tau protein hypothesis was first proposed in 1986, citing phosphorylation of tau as a likely contributor to the formation of neurofibrillary tangles in AD [15], leading to the starvation of neural cells by disturbing transport structures [16].

Synaptic Plasticity in Aging and Alzheimer Disease

Neural plasticity is the ability of the brain to perform structural and functional modification as a response to new experience, injury, or aging [17]. Architectural plasticity is described as the rise of new synaptic connections and removal of old ones, as well as the enlargement of synapses, often because of learning processes [18]. LTP includes the long-lasting strengthening of synaptic connections between neurons, which is decisive in the formation of long-term memory [19]. Long-term depression (LTD) weakens the efficacy of synaptic strengthening using several mechanisms to effectively use strengthening of synaptic connections by LTP [20]. Functional plasticity consists of LTP and LTD, and refers to the brain's ability to adjust to loss or damage of its tissue by transferring previously performed functions by destroyed areas to undamaged regions, and occurs by growing new nerve endings by axons of undamaged neurons to reconnect links of neural cells destroyed by injury in a process called axonal sprouting [21].

Aging is undoubtedly linked with decreased ability of learning and memory [22]. Impairment of brain functions is associated with deficiency in elicitation of LTP and shorter duration of maintenance of LTP, which are important for generation of new connections between neural cells [23]. Reduction in grey and white matter of the brain, cellular aging, and environmental factor also contribute to impairment of neural plasticity and predispose to neurodegenerative diseases [24].

AD involves loss of synaptic connections between neurons without the ability of remaining synapses to alter in response to new stimuli, which is one of the most essential mechanisms of AD dementia [25]. Maintaining plasticity of the brain in AD is crucial to reducing cognitive symptoms and slowing AD progression, which will certainly reduce the cost of medical care and allow most patients to have improved quality of life [26].

This review aims to present the current status of biomarkers of activity-dependent plasticity and persistent enhancement of synaptic transmission in Alzheimer disease.

Markers of Plasticity in the Development of AD

Research efforts are currently directed to the search for and analysis of biomarkers reflecting synaptic pathology in the cerebrospinal fluid to improve the diagnosis of neurodegenerative disorders in the early stage of the disease and to monitor clinical progression. There are pre- and postsynaptic markers that can regulate the functioning of cells of the central nervous system.

Fluid Synaptic Biomarkers in Dementia

Glial Fibrillary Acidic Protein

Glial fibrillary acidic protein (GFAP) is an intermediate cytoskeletal protein released by activated astrocytes during pathological states of the CNS, including trauma, ischemia, and neurodegeneration [27,28].

Elevated levels of GFAP in cerebrospinal fluid (CSF) were observed in AD [29]. Higher plasma levels of GFAP were observed in EOAD in comparison to LOAD [30]. Moreover, an increased CSF level of GFAP was also found to correlate with results of MMSE, being a promising follow-up marker in future studies [31]. Measurement of GFAP upon autopsy in temporal, occipital, and parietal cortices showed a correlation between a

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high level of GFAP in these regions and weak cognitive performance later in life [32]. A 2019 observational study also drew similar conclusions [31]. Higher levels of GFAP among adults with symptomatic AD were associated with poorer verbal episodic memory [33]. The elevation of GFAP in AD might be explained by astrogliosis (abnormal increase in the number of astrocytes), which is related to worse cognitive performance [34].

Neurogranin

Neurogranin (Ng) is a postsynaptic protein with highest expression in associative cortical areas of the brain [35]. It is essential in memory, learning, synaptic plasticity, and LTP [36]. Its level was found to be lower in the hippocampus and frontal cortex of AD patients in a postmortem study, with lower level among EOAD individuals, suggesting a link with synaptic loss and neurodegeneration [37].

Increased Ng concentration in CSF was identified among patients diagnosed with AD [38], with similar results in larger studies [39-41]. Additionally, elevated levels of Ng were correlated with future cognitive decline in prodromal AD [40], but other study using plasma neuronal-derived exosomes (NDEs) found decreased Ng levels years before the onset of AD dementia [42]. A meta-analysis of 13 high-quality evidence studies suggest that CSF Ng can predict a decline in Mini Mental State Examination (MMSE) scores in people with Aβ+ mild cognitive impairment (Aβ+ MCI), and moderate-quality evidence supports prediction of decline in memory and executive function [43]. The distinction in Ng expression between MCI and AD was studied in a meta-analysis [44] in which analysis of 9 studies including a total of 801 AD patients and 734 individuals with MCI without progression to AD presented higher levels of CSF Ng in AD compared to MCI. Comparison between stable MCI patients and MCI who progressed to AD (MCI-AD) also showed higher Ng CSF in MCI-AD individuals [44].

Synaptic Proteins

Synaptotagmin-1

Synaptotagmin-1 (Syt1) is a presynaptic vesicle protein that participates in quick Ca^{2+}-dependent neurotransmitter release [45]. Syt1's role is considered to be a Ca^{2+} sensor due to its 2 C_2 (C_2A, C_2B) domains, which interact with Ca^{2+} and phospholipids [45,46], and other proteins that are soluble N-ethylenimine sensitive factor attachment protein receptors (SNAREs), including syntaxin-1, synaptosomal-associated protein 25 (SNAP-25), and synaptobrevin-2, to form a tight SNAREs complex, which is crucial in forming membrane fusion between synaptic vesicle and plasma membranes [47]. Research conducted on animal models demonstrated its essential role in control of synaptic plasticity [48].

High concentrations of Syt1 in CSF were discovered in individuals with MCI and dementia caused by AD [49]. Blood neuro-exosomal Syt1 in combination with other synaptic proteins were found useful in predicting the occurrence of AD, even 5 to 7 years before cognitive impairment [50].

Synaptosomal-Associated Protein 25

Synaptosomal-associated protein 25 (SNAP-25) belongs to the SNAREs complex, which is involved in exocytosis of neurotransmitters during synaptic transmission [51]. Its exact action is to mediate the apposition of synaptic vesicles to the presynaptic membrane, which leads to Ca^{2+} fusion, through assembly with other synaptic proteins [51]. Research in mice proved that SNAP-25 takes part in controlling long-term synaptic plasticity and synaptic transmission [52].

Decreased expression of SNAP-25 was discovered in a postmortem study of brains of AD patients [53], whereas higher concentrations were discovered in CSF of AD patients in comparison to the control group [54-57]. SNAP-25 appears to be a promising biomarker due to its good results in the differentiation of dementia and MCI caused by AD from controls, as well as various clinical stages of AD, but with no correlation with MMSE score [56].

Growth-Associated Binding Protein 43

Growth-associated binding protein 43 (GAP-43) is an axonal phosphoprotein linked with the elongation of axons and guidance of the growth cone [58]. GAP-43 has a major role in synaptic plasticity because of its role in synaptogenesis [59], growth of presynaptic terminals [60], formation and regeneration of axons [61], and induction of LTP [62].

Several postmortem brain studies revealed decreased expression of GAP-43 in the frontal cortex and regional increase in the hippocampus among AD patients [63-65]. GAP-43 was increased in CSF in preclinical AD [66-67] and may be of great relevance in developing future diagnostic approaches for AD.

Neuronal Pentraxins

Neuronal pentraxins (NPTX) belong to a subfamily of pentraxins and consist of neuronal pentraxin 1 (NPTX1), neuronal pentraxin 2 (NPTX2), and neuronal pentraxin receptor (NPTXR) [68]. They are located in the synaptic cleft and are responsible for synaptogenesis [69], elimination of synapse [70], clearance of synaptic debris [71], and outgrowth of neurons [72].

Recent studies suggest that regulation of synaptic plasticity by NPTX occurs through neuronal activity, as low activity of neurons evokes NPTX1 [73], which contributes to apoptotic cell

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death of mature neurons [74]. In contrast, NPTX2 [73] is stimulated by high neuronal activity [72] by maintaining homeostasis of synaptic plasticity [72].

NPTXR is a receptor of NPTX1 and NPTX2 and recruits other NPTXR and NPTX2 [75]. The role of NPTXR in synaptic plasticity is stabilization of NPTX1 and NPTX2 at synapses [76] and clustering to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR), which has a major impact on synaptic transmission [77]. Moreover, NPTXR is likely to recruit AMPAR into glutamatergic synapses, which is crucial for LTP [77].

Expression of NPTX2 was found to be lower in brains of AD individuals, and its CSF levels is correlated with cognitive status and volume of the hippocampus, which suggests its promising role as an informative biomarker [78] for identification of patients with AD who are most likely to respond to anti-amyloid therapy, as its level is likely to be independent of Aβ load in asymptomatic AD [78]. It is even considered to be a good biomarker for prediction of cognitive decline in AD, as higher concentrations of NPTX2 correspond to decreased medial temporal lobe atrophy and substantially less decline of cognitive functions during 24-month follow-up [79].

NPTXR level in CSF of people with AD was found to be decreased in some studies [80-83]. It was also reported that NPTXR can predict AD progression treatment response [80,81]. A relationship between NPTXR and Aβ load was also found in a positron emission tomography (PET) study [82].

Fluid Biomarkers Modulating Synaptic Plasticity

Tau Protein

Tau protein is a microtubule-associated protein with a physiological role in stabilization of neuronal microtubules [84]. However, in certain conditions, tau protein can undergo modifications, including phosphorylation, which generates toxic aggregates, finally leading to neurodegeneration [84]. Tau protein impairs synaptic plasticity by inducing neuroinflammation through astroglial and microglial activation [85], which eventually leads to synaptic loss. In addition, some researchers suggest that hyperphosphorylation of tau lowers its affinity to microtubules, resulting in localization of tau in dendrites and presynaptic terminals [86], which impairs motility of synaptic vesicles, contributing to synaptic dysfunction [87,88].

The level of tau protein in the CSF was found to play a role in cortical plasticity among AD patients [89,90]. Tau deposition in the temporal lobe was correlated with its concentration in CSF, with a better prediction of cognitive performance in comparison to Aβ deposition in all regions of the brain [91]. Koch et al found that high levels of total tau (t-tau) in CSF were associated with impaired cortical plasticity of brains of AD patients with APOE4 (measured using transcranial magnetic stimulation (TMS)), but no similar relationship was found in patients with apolipoprotein 3 (APOE3) [92]. The correlation between level of tau protein and neuropsychological test performance may differentiate between MCI and AD individuals [93], but a notable overlap between AD patients and controls complicates its usefulness [93].

Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is a neurotrophin with high expression in the hippocampus [94]; it is crucial in memory formation [95], synaptic and hippocampal plasticity, and structural integrity of the brain [96].

Plasma level of BDNF was significantly higher in early stages of probable AD compared to patients with severe AD and healthy controls, and was significantly correlated with MMSE score [97], which might be related to its role in degradation of excessive amounts of Aβ or compensatory repair mechanism [98], but that study is quite old and contained only 30 AD individuals and 10 controls. More studies presented decrease in BDNF in AD and MCI individuals [99-104]. Additionally, there is a report of no association in BDNF serum levels among AD, amnestic MCI, and controls with BDNF gene polymorphism [105]. Decrease in serum BDNF in amnestic MCI patients was positively correlated with score on Auditory Verbal Learning Tests, reflecting episodic memory [100]. Moreover, low levels of BDNF might occur before neuronal injury in AD measured with reduction of hippocampus, as AD and MCI patients presented lower levels of BDNF in comparison to controls [101]. A recent study reported a relationship between disease-modifying effects of repetitive transcranial magnetic stimulation (rTMS) on the lateral parietal cortex of AD individuals and increased levels of BDNF, improvement of visual recognition memory functions, and clock-drawing test scores [106]. In that study, 15 AD patients underwent rTMS, which consisted of 10 sessions during 2 weeks [106]. One week before rTMS, all patients underwent neuropsychiatric testing, MRI screening, and blood sample collection. After 2 weeks, the same examinations were conducted after rTMS [106]. Two weeks after the rTM intervention, a significant improvement in WMS-Visual Reproduction Test Recognition and Clock-Drawing Test scores was observed, which were correlated with the increase in BDNF level [106]. Forlenza et al [107] revealed that decreased level of BDNF in CSF was a predictor of progression from MCI to AD, which may suggest involvement of BDNF in neurodegeneration in AD.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is a protein encoded by the VEGF-A gene [108]. Its physiological function is involved

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in the growth of blood vessels, delivery of oxygen and glucose, regulation of permeability, and vasodilatation of blood vessels [108,109]. VEGF was found to be a positive factor in the preservation of cognitive functions among older people, as it maintains cognitive abilities [110], participates in promotion of neurogenesis [111], and improvement of synaptic plasticity [112]. Modification of VEGF signaling through amyloid is believed to have a strong effect on cognition in AD, which was found in postmortem research on AD patients [113]. Exogenous administration of VEGF improved memory impairment and a reduced amyloid load and hyperphosphorylated tau in AD mice [114].

High availability of VEGF was found to be neuroprotective in preclinical AD [114]. However, 2 other studies [115,116] did not find this relationship due to a lack of significant statistical differences between AD patients and healthy controls [115] and higher levels of VEGF among AD individuals [116]. Larger studies have produced different results because they found less cognitive decline among AD patients with higher VEGF levels in CSF [117-118]. Additionally, interactions of VEGF, $A\beta_{42}$, and t-tau were reported to be useful in predicting memory decline among AD individuals [117].

D-Amino Acids

D-amino acids (D-serine, D-aspartate) participate in excitatory glutamatergic neurotransmission via N-methyl-d-aspartate-receptor (NMDAR) [119]. NMDAR signaling is important for synaptic plasticity and survival of neural cells, but over-transmission in the NMDAR signaling pathway leads to cell death and is believed to cause progression of neurodegenerative diseases, including AD [120]. High levels of D-aspartate in preclinical murine AD models accelerated brain aging and cognitive decline [121-123]. D-amino acids have been considered a promising biomarker in AD due to finding a 5-fold increase of D-serine in patients with probable AD in comparison to healthy controls [124], but other research did not find differences between AD patients and elderly controls [125].

Polyunsaturated Fatty Acids

Several studies support a link between proper diet, cognitive disorder, and AD [126-129]. Diet including food rich in polyunsaturated fatty acids (PUFA), like fish, whole grains, fresh fruits, and vegetables, was connected with a lower risk of cognitive decline than a diet rich in processed food, saturated fats, added sugars, and refined grains [130]. PUFAs include omega-3 fatty acids: α-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) [130]. Omega-6 fatty acids include linoleic acid (LA) and arachidonic acid (ARA) [131]. LA, ALA, and precursors omega-3 and omega-6 PUFAs cannot be synthesized by the human body and must be supplemented with diet [132,133]. Elevated concentrations of ARA in neuronal membranes were reported to improve synaptic functions because of the increased fluidity index of brain cells in the treated group, but no improvement of immediate memory was discovered among AD patients [133, 134].

Omega 3 PUFAs have been studied as a potential biomarker of cognitive abilities [135-137]. However, administration of high doses of DHA did not slow progression of brain atrophy in patients with mild and moderate AD during a 12-month randomized, double-blind, placebo-controlled clinical trial [138]. Interestingly, a study conducted on a larger group of patients found a positive association between the same dose (2000 mg/day) of DHA and increase in hippocampal volume in MCI patients after 1 year of supplementation [139]. Increased phagocytosis of Aβ by monocytes in flow cytometry was discovered after administration of a drink containing 1000 mg DHA and the same quantity of EPA in MCI and pre-MCI subjects [139]. In addition to DHA and EPA, it also included vitamin D and Resveratrol [136]. Transthyretin (TTR) is also a promising biomarker of plasticity because of its ability to reduce plaque formation, as it binds Aβ [140]. A randomized controlled clinical trial revealed increase of plasma TTR concentration after supplementation of n-3 fatty acids after 6 months among individuals with AD, but the utility of TTR as a biomarker of synaptic plasticity is unknown [136].

Amyloid-Beta Peptides

Amyloid-beta peptides (Aβ) are involved in the pathogenesis of AD [141]. Continuing progression of Aβ leads to cognitive decay and memory dysfunction due to its overaccumulation in the form of senile plaques as well as its oligomers, which exert synaptotoxic activity [141]. Intriguingly, a low physiological concentration of Aβ was found to be crucial for proper neurotrophy, neuroprotection [142], and positive modulation of synaptic plasticity and memory [143]. The exact mechanism of synaptic dysfunction by Aβ peptides is unclear [144]. It is generally believed that pathological amounts of Aβ peptides lead to indirect overstimulation of extrasynaptic N-methyl-D-aspartate receptors (eNMDARs), resulting in abnormal dysregulation of calcium ions, oxidative stress, mitochondrial dysfunction, and subsequent impairment of synaptic transmission [144]. Excessive amounts of Aβ peptides disturb NMDAR-dependent LTP and facilitate NMDA-dependent LTD, which is responsible for synaptic dysfunction [145]. Further studies revealed that Aβ peptides can activate NMDAR, leading to abnormal secretion of glutamate into the synaptic cleft and contributing to synaptic dysfunction by inhibition of LTP [146]. Moreover, pathological amounts of Aβ peptides disrupt uptake of glutamate, enhancing LTD [147].

Aβ peptides are present in various forms, which are composed of a different number of amino acids (from 39 to 43). The most common subtype is Aβ40, but with less tendency

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Table 1. Summary.

Marker	Changes in the AD	Role in AD	References
GFAP	Increase	Association with early Aβ pathology [165]	[29-33]
Ng	Increase	Involved in synaptic plasticity through LTP mediated by calcium-calmodulin pathway [166]	[38-44]
	Decrease		[37]
Syt1	Increase	Enhancement of synaptic connections neurons and LTP [167]	[49,50]
SNAP-25	Increase	Role in regulation of synaptic transmission [168]	[54-57]
	Decrease		[53]
GAP-43	Increase	Synaptic sprouting [58]	Hippocampus [63-67]
	Decrease		Frontal cortex [64,65]
NPTX2	Decrease	Regulation of synaptic remodeling [169]	[78]
	Increase		[79]
NPTXR	Decrease		[80-83]
Tau	Increase	Stabilization of microtubules in axons and dendrites [86]	[91-93]
BDNF	Increase	Regulation of neuronal survival and plasticity [170]	[97,106]
	Decrease		[99-104,107]
	No association		[105]
VEGF	Increase	Neuroprotective factor [109]	[114,117,118]
	No association		[115,116]
D-serine	Increase	Promotion of neuronal survival and prevention from neurodegeneration [119]	[124]
	No association		[125]
TTR	Increase	Neurogenesis, regeneration of neurons [136]	[136]
Aβ	Increase	Neurodegeneration in excessive Mount [152]	[155,156]
	Decrease		[152-154]
	No association		[157,158]

GFAP – glial fibrillary acidic protein; Ng – neurogranin; Syt1 – synaptophysin 1; SNAP-25 – synaptosomal-associated protein 25; GAP-43 – growth-associated binding protein 43; NPTX1 – neuronal pentraxin 1; NPTX2 – neuronal pentraxin 2; NPTXR – neuronal pentraxin receptor; BDNF – brain-derived neurotrophic factor; VEGF – vascular endothielial growth factor; TTR – transthyretin; Aβ – amyloid-beta.

to aggregate [148], in comparison to $A\beta_{42}$, which is responsible for neuronal dysfunction in AD [149]. Aβ oligomers correlate with cognitive decline [150] and can be found decades before the onset of AD [151]. However, studies on the usefulness of plasma Aβ as a cognitive change biomarker have produced contradictory results, as some studies found low baseline plasma Aβ levels to be linked with higher probability of cognitive impairment [152-154], whereas others associate high levels of plasma Aβ with increased risk of conversion to MCI or AD [155,156] or report no association [157,158]. All described biomarkers are also summarized in **Table 1**.

Future Developments

One of the difficulties in implementing blood biomarkers in AD is slow-progressing character of the disease, which complicates determination of the exact degree of blood brain barrier (BBB) loss. The description of BBB dysfunction might be helpful in future development of blood synaptic biomarkers [159]. Another challenge is the probable need to prepare new standardized protocols for analysis and preparation of samples [160], as blood is a complex fluid with several potentially confounding variables.

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A study found no significant correlation between blood and CSF levels of Aβ [161], whereas serum Aβ levels were higher in AD patients compared to controls, especially in individuals with familial AD [162]. However, the entanglement of various confounding factors makes reproducibility of results difficult and complicates the role of Aβ as a potential plasma biomarker [160]. Research on correlations between concentration of tau protein in plasma and CSF also produced insignificant results [163].

A recently developed method using neuronal-derived exosomes (NDEs) enables quantification of some synaptic proteins from plasma, including Syt1, Ng, ad GAP-43, with promising results in differentiating between healthy controls and AD patients. However, to fully prove its usefulness, further studies with larger samples are needed [164].

Conclusions

This review has presented an update on the current status of biomarkers of activity-dependent plasticity and persistent enhancement of synaptic transmission in AD. Biomarkers of synaptic plasticity in AD could be used to monitor disease progression or response to treatment. These biomarkers could have an increasing role in routine clinical practice because of the rising incidence of AD in a global aging population. Therefore, the identification and clinical application of diagnostic, prognostic, and treatment response biomarkers of synaptic plasticity should focus on their widespread clinical applications.

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