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Reviews in Alzheimer's disease and related dementias

Edited by
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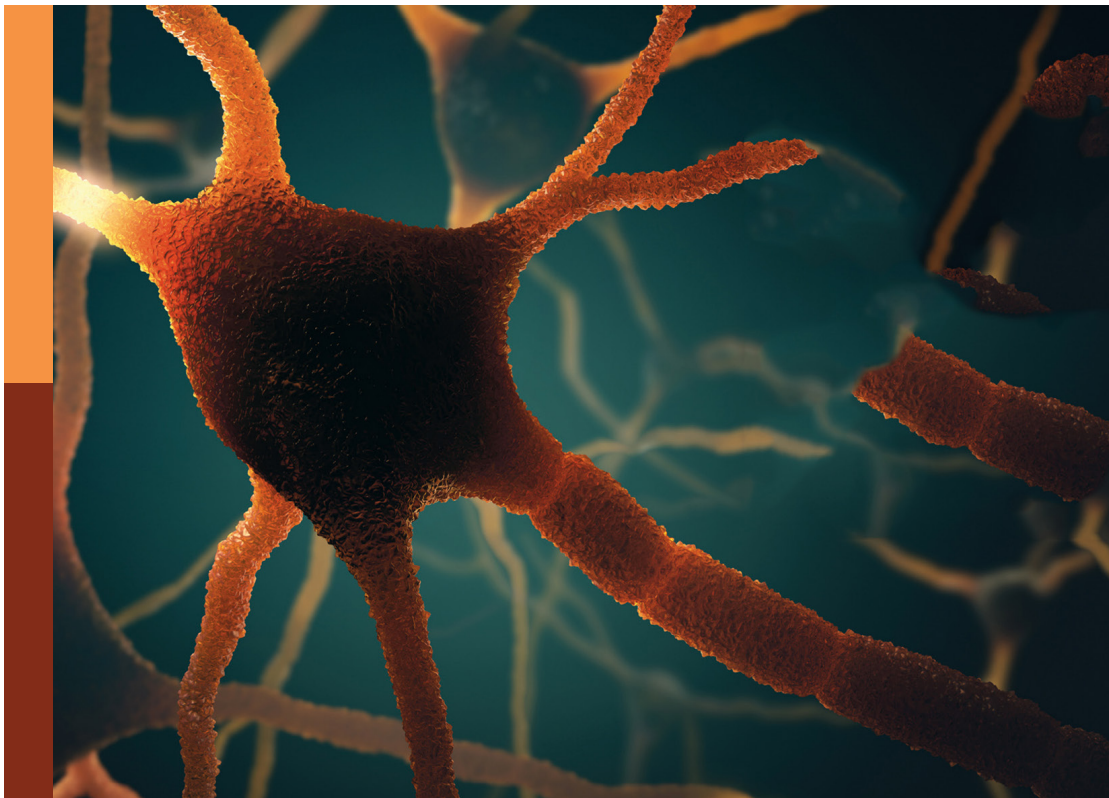
Published in
Frontiers in Aging Neuroscience



ISSN 1664-8714
ISBN 978-2-8325-3897-5
DOI 10.3389/978-2-8325-3897-5

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Reviews in Alzheimer's disease and related dementias

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Citation

Li, T., Gao, J., eds. (2023). *Reviews in Alzheimer's disease and related dementias*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3897-5

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frontiers | Frontiers in Aging Neuroscience

TYPE Systematic Review
PUBLISHED 10 January 2023
DOI 10.3389/fnagi.2022.1077732

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Alzheimer's Disease and Related
Dementias,
a section of the journal
Frontiers in Aging Neuroscience

RECEIVED 23 October 2022
ACCEPTED 20 December 2022
PUBLISHED 10 January 2023

CITATION
Guo L, Yang X, Zhang Y, Xu X and Li Y
(2023) Effect of exercise on cognitive
function and synaptic plasticity in
Alzheimer's disease models: A
systematic review and meta-analysis.
Front. Aging Neurosci. 14:1077732.
doi: 10.3389/fnagi.2022.1077732

Effect of exercise on cognitive function and synaptic plasticity in Alzheimer's disease models: A systematic review and meta-analysis

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Introduction: Cognitive decline is a central manifestation of Alzheimer's disease (AD), and its process is inseparable from changes in synaptic plasticity. The aim of this review was to summarize and evaluate the effectiveness of exercise on cognitive function and synaptic plasticity in AD animal models.

Materials and methods: Eligible studies were searched from PubMed, MEDLINE, EMBASE, Web of Science, and Cochrane Library from April to May 2022. The risk of bias was evaluated by Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE). The Morris water maze (MWM) test and synaptic plasticity were considered outcome measures. Data were analyzed using random-effects meta-analyses using the software Stata. Heterogeneity was examined by using I2 test. Sensitivity analysis and publication bias were also assessed.

Results: A total of 20 randomized controlled studies were eligible for study inclusion. Compared with controls, exercise decreased escape latency (SMD = −0.86, 95% CI: −1.21 to −0.50, $P < 0.001$), increased platform crossover numbers (SMD = 1.34, 95% CI: 0.57–2.11, $P = 0.001$) and time in the target quadrant (SMD = 1.65, 95% CI: 0.95–2.36, $P < 0.001$) and the expression of PSD95 (SMD = 0.73, 95% CI: 0.25–1.21, $P = 0.003$) in AD animals. The results of the subgroup analysis showed that exercise before AD had a greater effect on escape latency (SMD = −0.88, 95% CI: −1.25 to −0.52, $P < 0.001$), platform crossover numbers (SMD = 1.71, 95% CI: 1.23–2.18, $P < 0.001$), time in the target quadrant (SMD = 2.03, 95% CI: 1.19–2.87, $P < 0.001$) and the expression of PSD95 (SMD = 0.94, 95% CI: 0.19–1.69, $P = 0.014$) than exercise after AD. The results of the subgroup analysis also showed that treadmill running might be an appropriate exercise type.

Conclusion: Our findings suggested that exercise had a potential effect on improving cognitive function and synaptic plasticity. It can play a better neuroprotective role before AD.

Systematic review registration: PROSPERO, identifier: CRD42022328438.

KEYWORDS

exercise, cognitive function, synaptic plasticity, Alzheimer's disease, animal

1. Introduction

Alzheimer's disease (AD) is a fatal, aging-related, and gradually progressing brain condition that is characterized by memory loss and cognitive deterioration (Alzheimer's disease facts and figures, 2022). AD is the most prevalent form of dementia that may contribute to 60–70% of cases (Soria et al., 2019), and it places a heavy financial burden on society (Tahami Monfared et al., 2022). In approximately the next three decades, this societal burden, which is currently estimated to be worth over $958 billion globally, is projected to multiply many times (Jia et al., 2018; Cimler et al., 2019; Clay et al., 2019). It is rapidly turning into one of the most costly, fatal, and serious diseases of this century (Livingston et al., 2020). The World Health Organization (WHO) has recognized AD as a global public health priority (WHO, 2021). It is predicted that 12.7 million persons aged 65 and older will have AD by 2050 (Alzheimer's disease facts and figures, 2022). The number and percentage of older persons with AD will increase together with the expansion of the population 65 and older. In summary, AD is emerging as a growing and pervasive threat to global health.

The pathology of AD is characterized by the accumulation of amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the hippocampus, both of which are essential for learning and memory (Busche and Hyman, 2020). Previous studies have shown that Aβ and tau can harm memory by preventing synaptic plasticity in the hippocampus (Forner et al., 2017). This synaptic plasticity includes activity-dependent changes in synaptic remodeling, axonal sprouting, dendritic remodeling, dendritic spine dynamics, and synaptic proteins. In a concentration-dependent manner, oligomer Aβ can impair long-term potentiation (LTP) while enhancing long-term depression (LTD), the consequent disruption of glutamatergic transmission results in the loss of dendritic spines and causes memory deficits (Rajmohan and Reddy, 2017). Before plaque development, synaptic function damage was seen in young mice, which suggested that Aβ oligomers caused synaptic abnormalities beforehand (Hong et al., 2016). Synaptic pathology is thus an early stage of disease development. However, currently, there is no treatment available to target synaptic damage. In addition, the effectiveness of current disease-modifying therapy and anti-dementia medications is limited (Lane et al., 2018). Therefore, it is urgent to seek alternative therapies to prevent and treat synaptic damage.

Excitingly, there have been multiple randomized controlled trials (RCTs) and several reviews provided support for the beneficial effects of exercise on cognitive function and synaptic plasticity of AD (Choi et al., 2018; Da Costa Daniele et al., 2020; De Miguel et al., 2021). Both the WHO (2021) and the NICE guidelines (NICE, 2015) recommend implementing exercise in the standard treatment of AD. Exercise may exert beneficial effects on cognitive function and synaptic plasticity through various mechanisms. Such as promoting the release of neurogenic factors (Choi et al., 2018), maturation of new neurons (Lattanzi et al., 2022), and cerebral angiogenesis (Tang et al., 2018), which ultimately increases neurogenesis and upregulates synaptic protein expression. Postsynaptic proteins were reported to be lost at a higher rate than presynaptic proteins in AD (Gylys et al., 2004). Postsynaptic density protein 95 (PSD95), the most important and abundant scaffolding protein of the postsynaptic membrane, is mainly found in the mature excitatory glutamatergic synapse (Coley and Gao, 2018; Mardones et al., 2019). It is necessary for receptor activity and stability of the postsynaptic membrane (Dore et al., 2021), which could be affected by exercise. However, controversial results about the effects of exercise on cognition and synapses have also been reported (Wang et al., 2021). Meanwhile, there is no systematic review of the effects of exercise on synaptic plasticity to date. Therefore, it is thus necessary to update the knowledge about the effects of exercise on cognitive function and synaptic plasticity.

Thus, based on the current controversies and the limitations of the systematic reviews, the purpose of this study is to systematically review the current literature that evaluated the effect of exercise on AD model in MWM tests and synaptic plasticity to determine: (i) the positive effects of exercise on cognitive function and synaptic plasticity; (ii) the differential preventive and therapeutic effects of exercise, and (iii) the different effects of exercise types on cognitive function and synaptic plasticity.

2. Materials and methods

This systematic review was designed following the writing guidelines in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews (Page et al., 2021). The study was registered in The International Prospective Register of Systematic Reviews (PROSPERO), and the number was CRD42022328438. All of the studies retrieved were animal studies related to exercise and cognitive function.

2.1. Search strategy

PubMed, MEDLINE, EMBASE, Web of Science, and Cochrane Library were searched for studies that were published between April 1, 2012 and April 1, 2022. The reference lists of previous systematic reviews were carefully examined for new references. The strategy was formulated based on the combination of the Medical Subject Headings (MeSH) and free text terms as follows: (exercise OR resistance training OR physical exercise OR aerobic OR treadmill OR running OR voluntary OR involuntary OR swimming) AND (synapse* OR

neuronal plasticity OR synaptic OR neuroplasticity OR plasticity OR synaptogenesis OR dendritic OR dendron OR long-term potentiation OR LTP) AND (Alzheimer disease OR dementia OR Alzheimer OR AD OR cognition). The detailed search strategy was provided in the Supplementary material.

2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

Studies were considered if all of the following standards were met: (1) had animal models for Alzheimer's disease, either by genetic variants (transgenic) or drug-induced; (2) included both control group (sedentary) and exercise group; (3) had Morris Water Maze (MWM) test or at least one indicator of synaptic plasticity; (4) randomized controlled trials; (5) published in English.

2.2.2. Exclusion criteria

Studies were excluded if any of the following standards were met: (1) using physical exercise combined with any type of medicines or other non-pharmacological treatments in the animal model; (2) absence of full text, literature review studies, course completion papers, dissertations, theses, and annals abstracts.

2.3. Data extraction

Two reviewers collected data based on the following lists separately. The divergences were solved by consulting a third reviewer.

Extracted data from each study included: (1) the first author's name, publication year; (2) animal data including the species, gender, age, and sample size of each group; (3) exercise protocol including type, intensity, time, frequency, and duration of exercise; (4) outcome assessment including escape latency, number of platform crossings, time in the target quadrant selected in the MWM test and the biomarkers of synaptic plasticity. The final result was extracted if outcomes were presented at different time points; (5) the analyzed brain region; (6) the timing of the implementation of exercise: according to previous reports, the pathological changes (diffuse amyloid plaques) were first observable in the brain for particular mouse model of 5* FAD (Gatt et al., 2019), APP/PS1 (Zhu et al., 2017) and 3* Tg (Javonillo et al., 2022) at 1.5–2 months of age, 3 months of age, and 4 months of age, respectively. According to the characteristics of each animal model, we divided the animals included into exercise before AD group and exercise after AD group.

The data such as mean and standard deviation (SD) or standard error of mean (SEM), which were not provided in the texts or tables, were extracted from the graphs through the free software WebPlotDigitizer (Drevon et al., 2017). By multiplying the reported SEM by the square root of the sample size to convert to SD we used (Vasconcelos-Filho et al., 2021).

2.4. Quality assessment

Two reviewers assessed study quality independently using a ten-item scale introduced by "SYRCLE's Risk of Bias (RoB) tool for animal studies" (Hooijmans et al., 2014), and the divergences were solved by consulting a third reviewer. The criteria for evaluation under the tool were: random allocation sequence; similar baseline characteristics; allocation concealment; random housing; blinded intervention; random selection for outcome assessment; blinded assessment of outcome; incomplete outcome data; selective outcome reporting; other sources of bias. Each criterion in a 10-point scale for a quality index was assigned a point value of one. A "Yes" response indicated a low risk of bias, a "No" response indicated a high risk of bias, and a "NC" response indicated a level of prejudice that was unsure due to insufficient data. Each item received one point for answering "Yes".

2.5. Statistical analysis

Meta-analysis was performed using the software Stata (Version 17.0). The mean ± SD was calculated with 95% confidence interval (CI) and standardized mean difference (SMD) using randomized effect models to account for potential heterogeneity. I2 test was used to calculate the degree of heterogeneity among studies, with values 30%, 30–60%, and >60% representing low, moderate, and high levels of heterogeneity, respectively (Hernandez et al., 2020). When there was high heterogeneity, sensitivity analysis was performed by eliminating the data one by one to examine its impact on the result. Funnel plots and Egger's test were used to evaluate publication bias.

3. Results

A total of 8,426 studies were found in the initial search, and after the removal of duplicates, 4,996 remained for screening. Of these, 85 full-text articles were reviewed after screening titles and abstracts. After reviewing the full texts, 62 studies were excluded for the following reasons: nine for animals that were not models of AD; five for no exercise as an isolated intervention; one for no long-term exercise; 47 for no assessments or reports of results related to MWM or synaptic plasticity. In the end, 20 studies met the inclusion criteria and were included in the qualitative analysis (Wang et al., 2013, 2021; Kim et al., 2014; Revilla et al., 2014; Cho et al., 2015; Dao et al., 2015, 2016; Zhao et al., 2015, 2020; Wu et al., 2018; Lourenco et al., 2019; Belaya et al., 2020;

Liu et al., 2020, 2022; Li et al., 2021, 2022; Mu et al., 2022; Park et al., 2022; Xu et al., 2022; Yang et al., 2022). Twelve for the quantitative analysis because of the lacked data on synaptic plasticity of the eight articles (Revilla et al., 2014; Cho et al., 2015; Belaya et al., 2020; Liu et al., 2020, 2022; Zhao et al., 2020; Li et al., 2021, 2022; Wang et al., 2021; Mu et al., 2022; Park et al., 2022; Xu et al., 2022). The flow diagram of the selection process is shown in Figure 1.

3.1. Study characteristics

The included studies used two species: mice ($n = 15$) and rats ($n = 5$). AD models were drug-induced and transgenic, with the latter being more prevalent. Transgenic models included: APP/PS1 mice ($n = 6$), 3×Tg-AD mice ($n = 6$), 5×FAD mice ($n = 1$), TgF344 rats ($n = 1$). The non-transgenic models included: injection of Aβ ($n = 5$) and streptozotocin ($n = 1$). There were 15 studies only using male animals, one using both sexes, and four of them did not describe the sex of animals used in the experiment. Sixteen studies mentioned age of the experimental animals. In mouse-related studies, age ranged from 1 to 24 months; in rat-related studies, age ranged from 2 to 2.5 months.

Four types of intervention were used in the included studies: treadmill exercise ($n = 10$), wheel running ($n = 7$), swimming ($n = 2$) and resistance training ($n = 1$). The duration of the intervention ranged from 1 to 8 months. However, only one study was conducted for 12 days. Behavioral tests were carried out in 16 studies to assess animal learning and memory function: MWM ($n = 10$), Novel Object Recognition (NOR, $n = 5$), and Y-maze test ($n = 3$). Several relevant indicators for evaluating synaptic plasticity were applied, for example, dendritic spine density through Golgi staining, the number of synapses through electron microscopy, LTP through *in vivo* electrophysiology, and

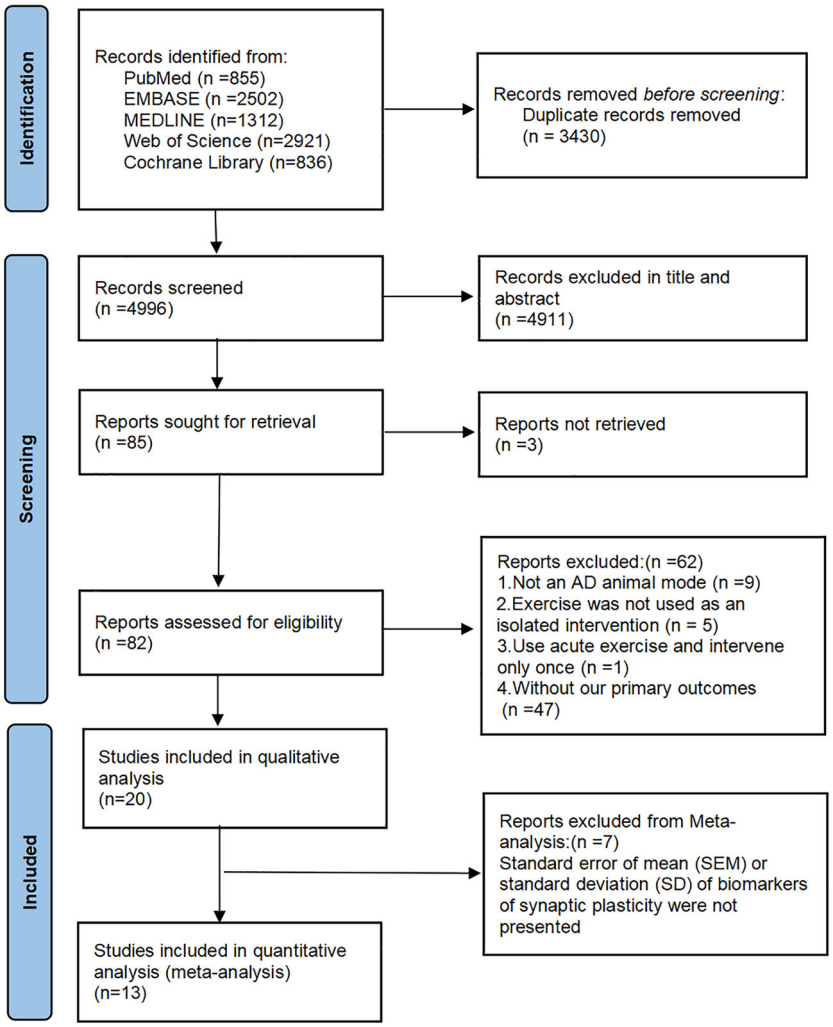

FIGURE 1
The flow diagram of the study selection process.

several synaptic-associated proteins through western blotting. PSD95 was analyzed in the hippocampus ($n = 11$) and cortex ($n = 4$), and one of the studies analyzed the length of the apical dendrites. It should be noted that a total of 20 studies were included in this review. Since four studies used two groups of RCTs, respectively, the characteristics of 24 RCTs need to be described. All these data can be found in Table 1.

3.2. Study quality evaluation

Table 2 showed the methodological quality assessments of the 20 included studies, with study quality scores ranging from 3 to 6 out of a total 10. No study was considered to have low risk of sequence generation and allocation concealment (selection bias), blinding (performance bias) and random outcome assessment (detection bias). Fourteen studies were thought to have low risk of baseline characteristics. Seventeen studies were judged as having low risk of random housing. Sixteen studies were thought to have low risk of incomplete data. However, only four studies were thought to have low risk of blinding against detection bias. All 20 studies were considered with low risk for selective outcome reporting and other sources of bias.

3.3. Results of the meta-analysis

3.3.1. Effect of exercise on cognitive function in AD models: Escape latency of MWM

Since three studies (Cho et al., 2015; Wang et al., 2021; Liu et al., 2022) performed RCTs for exercise intervention before and after AD, finally, 11 RCTs from eight studies (Cho et al., 2015; Zhao et al., 2020; Li et al., 2021, 2022; Wang et al., 2021; Liu et al., 2022; Park et al., 2022; Xu et al., 2022) including 240 animals reported the impact of exercise on decreasing escape latency compared with the control group. The results demonstrated that the exercise group had a significant effect on decreasing escape latency compared with the control group (SMD = −0.86, 95% CI: −1.21 to −0.50, $P < 0.001$). There was a moderate heterogeneity between the studies ($I^2 = 42.3\%$). The results of the subgroup analysis showed that exercise had significant effects in both the before AD group ($n = 6$, SMD = −0.88, 95% CI: −1.25 to −0.52, $P < 0.001$) and the after AD group ($n = 5$, SMD = −0.86, 95% CI: −1.63 to −0.09, $P = 0.029$) (Figure 2A).

3.3.2. Effect of exercise on cognitive function in AD models: Number of platform crossings of MWM

Since three studies (Cho et al., 2015; Wang et al., 2021; Liu et al., 2022) performed RCTs for exercise intervention before and after AD, finally, number of platform crossings was adopted as an outcome in 10 RCTs from seven studies (Cho et al., 2015; Zhao et al., 2020; Li et al., 2021, 2022; Wang et al., 2021; Liu et al., 2022; Xu et al., 2022) including 220 animals. All these studies except for one study (Wang et al., 2021) reported the positive effect of exercise on increasing platform crossover numbers (SMD = 1.34, 95% CI: 0.57–2.11, $P = 0.001$). There was a high heterogeneity between the studies ($I^2 = 83.1\%$). In the subgroup analysis of platform crossover numbers, there was a significant effect of exercise was observed in the before AD group ($n = 6$, SMD = 1.71, 95% CI: 1.23–2.18, $P < 0.001$), but no significant difference was found in the after AD group ($n = 4$, SMD = 0.73, 95% CI: −0.96 to 2.42, $P = 0.398$). It instructed that exercise after AD didn't increase platform crossover numbers (Figure 2B). The remaining study did not mention the relevant data and failed for meta-analysis.

3.3.3. Effect of exercise on cognitive function in AD models: Time in the target quadrant of MWM

Since three studies (Cho et al., 2015; Wang et al., 2021; Liu et al., 2022) performed RCTs for exercise intervention before and after AD, finally, 10 RCTs from seven studies (Cho et al., 2015; Zhao et al., 2020; Wang et al., 2021; Li et al., 2022; Liu et al., 2022; Park et al., 2022; Xu et al., 2022) including 210 animals adopted time in the target quadrant as an outcome indicator. The results of the meta-analysis displayed that the exercise group had a significant effect on increasing time in the target quadrant, compared with the control group (SMD = 1.65, 95% CI: 0.95–2.36, $P < 0.001$). There was a high heterogeneity between the studies ($I^2 = 77.9\%$). The results of the subgroup analysis showed that exercise had significant effects in both the before AD group ($n = 5$, $P < 0.001$) and the after AD group ($n = 5$, $P = 0.02$), however, compared with exercising after AD, exercising before AD seemed to have a more striking effect on increasing time in the target quadrant (SMD = 2.03, 95% CI: 1.19–2.87 vs. SMD = 1.27, 95% CI: 0.20–2.35) (Figure 2C). Likewise, the remaining study did not mention the data of the time in the target quadrant and failed for meta-analysis.

3.3.4. Effect of exercise on synaptic plasticity in AD models

Since two studies (Wang et al., 2021; Liu et al., 2022) performed RCTs for exercise intervention before and after AD and three analyzed both hippocampus and cortex (Liu et al., 2020; Wang et al., 2021; Mu et al., 2022), finally, 16 RCTs from 10 studies (Revilla et al., 2014; Belaya et al., 2020; Liu et al., 2020, 2022; Li et al., 2021, 2022; Wang et al., 2021; Mu et al., 2022; Park et al., 2022; Xu et al., 2022) including 344 animals reported the effect of exercise on PSD95 expression

TABLE 1 Characteristics of the included studies.

Study	AD model	Exercise protocol	Start exercise time	Outcome measures	Main molecular results
Yang et al. (2022)	TgF344 rats (n = 11), male, 2-month	Treadmill running:18 m/min, 45 min/day, 3 days/week Duration: 8 months	Before AD	Dendritic spine density: Golgi staining; the number of synapses: electron microscopy	None
Xu et al. (2022)	3×Tg mice (n = 11), male, 8-week	Wheel running: 1 h/day, 5 days/week Duration: 5 months	Before AD	Cognition: MWM, NOR; dendritic spine density: Golgi staining; PSD95, SYN: IHC,WB	⬆ Hippocampus (PSD95, SYN)
Mu et al. (2022)	3×Tg mice (n = 10), male, 3-month	Treadmill running:12 m/min*10 min +15 m/min*50 min, 1 h/day, 5 days/week Duration: 12 weeks	Before AD	Dendritic spine density: Golgi staining; the number of synapses: electron microscopy; PSD95, SYN: WB	⬆ Hippocampus and cortex (PSD95, SYN)
Li et al. (2022)	Aβ induced ICR mice, male, 8-week	Wheel running: 24 h/day Treadmill exercise: 5 m/min*5 min + 10 m/min*40 min+3 m/min*5 min, 50 min/day, 6 days/week Duration: 4 weeks	After AD	Cognition: MWM, NOR; PSD95, SYP: WB	⬆ Hippocampus (PSD95, SYP)
Liu et al. (2020)	APP/PS1 mice (n = 12), male, 3-month	Wheel running: 4 h/day, 5 days/week Duration: 8 weeks	Before AD	Cognition: MWM, NOR, Y-maze test; PSD95, SYN: WB	⬆ Hippocampus (PSD95, SYN)
Liu et al. (2022)	APP/PS1 mice (n = 12), male, 7-month	Wheel running: 4 h/day, 5 days/week Duration: 8 weeks	After AD	Cognition: MWM, NOR, Y-maze test; PSD95, SYN: WB	None
Park et al. (2022)	3×Tg mice (n = 10), male, 5-month	Treadmill running: 10 m/min*40 min (1–3 w) + 11 m/min*40 min (4–6 w) + 12 m/min*50 min (7–9 w) + 13 m/min*50 min (10–12 w), 6 days/week Duration: 8 weeks	After AD	Cognition: MWM; PSD95, SYN: WB	⬆ Hippocampus (PSD95, SYN)
Wang et al. (2021)	APP/PS1 mice (n = 7), male, 10-week	Wheel running Duration: 16 weeks	Before AD	Cognition: MWM; PSD95, SYN: WB	⬆ Hippocampus and cortex (SYN)
Wang et al. (2021)	APP/PS1 mice (n = 7), male, 24-week	Wheel running Duration: 16 weeks	After AD	Cognition: MWM; PSD95, SYN: WB	⬆ Hippocampus and cortex (SYN)
Li et al. (2021)	APP/PS1 mice (n = 15), 3-month	Treadmill running: 5 m/min*5 min + 8 m/min*5 min + 12 m/min*30 min + 5 m/min*5 min, 45 min/day, 5 days/week Duration:12 weeks	Before AD	Cognition: MWM; the number of synapses: electron microscopy. SYN, PSD95, MAP2,: WB	⬆ Hippocampus (SYN, PSD95, MAP2)
Belaya et al. (2020)	5×FAD mice (n = 20), male, 6-week	Wheel running Duration:6 months	Before AD	Cognition: MWM; PSD95, SYN: WB	⬆ Hippocampus (PSD95)
Liu et al. (2020)	3×Tg mice (n = 8), male, 9-month	Resistance training: weight-bearing climbing, once every 2 days Duration:4 weeks	After AD	Cognition: NOR, Y-maze test; PSD95: WB	⬆ Hippocampus and cortex (PSD95)
Zhao et al. (2020)	APP/PS1 mice (n = 9), male, 3-month	Treadmill running: 5 m/min*5 min + 8 m/min*5 min + 12 m/min*30 min + 5 m/min*5 min, 45 min/day, 5 days/week Duration:12 weeks	Before AD	Cognition: MWM; SYN, GAP43: WB	⬆ Hippocampus (SYN, GAP43)
Lourenco et al. (2019)	APP/PS1 mice, male and female, 2.5–3-month	Swimming: 20 min/d, 5 days/week Duration:3 weeks	Before AD	LTP: vivo electrophysiology;	None

(Continued)

TABLE 1 (Continued)

Study	AD model	Exercise protocol	Start exercise time	Outcome measures	Main molecular results
Wu et al. (2018)	Streptozotocin-induced Sprague–Dawley rats ($n = 9$), male, 2.5-month	Swimming: began at 10 min/day and was increased by 10 min every 2 d until the duration reached 1 h/day, 5 days/week Duration:4 weeks	Before AD	Cognition: NOR; SYN: confocal microscopy	⬆ Hippocampus (SYN)
Dao et al. (2016)	Aβ-induced Wistar rats, male	Treadmill running: 10 m/min*30 min (1–2 w)+15 m/min*45 min (3–4 w), 5 days/week Duration:4 weeks	After AD	LTP: vivo electrophysiology	None
Dao et al. (2015)	Aβ-induced Wistar rats, male	Treadmill running: 10 m/min*30 min (1–2 w) + 15 m/min*45 min (3–4 w), 5days/week Duration:4 weeks	Not clear	LTP: vivo electrophysiology	None
Cho et al. (2015)	3×Tg mice ($n = 12$), 4-month	Treadmill running: 5 m/min*5 min + 10 m/min*20 min + 5 m/min*5 min, 30 min/day, 5 days/week Duration:12 weeks	Before AD	Cognition: MWM; PSD95, SYN:WB	⬆ Hippocampus and cortex (PSD95, SYN)
Cho et al. (2015)	3×Tg mice ($n = 12$), 24-month	Treadmill running:5m/min*5min +10m/min*20min+5m/min*5min, 30min/day, 5days/week Duration:12 weeks	After AD	Cognition: MWM; PSD95, SYN:WB	⬆ Hippocampus and cortex (PSD95, SYN)
Zhao et al. (2015)	APP/PS1 mice ($n = 12$), 3-month	Treadmill running: 5 m/min*5 min + 8 m/min*5 min + 11 m/min*20 min, 30 min/day, 5 days/week Duration: 5 months	Before AD	Cognition: MWM; LTP: vivo electrophysiology	None
Zhao et al. (2015)	APP/PS1 mice ($n = 12$), 12-month	Treadmill running: 5 m/min*5 min + 8 m/min*5 min + 11 m/min*20 min, 30 min/day, 5 days/week Duration:5 months	After AD	Cognition: MWM; LTP: vivo electrophysiology	None
Revilla et al. (2014)	3×Tg mice, 1-month	Wheel running Duration:6 months	Before AD	PSD95, SYN: WB	⬆ Hippocampus (PSD95, SYN)
Kim et al. (2014)	Aβ-induced Sprague-Dawley rats ($n = 10$), male, 7-week	Treadmill running: 3 m/min*5 min + 5 m/min*5 min + 8 m/min*20 min, 30 min/day, 5 days/week Duration:4 weeks	After AD	Apical dendritic length: electron microscopy	None
Wang et al. (2013)	Aβ-induced C57bl/6 mice, male, 2-month	Wheel running Duration: 12 days	After AD	Cognition: Y-maze test; SYN: IHC	⬆ Hippocampus (SYN)

MWM, Morris water maze; NOR, Novel Object Recognition; LTP, long-term potentiation; PSD95, Postsynaptic density protein 95; SYN, Synaptophysin; SYP, Synaptophysin; MAP2, Microtubule-associated protein-2; GAP43, Growth associated protein-43; IHC, Immunohistochemistry; WB, Western Blotting.

of animals with AD. All of them except for one study (Wang et al., 2021) provided detailed data to show the significant effects of exercise on increasing the expression of PSD95 compared with the control group (SMD = 0.73, 95% CI: 0.25–1.21, $P = 0.003$). There was a high heterogeneity between the studies ($I^2 = 76.4\%$). In the subgroup analysis of PSD95 expression, exercise before AD group showed a significant effect ($n = 7$, SMD = 0.94, 95% CI: 0.19–1.69, $P = 0.014$), whereas exercise after AD group had no significant difference ($n = 5$, SMD = 0.47, 95% CI: −0.06 to 1.00, $P = 0.083$) (Figure 3).

3.3.5. Effect of exercise type on cognitive function in AD models

Greater reduction of escape latency was observed in treadmill running ($n = 5$, SMD = −1.40, 95% CI: −1.81 to −0.98, $P < 0.001$) in comparison to wheel running ($n = 6$,

TABLE 2 The methodological quality assessments of 20 included studies.

Study	A	B	C	D	E	F	G	H	I	J	Score
Yang et al. (2022)	NC	Y	NC	Y	NC	NC	NC	Y	Y	Y	5
Xu et al. (2022)	NC	Y	NC	NC	NC	NC	Y	Y	Y	Y	5
Mu et al. (2022)	NC	Y	NC	Y	NC	NC	NC	Y	Y	Y	5
Li et al. (2022)	NC	Y	NC	Y	NC	NC	NC	Y	Y	Y	5
Liu et al. (2022)	NC	Y	NC	Y	NC	NC	Y	Y	Y	Y	6
Park et al. (2022)	NC	Y	NC	Y	NC	NC	NC	Y	Y	Y	5
Wang et al. (2021)	NC	Y	NC	Y	NC	NC	NC	Y	Y	Y	5
Li et al. (2021)	NC	N	NC	Y	NC	NC	Y	Y	Y	Y	5
Belaya et al. (2020)	NC	Y	NC	Y	NC	NC	NC	Y	Y	Y	5
Liu et al. (2020)	NC	Y	NC	Y	NC	NC	NC	NC	Y	Y	4
Zhao et al. (2020)	NC	Y	NC	Y	NC	NC	NC	NC	Y	Y	4
Lourenco et al. (2019)	NC	N	NC	Y	NC	NC	NC	NC	Y	Y	3
Wu et al. (2018)	NC	Y	NC	NC	NC	NC	NC	Y	Y	Y	4
Dao et al. (2016)	NC	Y	NC	Y	NC	NC	Y	Y	Y	Y	6
Dao et al. (2015)	NC	NC	NC	Y	NC	NC	NC	Y	Y	Y	4
Cho et al. (2015)	NC	NC	NC	NC	NC	NC	NC	Y	Y	Y	3
Zhao et al. (2015)	NC	NC	NC	Y	NC	NC	NC	Y	Y	Y	4
Revilla et al. (2014)	NC	NC	NC	Y	NC	NC	NC	Y	Y	Y	4
Kim et al. (2014)	NC	Y	NC	Y	NC	NC	NC	NC	Y	Y	4
Wang et al. (2013)	NC	Y	NC	Y	NC	NC	NC	Y	Y	Y	5

A—random allocation sequence; B—similar baseline characteristics; C—allocation concealment; D—random housing; E—blinded intervention; F—random selection for outcome assessment; G—blinded assessment of outcome; H—incomplete outcome data; I—selective outcome reporting; J—other sources of bias. Y, yes; N, no; NC, unclear.

SMD = −0.41, 95% CI: −0.76 to −0.05, $P = 0.025$) (Figure 4A). Treadmill running showed a significant effect on increasing platform crossover numbers ($n = 4$, SMD = 2.38, 95% CI: 1.30–3.46, $P < 0.001$), whereas wheel running had no significant difference ($n = 6$, SMD = 0.67, 95% CI: −0.21 to 1.55, $P = 0.134$) (Figure 4B). Greater increase of time in the target quadrant was observed in treadmill running ($n = 4$, SMD = 2.89, 95% CI: −2.04 to 3.75, $P < 0.001$), compared with wheel running ($n = 6$, SMD = 0.90, 95% CI: 0.39–1.41, $P = 0.001$) (Figure 4C).

3.3.6. Effect of exercise type on synaptic plasticity in AD models

Figure 5 demonstrated that, independently of the type of exercise, the expression of PSD95 was increased (SMD = 0.73, 95% CI: 0.25–1.21, $P = 0.003$). However, treadmill running demonstrated greater increase of PSD95 ($n = 4$, SMD = 1.68, 95% CI: 0.21–3.14, $P = 0.025$), whereas wheel running ($n = 10$, SMD = 0.49, 95% CI: −0.03 to 1.00, $P = 0.065$) and resistance training ($n = 2$, SMD = 0.33, 95% CI: −0.37 to 1.03, $P = 0.360$) had no significant difference.

3.4. Results of the qualitative analysis

3.4.1. Effect of exercise on synaptic plasticity in AD models: Dendritic spine density

Totally, three studies (Mu et al., 2022; Xu et al., 2022; Yang et al., 2022) have reported an association between a higher density of dendritic spines and exercise. Dendritic spines are small projections on the dendrite stem that form synapses with the axons of neurons to receive and integrate information (Chidambaram et al., 2019), which are highly correlated with hippocampus-dependent spatial navigation (Bolding et al., 2019). The results displayed that the dendritic spine density of the hippocampus was obviously higher in the exercise group than the sedentary controls. Furthermore, two studies (Mu et al., 2022; Xu et al., 2022) reported in detail that exercise pretreatment blocked the decrease in the number of thin spines, mushroom spines, and stubby spines both in the hippocampus and prefrontal cortex. In the study by (Mu et al., 2022), there was also reported that treadmill exercise enhanced the axon length and dendritic complexity.

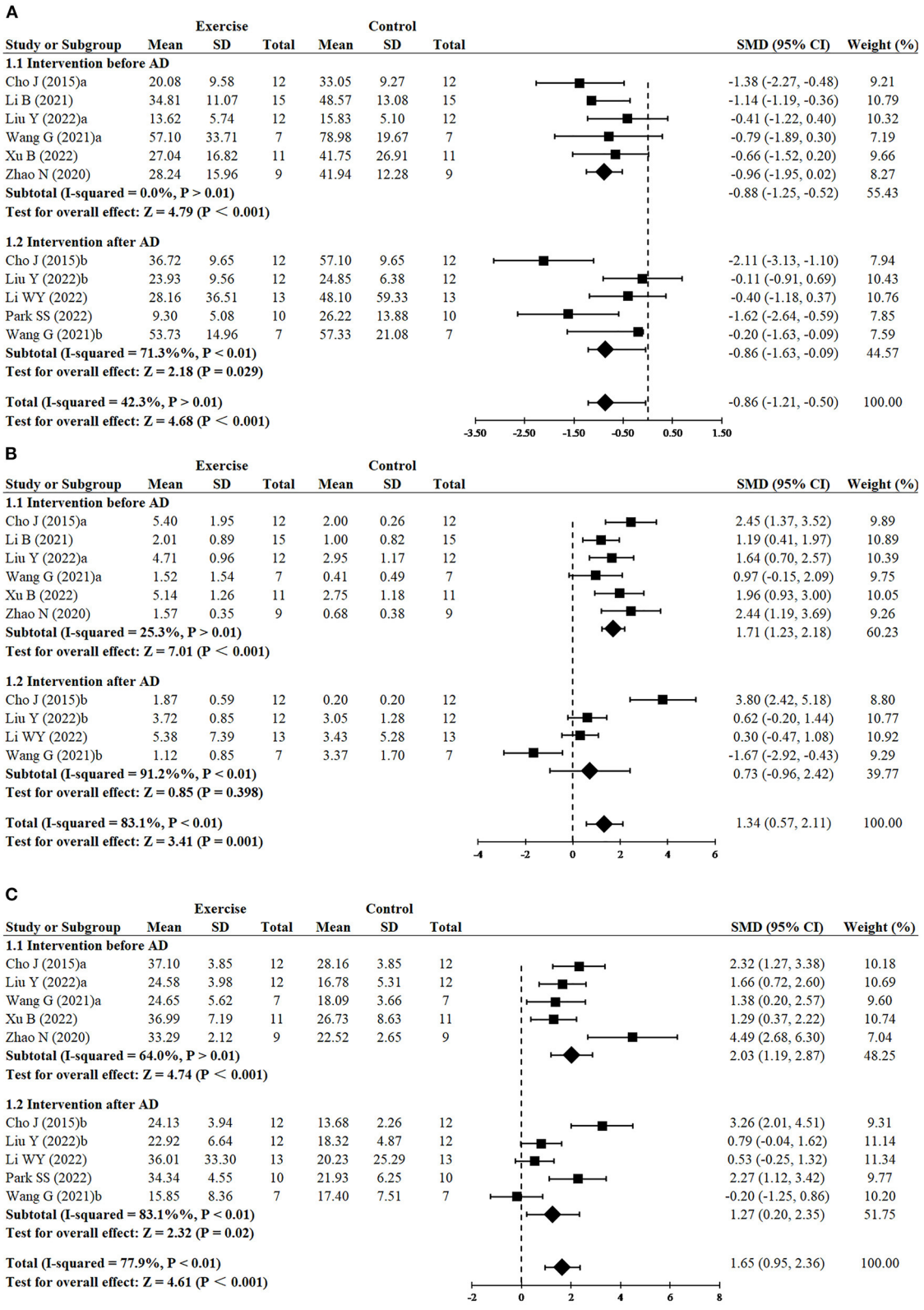

FIGURE 2
Forest plots showing the effect of exercise on cognitive function in AD models. **(A)** The effect of exercise on the escape latency of MWM. **(B)** The effect of exercise on the number of platform crossings of MWM. **(C)** The effect of exercise on the time in the target quadrant of MWM.

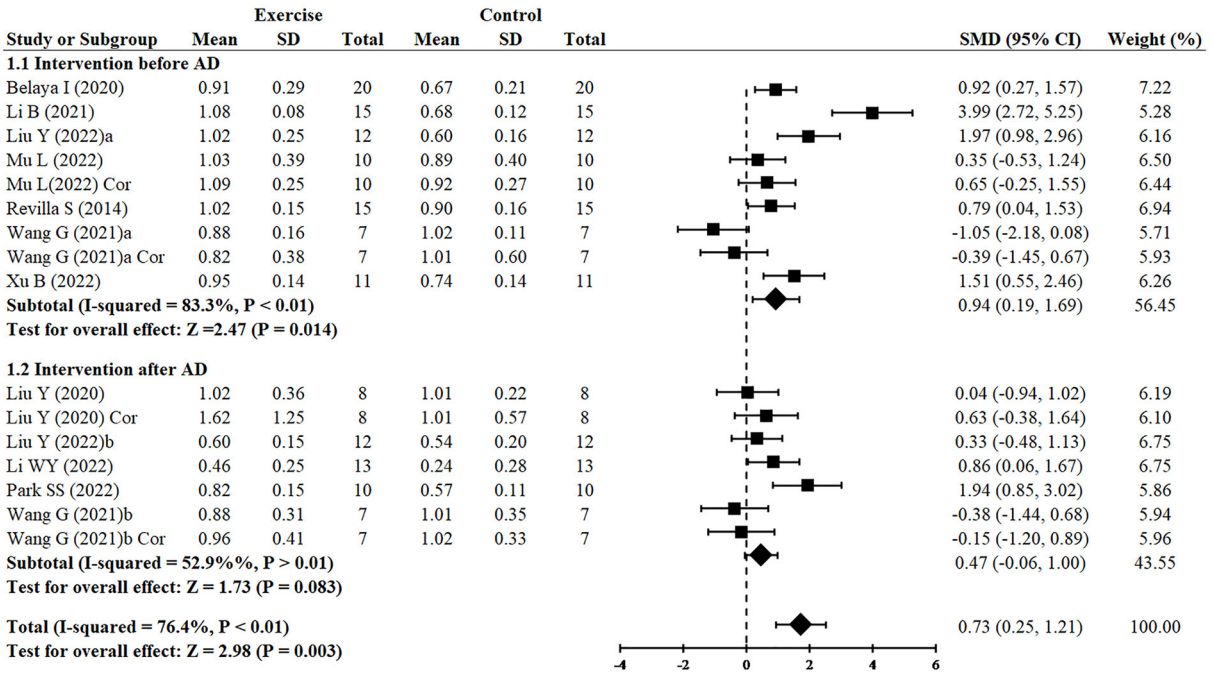

FIGURE 3
Forest plot showing the effect of exercise on the expression of PSD95 in AD models.

3.4.2. Effect of exercise on synaptic plasticity in AD models: The number of synapses

Overall, three articles (Li et al., 2021; Mu et al., 2022; Yang et al., 2022) mentioned a positive correlation between more synapses and exercise. And two articles (Li et al., 2021; Mu et al., 2022) further measured and analyzed the ultra-structural parameters by electron microscopy. They indicated that exercise also increased the length of the synaptic active zone, the width of the synaptic cleft, synaptic curvature, and the thickness of the postsynaptic density in the hippocampus, which greatly improved the efficiency of synaptic transmission. In addition to the hippocampus, Mu et al. (2022) and Yang et al. (2022) also evaluated the positive effect of exercise on the prefrontal cortex.

3.4.3. Effect of exercise on synaptic plasticity in AD models: LTP

In all, four studies (Dao et al., 2015, 2016; Zhao et al., 2015; Lourenco et al., 2019) used electrophysiological experiments to detect LTP, which found that PS amplitude and fEPSP slope were reduced significantly in AD models. LTP is a form of synaptic plasticity accepted as an electrophysiological model of learning and memory (Zhao et al., 2015). All results showed that exercise could increase the fEPSP slope significantly in both young and old AD models, indicating that exercise prevented the impairment of synaptic transmission. Nevertheless, one study (Dao et al., 2016) reported that exercise only partially prevented the effect of Aβ on PS amplitude. Different from the aforementioned studies, Dao et al. (2015) and Zhao et al. (2015) reported that there was no significant difference of PS amplitude between the sedentary and exercise mice.

3.5. Sensitivity analysis

We performed sensitivity analysis based on the outcomes of escape latency, number of platform crossings, time in the target quadrant, and the expression of PSD95. After each study was successively removed, the effects of the remaining studies were within the 95% CI of the total effect. It demonstrated that the meta-analysis had a low level of sensitivity and produced stable and reliable results (Supplementary Figures 1–4).

3.6. Publication bias

We conducted publication bias test with funnel plot (Figure 6) and Egger's test for the four outcomes. The symmetry indicating there was no significant publication bias of escape latency ($P = 0.211$) and number of platform crossings ($P = 0.310$). However, the funnel plot's visual inspection revealed significant asymmetry and the Egger's test identified potential evidence of publication bias of time in the target quadrant ($P = 0.012$) and PSD95 ($P < 0.001$). Then, a sensitivity analysis

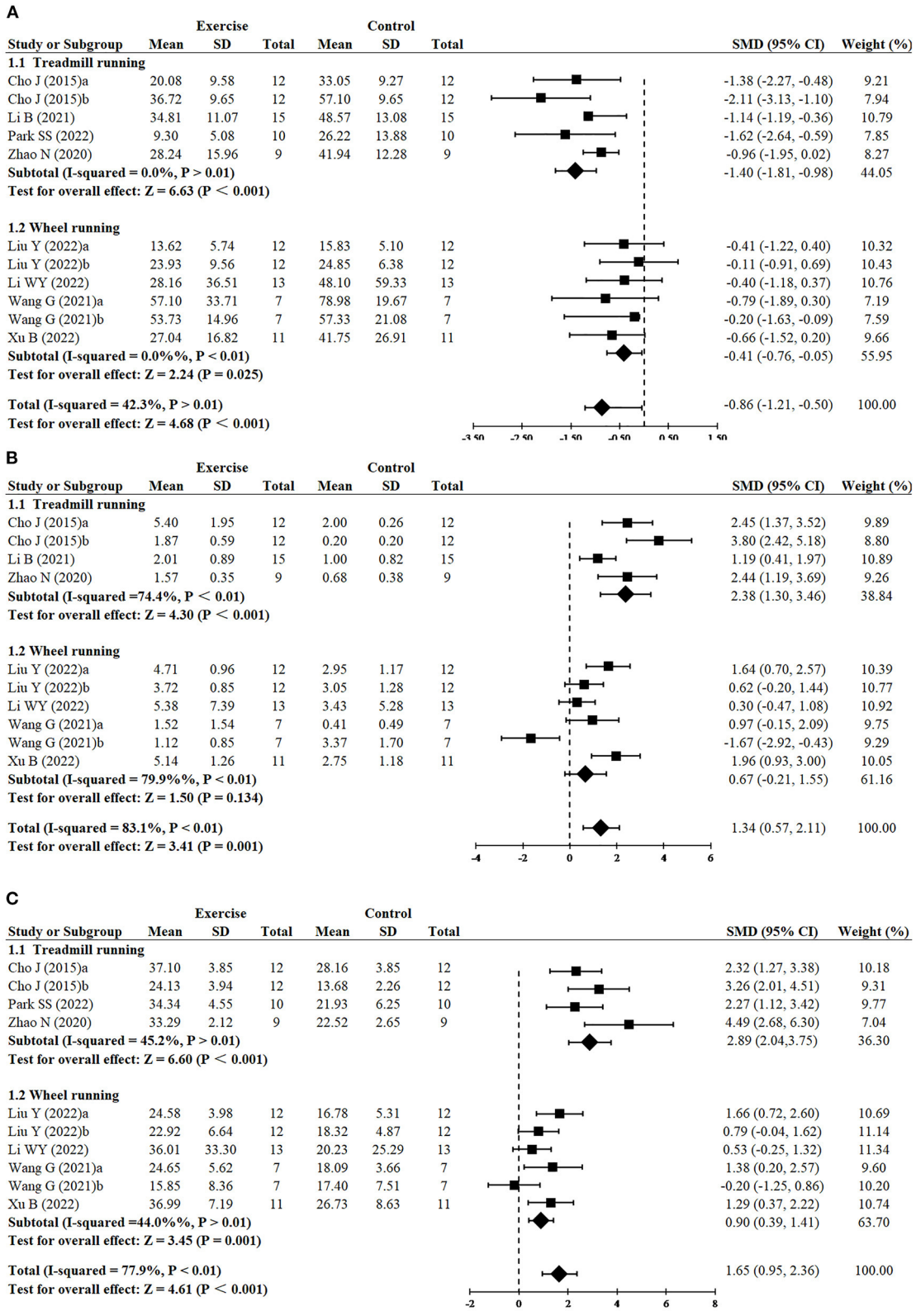

FIGURE 4
Subgroup analysis of exercise type on cognitive function in AD models. **(A)** Subgroup analysis of exercise type on the escape latency of MWM. **(B)** Subgroup analysis of exercise type on the number of platform crossings of MWM. **(C)** Subgroup analysis of exercise type on the time in the target quadrant of MWM.

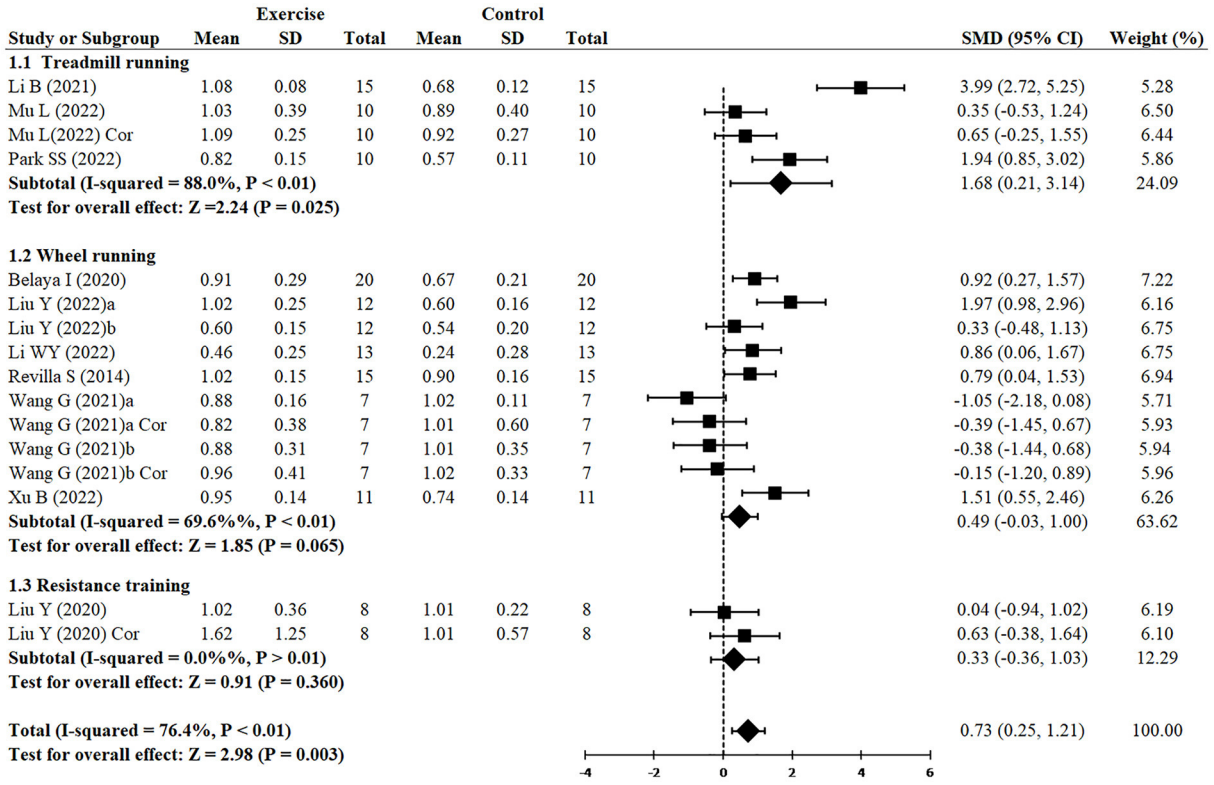

FIGURE 5
Subgroup analysis of exercise type on the expression of PSD95 in AD models.

using the trim-and-fill method was performed, which indicated that there was no need to trim any existing studies and fill any other unpublished studies. Therefore, it was considered to have no significant risk of publication bias and the risk of bias caused by other factors.

4. Discussion

To our knowledge, this is the first systematic review and meta-analysis to examine the effect of exercise on cognitive and synaptic function in animal models of AD, using the MWM test and synaptic plasticity as outcome indicators. Our study highlighted the positive effect of exercise on cognitive function and synaptic plasticity in animal models of AD. And the effect of exercise on cognitive function and synaptic plasticity was more significant in the exercise before AD group than the exercise after AD group. Our findings suggested that exercise had a potential effect on improving cognitive and synaptic function in animal models of AD.

According to reports from four included studies (Dao et al., 2015, 2016; Zhao et al., 2015; Lourenco et al., 2019), exercise can improve LTP damage by increasing the slope of field excitatory postsynaptic potential (fEPSP). It was consistent with Loprinzi PD's conclusions (Moore and Loprinzi, 2021). This may be related to the fact that exercise stimulated skeletal muscles. According to studies, active skeletal muscles can secrete numerous substances that have a protective effect on the brain (Sui et al., 2021). Western blotting and *in vivo* electrophysiology had indicated that exercise could increase Calcium/calmodulin-dependent protein kinase IV (CaMKIV) availability, which in turn will enhance cAMP-response element binding protein (CREB) phosphorylation and subsequent CREB-mediated transcriptions (Dao et al., 2016). CREB regulates the transcription of brain-derived neurotrophic factor (BDNF), which is closely related to LTP and spatial long-term memory (Brann et al., 2021). Moreover, analysis of the number of synapses and spine density in five included studies (Kim et al., 2014; Li et al., 2021; Mu et al., 2022; Xu et al., 2022; Yang et al., 2022) showed that exercise increased the number of synapses and spines, especially the thin and mushroom-type spines in the hippocampus of AD. BDNF played an essential role in this process (von Bohlen Und Halbach and von Bohlen Und Halbach, 2018). Furthermore, both BDNF signaling and its downstream mediators CREB and CaMKIV could be regulated by uncoupling protein 2 (UCP2) (Dao et al., 2015). Based on these results, it is possible to hypothesize that exercise may modulate synaptic plasticity by affecting UCP2. Exercise

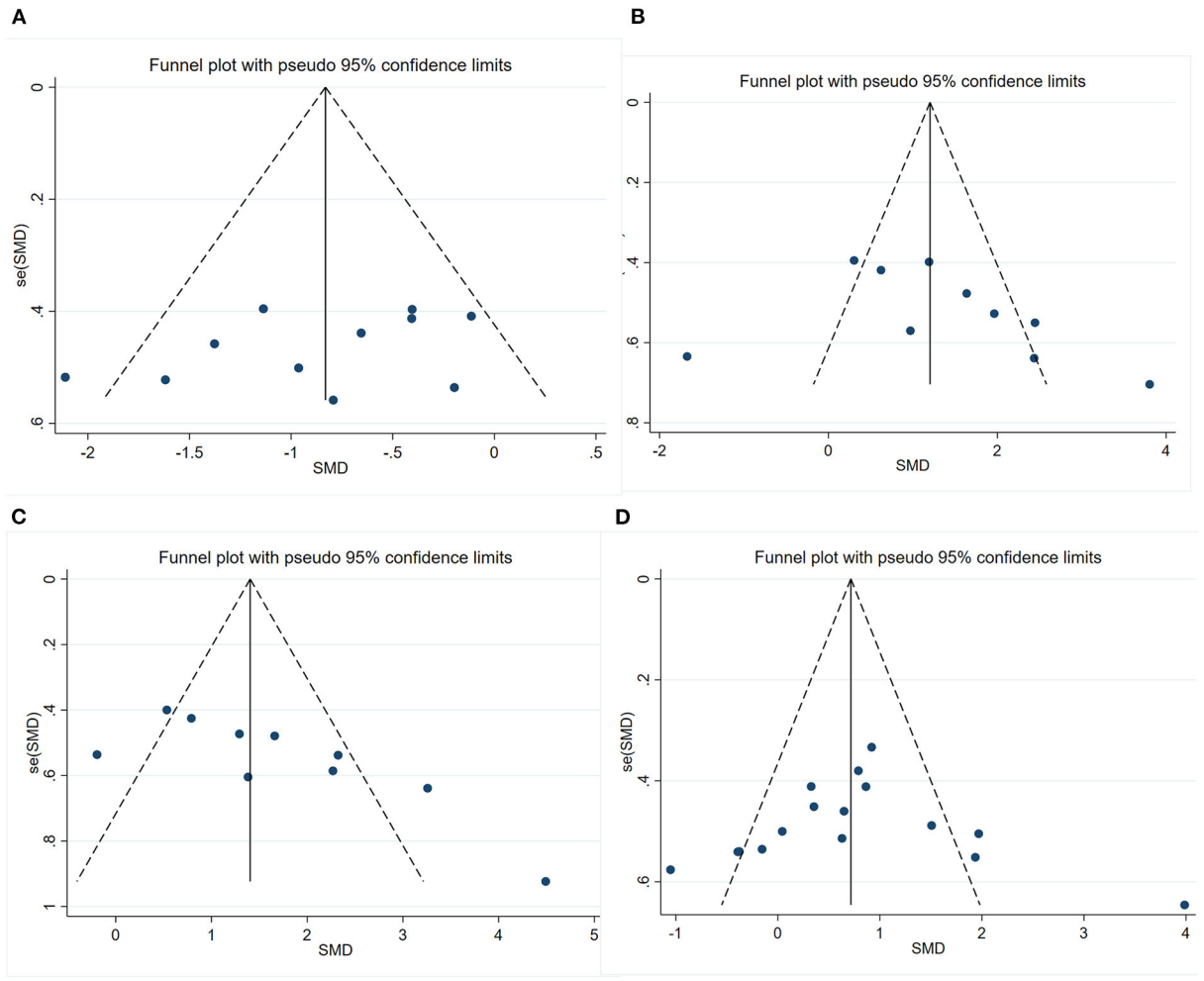

FIGURE 6
Funnel plots showing the effect of exercise on cognitive function and synaptic plasticity in AD models. **(A)** Funnel plot for the effect of exercise on the escape latency of MWM. **(B)** Funnel plot for the effect of exercise on the number of platform crossings of MWM. **(C)** Funnel plot for the effect of exercise on the time in the target quadrant of MWM. **(D)** Funnel plot for the effect of exercise on the expression of PSD95.

probably increases fEPSP by regulating UCP2, thus ameliorating LTP impairment. However, the mechanism is still unclear, and more research is needed to explore and clarify the mechanism in the future.

PSD95 is a key synaptic protein that regulates synaptic transmission and plasticity. Our results showed that exercise increased the expression of PSD95 in the brain of AD models (SMD = 0.73, P = 0.003). There was evidence indicating that the expression of PSD95 was regulated by Neuregulinl (NRG1), which is a signaling protein that mediates interactions between cells and is essential for the development and maintenance of the nervous system (Ting et al., 2011). NRG-1-ICD, a hydrolytic product of NRG-1, entered the nucleus and interacted with transcription factors of zinc finger structure (Sun et al., 2019; Padjasek et al., 2020), eventually upregulating the transcriptional activity of the PSD95 promoter and increasing the expression of PSD95. Besides, it has been shown that the NRG1 signaling pathway can be regulated through exercise (Ennequin et al., 2015). Therefore, we hypothesize that exercise probably increases PSD95 expression by activating the NRG1 signaling pathway and promoting the movement of NRG-1-ICD into the nucleus. However, it requires more future exploration.

Our subgroup analysis found that exercise before AD had a superior effect on cognitive function and synaptic improvement than exercise after AD. Particularly for the number of platform crossings (1.71 vs. 0.73 SMD for exercise before AD and exercise after AD, respectively) and the expression of PSD95 (0.94 vs. 0.47 SMD for exercise before AD and exercise after AD, respectively). It may be related to the different degrees of pathological changes in animal models of AD in different cognitive status. Compared with the subgroup of exercise before AD, animals in the subgroup of exercise after AD were older.

They had severe pathological changes like plaque deposition and neuroinflammation in the brain (Zhao et al., 2015), which were difficult to reverse. Thus, the effect of exercise may not be sufficient to counteract cognitive decline and AD pathological changes (Xu et al., 2013). Or there might be a minor benefit in some respects, but this does not translate into restored cognitive function after exercise. It was also confirmed by our findings, exercise had a positive effect on outcome indicators of escape latency and time in the target quadrant, but not on other indicators.

The timing of treatment was a key element in the benefits of exercise on AD (Moore and Loprinzi, 2021). Our findings were consistent with recent opinions of some scholars that prevention rather than treatment should be emphasized for AD. Therefore, if the brain function is relatively healthy, exercise can assist to prevent or delay the onset of AD. Contrarily, if nerve function is severely impaired, exercise does not prevent neurodegeneration. In this sense, to reduce the risk of AD or to slow its progression, early or preventative exercise intervention is required.

This study included six AD models: four transgenic animal models and two drug-induced animal models. APP/PS1 double-transgenic mice expressed both Swedish (KM670/671NL) mutation of the APP gene and the FAD-linked PSEN1 gene without exon 9 (dE9). It is characterized by plaque deposition and neuron loss (Yokoyama et al., 2022). The course of the disease is generally manifested as cognitive behavioral changes at 3 months of age, senile plaques at 5 months of age, and a large number of senile plaques at 12 months of age (Zhu et al., 2017). 3×Tg mice, a representative missense mutation linked to tauopathies mode mice, is characterized by plaques and neurotangles in brain regions (Yokoyama et al., 2022). Long-term memory impairment begins at 4 months of age in 3×Tg mice (Javonillo et al., 2022), which is often used to study the interactions between amyloid and tau pathologies. These two types of mice were the most used AD models in this study. 5×FAD mice were generated by coexpressing the five FAD mutations in APP/PS1 double-transgenic mice, which caused the appearance of Aβ plaques in the brain at the age of 2 months and reached saturation at 6 months, together with robust gliosis (Gatt et al., 2019; Yokoyama et al., 2022). TgF344 rats, transgenic rats bearing mutant human APP and PS1, were first reported by Robert in 2013 (Cohen et al., 2013). It manifests age-dependent cerebral amyloidosis, tauopathy, gliosis, apoptotic loss of neurons, and cognitive disturbance. Injection of Aβ and streptozotocin is relatively simple, reproducible, and stable. However, drug induction only targets a certain aspect of AD pathology, which is far from the complicated pathological process of AD (Kamat, 2015). It should be noted that the phenotypes of different AD models were different, however, they gradually captured the full pathology of AD with aging, including cognitive impairment and synaptic damage. As described above, there were various types of AD models, which played an important role in research, especially in AD research.

In our review, eight included studies (Cho et al., 2015; Zhao et al., 2020; Li et al., 2021, 2022; Wang et al., 2021; Liu et al., 2022; Park et al., 2022; Xu et al., 2022) assessed hippocampal-dependent learning and memory using MWM test. We found that exercise could reduce the time of escape latency (SMD $= -0.86$, $P < 0.001$), increase crossovers (SMD $= 1.34$, $P = 0.001$) and time in the target quadrant (SMD $= 1.65$. $P < 0.001$) in animal models of AD. However, when using a large pool diameter or shrinking the platform-site size, platform crossings measured during the trials may be biased (Othman et al., 2022). The pool diameters of the included studies used were 100 cm (Liu et al., 2022), 120 cm (Cho et al., 2015; Li et al., 2022; Xu et al., 2022) and 150 cm (Zhao et al., 2020) and platform diameters were 9 cm (Xu et al., 2022), 10 cm (Li et al., 2022) and 12 cm (Zhao et al., 2020), respectively. Furthermore, only three studies performed adaptation training to detect complete visual function in mice (Zhao et al., 2020; Li et al., 2022; Park et al., 2022). Other studies did not report these details, which may have biased the results somewhat (Vorhees and Williams, 2014). Hence, experimental tools should be carefully selected and report these details as much as possible in future trials.

There were several limitations to our study. Firstly, the included studies used multiple AD models, and the size of the sample group was relatively small, which may influence the effects of exercise. But the number of included studies was relatively small and did not allow for subgroup analysis according to types of AD models. Secondly, the studies included did not have data on the senescence-accelerated mouse prone-8 (SAMP8) mice, a non-transgenic but robust AD model, which played an important role in anti-aging research. Thirdly, the MWM tools used in the included studies were inconsistent. A platform suitable for the size of the experimental animal should be selected to obtain more rigorous results. Finally, the quality of included studies was not ideal, and some details were poorly reported or even absent, such as unclear random allocation methods and the lack of randomization and blinding principles. Based on the above limitations, future studies should be rigorously designed, and the results should be reported completely and transparently.

5. Conclusion

In conclusion, our review provided evidence that exercise had a positive effect on improving learning memory ability and enhancing synaptic plasticity of AD. The results of the subgroup analysis also indicated that early or preventive exercise intervention is a better way to reduce the risk or slow the progression of AD. Further investigations on the

mechanisms underlying the beneficial effects of exercise on AD are warranted. However, there was a certain heterogeneity in the included studies, and results should be reported with caution.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

LG and YL contributed to the subject design and conception of this review. LG, XY, and YZ contributed to retrieving materials and extracting data, summarized the extracted data, and performed the data analysis. LG, XY, and XX drafted the manuscript. YL revised important parts of the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 72204075), the National Natural Science Foundation of China (Grant No. 82171582), and the Hebei Provincial Postdoctoral Science Foundation (Grant No. B2022003032).

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China and the Hebei Provincial Postdoctoral Science Foundation. Additionally, we sincerely appreciate the hard work of the outstanding editors and reviewers.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.1077732/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

TYPE Mini Review
PUBLISHED 10 February 2023
DOI 10.3389/fnagi.2023.1122300

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Alzheimer's Disease and Related Dementias, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 12 December 2022
ACCEPTED 30 January 2023
PUBLISHED 10 February 2023

CITATION
Huang J, Huang N, Cui D, Shi J and Qiu Y (2023) Clinical antidiabetic medication used in Alzheimer's disease: From basic discovery to therapeutics development. *Front. Aging Neurosci.* 15:1122300. doi: 10.3389/fnagi.2023.1122300

Clinical antidiabetic medication used in Alzheimer's disease: From basic discovery to therapeutics development

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Alzheimer's disease (AD) is a common neurodegenerative disease. Type 2 diabetes mellitus (T2DM) appears to increase and contributing to the risk of AD. Therefore, there is increasing concern about clinical antidiabetic medication used in AD. Most of them show some potential in basic research, but not in clinical research. So we reviewed the opportunities and challenges faced by some antidiabetic medication used in AD from basic to clinical research. Based on existing research progress, this is still the hope of some patients with special types of AD caused by rising blood glucose or/and insulin resistance.

KEYWORDS

Alzheimer's disease, type 3 diabetes mellitus (T3DM), antidiabetic medication, type 2 diabetes mellitus, clinical research

Introduction

At present, Alzheimer's disease (AD) lacks effective treatment methods and drugs. It is only delayed by some drugs that act on neurotransmitters (Marucci et al., 2021). In recent years, some progress has been made in anti-AD drugs, such as the Aducanumab approved by United States Federal Drug Administration (FDA), GV-971 approved by the National Medical Products Administration (NMPA), and Lecanemab, an initial decision on the drug's approval by the FDA is expected by 2023, but they are all controversial (Karlawish and Grill, 2021; Xiao et al., 2021; The Lancet, 2022). The failure of a large number of drug studies on AD is largely related to the unknown pathogenesis of AD. Therefore, similar to the research of anti-tumor drugs, it is very promising to conduct more accurate subtype classifications for AD patients, and then conduct treatment drug research.

Epidemiological investigations of Type 2 diabetes mellitus (T2DM) and AD indicated that T2DM appears to increase and contributing to the risk of AD. Learning cognitive dysfunction, neuronal loss, etc., appear in T2DM patients (Noreen et al., 2018; Li et al., 2021). Further studies show they share lots of common link, including similar pathological features, etiology, targets, and involving same signaling pathways (Doherty et al., 2013; Chung et al., 2018; Zhang et al., 2018; Takeuchi et al., 2019; Gharibyan et al., 2020; Sun et al., 2020; Dekeryte et al., 2021; Liu et al., 2021; Yen et al., 2021). Thus, some researchers propose a theory that AD is Type 3 diabetes mellitus (T3DM) (Steen et al., 2005). Then, a growing number of studies have been carried out and showed that drugs for the treatment of T2DM also have certain improvement effect on AD

(Akimoto et al., 2020). Most of them show some potential in basic research, but not in clinical research (**Table 1**). So we reviewed the opportunities and challenges faced by some antidiabetic medication used in AD from basic to clinical research. Based on existing research progress, this is still the hope of some patients with special types of AD caused by rising blood glucose or/and insulin resistance.

Metformin

Metformin (MET) is a common oral anti-diabetic drug, which can lower blood glucose in many ways. Among these mechanisms regulated by MET to lower blood glucose, the regulatory mechanism centered on AMP-activated protein kinase (AMPK) plays an important role not only in diabetes mellitus (DM) but also in AD (Markowicz-Piasecka et al., 2017; Ma et al., 2022). In streptozotocin (STZ)-induced Swiss Webster mice, MET improves spatial memory in diabetic mice, which can be associated with reducing p-Tau and β-amyloid (Aβ) plaque load and inhibition of neuronal death (Oliveira et al., 2021). And in APP/PS1 mice, MET increases the level of p-AMPK and insulin degrading enzyme (IDE) protein in mice, and significantly reduces the Aβ level in the brain. Although it does not affect the enzyme activity of Aβ-related secretion enzymes (Lu et al., 2020). Additionally, in the APP/PS1 mouse injected Tau, MET can promote the phagocytosis of pathological Aβ and Tau proteins by enhancing microglial autophagy capability (Chen et al., 2021). But this performance shows a certain gender difference. In AβPP mice aged 12–14 months, MET activates AMPK to show a protective effect in female mice, but it shows a damage effect in male mice (DiTacchio et al., 2015). The results of these pre-clinical studies show that MET has a certain potential treatment effect on AD.

Although in many preclinical studies, MET shows an exciting role, the results in clinical studies are indeed unsatisfactory. First of all, there are still certain controversy in whether MET reduces the risk of AD. Studies have shown that MET can be a reduced AD risk in the general population (Zheng et al., 2022). But analyzing among Asians, MET has the risk of increasing the prevalence of AD (Ha et al., 2021; Luo et al., 2022). We believe that this is not consistent with the selection and analysis goals of data. To a large extent, the risk of AD population based on DM-based diseases can be considered as useful. We speculate that this is related to some AD patients without blood glucose changes. The AMPK activator represented by MET may be defined as a significant role in AD patients with T3DM. And some clinical studies have also verified our speculation. The use of MET does not increase the risk of AD. And long-term and large doses of MET are related to the risk of lowering AD with elderly DM (Sluggett et al., 2020). Therefore, we believe that we should have targeted design clinical trials to screen patients with abnormal blood glucose or have DM themselves, or early intervention for patients with DM merged mild cognitive impairment. And when considering the selection of drugs, the stage, type, and gender of the disease itself should be comprehensively considered.

GLP-1 agonists

Glucagon-like peptide-1 (GLP-1) is one of the important targets for the treatment of diabetes. As an intestinal peptide, GLP-1 has glucose concentration dependent hypoglycemic effect *via* the potentiation of glucose-induced insulin secretion and the suppression of glucagon secretion (Keshava et al., 2017; Deacon, 2020). Moreover, numerous studies have demonstrated GLP-1 has potential neuroprotective and neurotrophic effects (Liu et al., 2021), so that GLP-1 based therapies may have favorable effects on AD. Such as liraglutide (LRGT), dulaglutide, lixisenatide, exenatide, and NLY01 have a significantly association with lowering risk of AD (Akimoto et al., 2020). The anti-AD effect of GLP-1 receptor (GLP-1R) agonist (GLP-1RA) has attracted the attention of researcher.

Liraglutide improves memory impairment in various AD models, decreasing AD-related insulin receptor (INSR), synaptic and Tau pathology in specific brain regions (Batista et al., 2018; Duarte et al., 2020). These effects involve multiple pathways. In Aβ, specifically, LRGT attenuates brain estradiol and GLP-1 and activates protein kinase A (PKA) levels, oxidative/nitrosative stress and inflammation in 11-month-old AD female mice, reduces their cortical $A\beta_{1-42}$ levels (Duarte et al., 2020). LRGT can both reduce the overproduction of Aβ and increase its removal. One side, amyloid precursor protein (APP) is metabolized to Aβ by β-secretases and γ-secretases. LRGT decreases the formation of Aβ *via* inhibiting the activity of β-secretases and γ-secretases (Qi et al., 2016; Zhang et al., 2019; Jantrapirom et al., 2020). The other, binding to GLP-1R, LRGT activates the phosphoinositide-3 kinase/mitogen-activated protein kinase (PI3K/MAPK) dependent pathways, consequently following trafficking and clearing Aβ by increasing the presence of Aβ transporters in cerebrospinal fluid (Wiciński et al., 2019). In Tau, LRGT also reduces p-Tau, Aβ, *via* the protein kinase B/glycogen synthase kinase-3β (Akt/GSK-3β) pathways, reversing the p-INSR whose major downstream signaling molecules include insulin substrate 1, Akt and GSK-3β (Chen et al., 2017). At the same time, LRGT can reduce hyperphosphorylation of Tau, neurofilaments (NFs) and neuronal degeneration through restoring protein phosphatase-2A (PP2A) activity and altering in c-Jun N-terminal protein kainse (JNK) and extracellular regulated protein kinases (ERK) signaling apparently (Zhang et al., 2019; Jantrapirom et al., 2020). Additionally, LRGT ameliorates mitochondrial dysfunction and prevents neuronal loss with activation of the cAMP/PKA pathway in the brain of 5 × FAD mice. Activating the cAMP/PKA pathway, GLP-1 increases the p-DRP-1-s637 and mitigates mitochondrial fragmentation in Aβ-treated astrocytes. Then it further improves the Aβ-induced energy failure, mitochondrial reactive oxygen species (ROS) overproduction, mitochondrial membrane potential (MMP) collapse, and cell toxicity in astrocytes (Xie et al., 2021). In addition, Dulaglutide decreases the hyperphosphorylation of Tau and NFs proteins through improving the PI3K/Akt/GSK-3β signaling pathway (Zhou et al., 2019). Lixisenatide also plays an important role in memory formation, synaptic plasticity and cell proliferation of rats. It can reduce amyloid plaques, NFTs and neuroinflammation in the hippocampi of 12-month-old 3 × Tg female mice, which may be related to activating PKA-cAMP response element binding (CREB) signaling pathway and inhibiting p38-MAPK (Cai et al., 2018).

Generally speaking, these protection effects to a large extent rely on multiple pathways with regulatory regulation of insulin signal pathways as the core, thereby removing neurotoxic substances (Aβ and/or Tau). At the same time, it is difficult to define whether the control of inflammation and the protection of mitochondria is the cause or result. In addition, it is worth noting that a large number of preclinical studies on it come from China. And limited clinical research, it is difficult to prove the complex connection

TABLE 1 Clinical antidiabetic medication used in AD.

Medication	Pre/clinical	Main results	References
MET	Preclinical	Improves spatial memory in diabetic mice, promotes the phagocytosis of pathological Aβ and Tau proteins by enhancing microglial autophagy capability, impaired glucose metabolism and mitochondrial dysfunction	Chiang et al., 2016; Chen et al., 2021; Oliveira et al., 2021
	Clinical	Reduces AD risk in the general population, beneficial effects on cognitive performance, long-term and high-dose metformin use is associated with a lower risk of incident AD in older people with diabetes	Sluggett et al., 2020; Pomilio et al., 2022; Zheng et al., 2022
	Clinical	The available evidence does not support the idea that MET reduces risk of AD, and it may increase the risk in Asians	Ha et al., 2021; Luo et al., 2022
GLP-1RA	Preclinical	Reduce the overproduction of Aβ and increase its removal, reduce hyperphosphorylation of Tau, neurofilaments, ameliorate mitochondrial dysfunction and prevents neuronal loss	Qi et al., 2016; Chen et al., 2017; Cai et al., 2018; An et al., 2019; Wiciński et al., 2019; Zhang et al., 2019; Zhou et al., 2019; Duarte et al., 2020; Jantrapirom et al., 2020; Xie et al., 2021
	Clinical	Administration of GLP-1 agonists may reduce the risk of AD in patients with T2DM	Akimoto et al., 2020
PPAR-γ agonists	Preclinical	Ameliorates Aβ deposition, controlling Aβ-induced dysfunctions of neuronal activity in the DG underlying memory loss in early AD	Jahrling et al., 2014; Toba et al., 2016; Badhwar et al., 2017; Hsu et al., 2017; Yang et al., 2017
	Clinical	PGZ (15–30 mg) has been demonstrated the greatest efficacy compared to placebo, subjects receiving RSG exhibits better delayed recall	Watson et al., 2005; Cao et al., 2018
	Clinical	Daily 0.8 mg oral PGZ does not significantly delay the onset of mild cognitive impairment due to AD, no evidence of clinically significant efficacy in cognition was detected for 2 or 8 mg RSG extended-release as adjunctive therapy	Harrington et al., 2011; Burns et al., 2021
DPP4i	Preclinical	DPP-4i drugs mainly improve inflammation and oxidative stress through the GLP-1/GLP-1R signaling pathway, affecting the production and clearance of toxic proteins	Kosaraju et al., 2013a, 2017; Chen et al., 2019; Siddiqui et al., 2021
	Clinical	DPP-4i is associated with low amyloid burden and favorable long-term cognitive outcome in diabetic patients with ADCI, sitagliptin's improvement of AD patient MMSE scores, vildagliptin to treatment improves the cognitive function of the older patients with T2DM	Isik et al., 2017; Ates Bulut et al., 2020; Jeong et al., 2021
SGLT2i	Preclinical	EMP ameliorate the cognitive deficits in APP/PS1xdb/db mice, GBC improves memory impairment with increasing insulin and reducing glucose and hippocampal inflammation in rats with T2DM	Lin et al., 2014; Esmaeili et al., 2020; Hierro-Bujalance et al., 2020
	Clinical	Long-term use of SGLT2i can improve cognitive function, especially for elderly diabetics	Wium-Andersen et al., 2019; Mui et al., 2021; Low et al., 2022; Mone et al., 2022

between correlation and clinical effectiveness. It is necessary to design more randomized controlled trial such as ELAD Study (Femminella et al., 2019). The clinical trials of it are worthy of attention. We look forward to these random dual-blind experiments that can have good results.

PPAR-γ agonists

The peroxisome proliferator-activated receptor γ (PPAR-γ) is a prototypical ligand-activated nuclear receptor that coordinates lipid, glucose and energy metabolism. The PPAR-γ agonists have emerged as potent insulin sensitizers used in the treatment of T2DM. Pioglitazone (PGZ) is a member of the thiazolidinedione (TZD) family. In a pre-clinical study, it improves cognitive deficits in AD animal models by reducing Aβ levels. And it normalizes the p35 protein and p-CRMP2 levels in the cerebellum, ameliorates impaired motor coordination ability and long-term depression (LTD) in APP/PS1 mice at the pre-Aβ accumulation stage (Toba et al., 2016). It also enhances peripheral and brain insulin sensitivity in diet-induced insulin resistance model rats, ameliorates $A\beta_{1-42}$ deposition in the hippocampus by increasing IDE and PPARγ expression. Notably, activating the PI3K/Akt/GSK-3β pathway is also demonstrated to serve a role in PGZ-induced $A\beta_{1-42}$ degradation, which is abrogated by the PPARγ antagonist GW9662 (Yang et al., 2017). Furthermore, PGZ treatment could inhibit Cdk5 activity by decreasing p35 protein level. More importantly, PGZ corrects long-term potentiation (LTP) deficit caused by Aβ exposure in cultured slices and rescues impaired LTP and spatial memory (Badhwar et al., 2017). Although clinical studies have shown that PGZ has the potential of AD for treatment, the results of clinical trials are indeed unsatisfactory. Daily 0.8 mg oral PGZ did not significantly delay the onset of mild cognitive impairment due to AD (Burns et al., 2021). Interestingly, PGZ 15–30 mg demonstrates the greatest efficacy compared to placebo in network meta-analysis (Cao et al., 2018).

The rosiglitazone (RSG) improves hippocampus-dependent cognitive deficits in some AD patients and ameliorates deficits in the Tg2576 mouse for AD amyloidosis (Jahrling et al., 2014). Then the research further verified RSG treatment rescues cognitive deficits and reduces aberrant activity of granule neurons in the dentate gyrus (DG) (Hsu et al., 2017). Clinical trials of RSG have shown some contradictions. Early studies showed some anti-AD potential of RSG (Watson et al., 2005), while subsequent clinical trials fail to achieve the desired results (Harrington et al., 2011). Therefore, in clinical trials on RSG, screening for multiple subgroups in the AD patient population and enrolling patients using predictive biomarkers has received attention (O'Bryant et al., 2021). We speculate that with the

further development of AD typing and biomarkers, such studies may bring new hope.

DPP-4 inhibitors

Different from GLP-1 agonists, dipeptidyl peptidase 4 inhibitors (DPP4i) do not possess inherent glucose-lowering activity. It inhibits the activity of the enzyme DPP4, then it decreases blood glucose level through GLP1 to treat T2DM (Stoian et al., 2020). DPP-4i contains saxagliptin, vildagliptin, linagliptin, sitagliptin. They have beneficial effects on amyloid aggregation and longitudinal cognitive outcome in diabetic AD-related cognitive impairment (ADCI) (Jeong et al., 2021). However, the mechanism by which they work seems different.

Sitagliptin has been demonstrated to have antioxidative and antiapoptotic properties by modifying glutamate and glutathione levels within the region of hippocampus in mice (El-Sahar et al., 2015). Meanwhile, it increases the synaptic proteins and the O-Glycosylation (Chen et al., 2019). Moreover, sitagliptin improves the impaired cognitive by the potential mechanisms that regulating neuroinflammation, antioxidation, and antiapoptotic, and the level of GLP-1 and GLP-1R (Wiciński et al., 2018). Finally achieve the goal of protecting learning and memory. Interestingly, preliminary clinical results show that sitagliptin's improvement of AD patient mini-mental state examination (MMSE) scores is better than MET (Isik et al., 2017). With a higher selectivity, saxagliptin has the same effect as sitagliptin that protect learning and memory through GLP-1/GLP-1R signaling pathway (Kosaraju et al., 2013a; Chen et al., 2019). Like sitagliptin, linagliptin treatment mitigates the cognitive deficits that attributed to the improvement of incretin levels and attenuate Aβ, p-Tau and neuroinflammation in the brain mice of 3 × Tg-AD and $A\beta_{1-42}$ induced rat model of AD (Kosaraju et al., 2017; Siddiqui et al., 2021). Moreover, linagliptin can ameliorate cognitive deficits through insulin pathway (Siddiqui et al., 2021) and restore the impaired insulin signaling caused by Aβ in neuronal cells (Kornelius et al., 2015). Vildagliptin also demonstrates a unique mechanism for Aβ and Tau clearance and reverses the cognitive deficits and pathology observed in AD possibly *via* modulating Klotho protein together with Akt pathway (Kosaraju et al., 2013b; Yossef et al., 2020). The addition of vildagliptin to treatment improved the copying subdomain of cognitive function and metabolic control of the older patients with T2DM (Ates Bulut et al., 2020).

These results indicate that DPP-4i drugs mainly improve inflammation and oxidative stress through the GLP-1/GLP-1R signaling pathway, affecting the production and clearance of toxic proteins, thereby improving cognitive function. But most of the studies are basic research, although there are a small number of clinical studies on sitagliptin and vildagliptin in cognition, but they are all preliminary and short-term, and the sample size is small. Our suggestion would be best to carry out the anti-AD research of DPP-4i after a breakthrough in the anti-AD research of GLP-1/GLP-1R or the combination of DP-4i and the first approved effective anti-AD drug.

SGLT2 inhibitors

Sodium glucose cotransporter 2 inhibitors (SGLT2i) can reduce blood glucose by inhibiting its reabsorption in proximal tubules and by promoting urinary glucose excretion. A growing numbers evidence indicates that SGLT2i such as empagliflozin (EMP), canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin have neuroprotective potential in a murine mixed model of T2DM and AD (Lin et al., 2014; Rizvi et al., 2014; Shaikh et al., 2016; Hierro-Bujalance et al., 2020).

Empagliflozin help to limit cortical thinning and reduce neuronal loss, hemorrhage, microglia burdens and SPs burden, also improves cerebral microvascular eventually ameliorate the cognitive deficits in APP/PS1xdb/db mice (Lin et al., 2014; Hierro-Bujalance et al., 2020). Dapagliflozin and invokana might act as potent dual inhibitors of SGLT2 and AchE, which contributes to cognitive improvement, as well as ertugliflozin and sotagliflozin (Rizvi et al., 2014; Shaikh et al., 2016). Glibenclamide (GBC) treatment improves memory impairment with increasing insulin and reducing glucose and hippocampal inflammation in rats with T2DM and sporadic AD (Esmaeili et al., 2020). And SGLT2i exert anti-inflammatory and antioxidant effects at the cellular level mainly *via* regulation of the molecular target of rapamycin (mTOR) pathway, which could ameliorate the progression of AD (Esterline et al., 2020; Katsenos et al., 2022). And in nested case control study evaluating diagnoses of dementia in patients with T2DM, SGLT2i use showed a 42% reduction in dementia risk (Wium-Andersen et al., 2019). Interestingly, in the population-based cohort study of T2DM patients treated with SGLT2i and DPP4i, the use of SGLT2i is associated with lower risks of dementia, compared with DPP4i (Mui et al., 2021). And a prospective study shows significant beneficial effects of the EMP on cognitive in frail older adults with diabetes (Mone et al., 2022). In addition, SGLT2I's $\geq$ 3 years use is related to the improvement of cognitive scores (Low et al., 2022). According to the existing evidence, long-term use of SGLT2i can improve cognitive function, especially for elderly diabetics. However, the role of AD patients still needs further study.

Conclusion

Based on the facts that T2DM and AD share common features, drugs used to treat T2DM are being investigated for efficacy in AD. Consequently, studies on drugs used for T2DM in AD found these treatments may represent a promising approach to fight AD, which include MET, GLP-1RA, PPAR-γ agonists, DPP-4i and SGLT2i (Cao et al., 2018). However, there are differences in their effects in basic and clinical research on anti-AD (**Table 1**). At the same time, the anti-AD effect of insulin is also controversial, but there are too many studies involved, so this review will not discuss it for the time being. We believe that the difference between the results of clinical antidiabetic medication in anti-AD treatment clinical trials and basic experiments is mainly related to the following: (1) We speculate that they are not effective for all types of AD, but may be a special type: AD patients who also suffer from diabetes. They may even be useful only for cognitive dysfunction caused by insulin resistance. (2) These effects interact with the improvement of insulin resistance, so perhaps early intervention may have a better effect. (3) Complex and interactive-oxidation, anti-neuroinflammation, and improve energy metabolism play an important role in it, so the combination of drugs to treat AD may have more potential. Such drugs are not a very good solution under the existing evidence conditions. Looking forward to more

refined pathological research on AD classification, it may rekindle hope for the clinical research of such drugs.

But screening subjects based on more subtypes, or recruiting patients using predictive biomarkers, would severely narrow the pool of subjects who ultimately meet inclusion criteria and would substantially increase the cost of clinical trials. Unless a reasonable combination of predictive biomarkers can be found, or there is a well-defined classification of AD subtypes. Otherwise, it will still be a bottomless pit to rush to carry out relevant and more refined clinical trials, and it is not worth investing too much energy. Moreover, hypoglycemia, the side effect of such drugs, is still not negligible. In the elderly, falls caused by hypoglycemia often cause serious consequences. Therefore, we have to consider the scope of application of this type of drug and the direction that needs to be considered in the design of such drugs. It is best to regulate the insulin pathway and have little effect on blood glucose (or be able to control blood glucose stably within a reasonable range). Weighing the pros and cons is an unavoidable multiple-choice question in drug development. In addition to genes, diabetes is often closely related to eating habits, and intestinal flora also play a key role in it. Whether these drugs affect the intestinal flora and thus affect AD is also an aspect worthy of attention. It is also worth noting that in the absence of strong evidence-based medical evidence, the use of hypoglycemic drugs for the prevention and treatment of AD will face many risks.

In the current situation, we should not be pessimistic. While looking forward to the progress of basic research on AD, we should more actively conduct group statistics or subtype analysis on existing failed clinical trials, especially large-sample clinical trials. Not only may there be unexpected surprises, but it will also play a guiding role in the development of future clinical trials.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Funding

This work was supported by the Funds of National Natural Science Foundation of China (Nos. 82060728 and U18243) and Shijingshan's Tutor Studio of Pharmacology (No. GZS-2016-07).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Aging Neuroscience

TYPE Mini Review
PUBLISHED 09 March 2023
DOI 10.3389/fnagi.2023.1142617

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Alzheimer's Disease and Related Dementias, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 11 January 2023
ACCEPTED 17 February 2023
PUBLISHED 09 March 2023

CITATION
Nilaver BI and Urbanski HF (2023) Mechanisms underlying TDP-43 pathology and neurodegeneration: An updated Mini-Review. *Front. Aging Neurosci.* 15:1142617. doi: 10.3389/fnagi.2023.1142617

Mechanisms underlying TDP-43 pathology and neurodegeneration: An updated Mini-Review

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TAR DNA binding protein 43kDa (TDP-43) plays an important role in several essential cell functions. However, TDP-43 dysfunction has been implicated in the development of various brain diseases including amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), and limbic predominant age-related TDP-43 encephalopathy (LATE). Recent investigations into the individual components of TDP-43 pathology show how broader TDP-43 dysfunction may precede these disease end states, and therefore could help to explain why TDP-43 dysfunction continues to be implicated in a rapidly expanding category of neurodegenerative diseases. The literature reviewed in this article suggests that dysregulation of TDP-43 initiated by some environmental and/or genetic insults can lead to a snowballing dysfunction across the cell, involving impaired gene expression, mRNA stability, as well as the function and coordination of those pathways directly regulated by TDP-43. Furthermore, the hallmarks of TDP-43 pathology, such as hyperphosphorylation and insoluble cytoplasmic accumulation of the protein may actually be artifacts of an upstream impairment in TDP-43's normal function. Overall, the present article summarizes current knowledge regarding TDP-43's normal and pathological cell functions and sheds light on possible mechanisms that underlie its causal role in neurodegeneration.

KEYWORDS

ALS, autophagy, dementia, LATE, phosphorylation, TDP-43

Introduction

TDP-43 and disease

TAR DNA binding protein 43 kDa (TDP-43) is a highly conserved ubiquitously expressed nuclear protein that plays an important role in several essential cell functions, including transcriptional repression, RNA splicing, mRNA transport, microRNA maturation, translational regulation, and the formation of stress granules (Sephton et al., 2011; de Boer et al., 2020). Under normal physiological conditions, TDP-43 is almost entirely located in the nucleus but its function depends on it being shuttled between the nucleus and cytoplasm in controlled amounts (de Boer et al., 2020). Levels of TDP-43 in the cell are tightly auto regulated; i.e., TDP-43 regulates its own expression by directly binding TARDBP mRNAs (Koyama et al., 2016). Its importance to normal cell functioning is evident, as TDP-43 genomic deletion is embryonically lethal (Sephton et al., 2011).

On the other hand, pathological TDP-43 has been implicated in a wide range of neurodegenerative conditions. For example, hyperphosphorylated and ubiquitinated TDP-43 inclusions in the cytoplasm of cells in the nervous system represent a major pathological feature of amyotrophic lateral sclerosis (ALS), and frontotemporal lobar degeneration (FTLD) (Dugger and Dickson, 2017). TDP-43 pathology has also been associated with Alzheimer's disease (AD), chronic traumatic encephalopathy (CTE), Lewy body disease (LBD), Huntington's disease, argyrophilic grain disease (AGD), and hippocampal sclerosis (Uchino et al., 2015; de Boer et al., 2020; Eck et al., 2021). Furthermore, TDP-43 deposits have been observed in non-demented aged individuals in a condition called limbic predominant age-related TDP-43 encephalopathy (LATE) (Eck et al., 2021). In the past decade, therefore, the number of conditions associated with TDP-43 pathology has increased greatly (de Boer et al., 2020).

TDP-43 pathology

TDP-43 pathology is usually characterized by insoluble, hyperphosphorylated and ubiquinated aggregates of TDP-43 in the cytoplasm, nucleus and cell processes of neurons and glia (Dugger and Dickson, 2017; de Boer et al., 2020). Mislocalization of TDP-43 within cellular compartments is also characteristic of the pathology (de Boer et al., 2020). Recall that normally TDP-43 is tightly auto-regulated and is almost entirely located in the nucleus. Consequently, depletion of TDP-43 in the nucleus, in association with abnormally high levels in the cytoplasm, is considered to be pathological. Indeed, TDP-43 mislocalization alone appears capable of causing mRNA instability, impaired gene regulation, mitochondrial dysfunction, impaired protein turnover, among other issues (de Boer et al., 2020). However, the underlying causes of TDP-43 mislocalization and aggregation remain unclear (Figure 1).

In the pathological condition, post-translational modifications are also typically made to the TDP-43 protein, especially hyperphosphorylation and/or fragmentation (de Boer et al., 2020). Although TDP-43 has 64 potential phosphorylation sites, and phosphorylation occurs during its normal function, pathology is associated with a degree of phosphorylation that is abnormally high (Eck et al., 2021). Common phosphorylation sites in pathological TDP-43 are Ser369, Ser379, Ser403/404, and Ser409/410, and it has been posited that these phosphorylation events have a direct causative role in pathogenesis (Eck et al., 2021). There are at least 20 disease linked missense mutations that create or remove phosphorylation sites, further implicating abnormalities in phosphorylation to pathogenesis (Eck et al., 2021).

TDP-43 phosphorylation: Kinases and phosphatases

While hyperphosphorylated TDP-43 is associated with a variety of neurodegenerative diseases, regulated phosphorylation is necessary for TDP-43's normal function (Eck et al., 2021). There are several kinases and phosphatases that add or remove phosphate groups from TDP-43. Currently, the kinases observed to phosphorylate TDP-43 are casein kinases 1 and 2 (CK1 and CK2), cell division cycle 7 (CDC7), and tau tubulin kinases 1 and 2 (TTBK1 and TTBK2) (Eck et al., 2021). The phosphatases that remove phosphate groups from TDP-43 are protein phosphatase 1 & 2 (PP1 and PP2), and calcinuerin (Eck et al., 2021).

Some studies aimed at ameliorating or aggravating TDP-43 pathology, by intervening with kinase and phosphatase activity, suggest that reducing TDP-43 phosphorylation can prevent accumulation and in some cases improve neurodegeneration. A study by Liachko et al. (2013) found that inhibiting the kinase CDC7 in transgenic *Caenorhabditis elegans* ALS models and human cell cultures could reduce TDP-43 phosphorylation, improve behavioral phenotypes, and reduce neurotoxicity. The authors also found that *C. elegans* with the phosphatase calcinuerin knocked out, had significantly worsened motor control phenotypes, along with phosphorylated TDP-43 aggregates, and neurodegeneration (Liachko et al., 2013). Several studies in mammalian cells treated with inhibitors

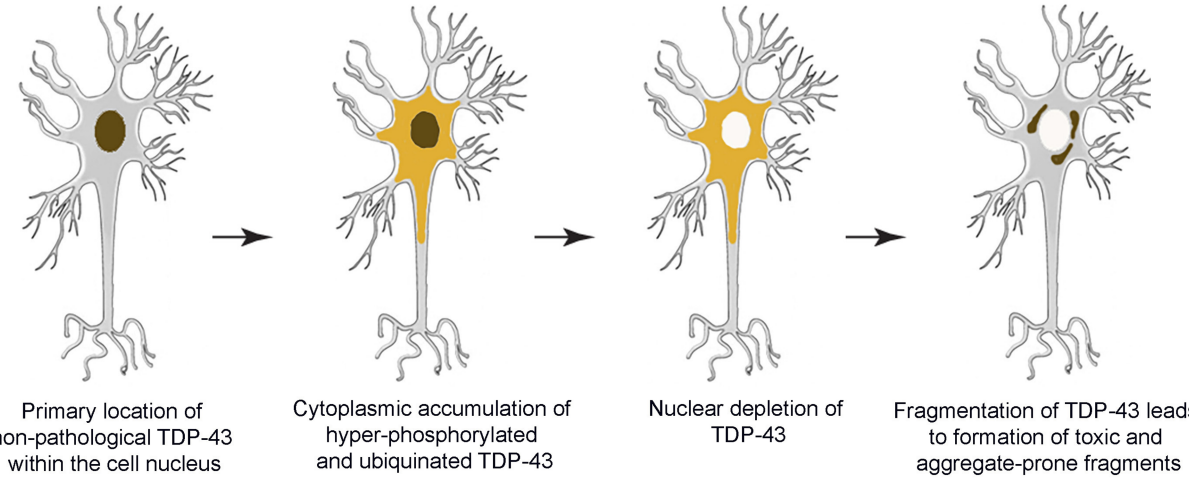

FIGURE 1
Schematic overview depicting progressive development of TDP-43 pathology within the brain.

of the phosphatases PP1 or calcinuerin have described an increase in phosphorylated TDP-43 aggregates (Liachko et al., 2016; Gu et al., 2018; Taylor et al., 2018). The upregulation of the kinase CK1 and the decreased activity of calcinuerin and other phosphatases has been observed in sporadic and familial ALS (Eck et al., 2021). Studies such as these have led some to posit that altering the activity of phosphatases and kinases may be a potential therapeutic intervention for ameliorating the formation of hyperphosphorylated TDP-43 deposits in TDP proteinopathies. However, evidence in support of this hypothesis is mixed and the exact roles of kinase and phosphatase enzymes in TDP-43 pathology remain to be elucidated.

Phosphorylated TDP-43 prion-like seeding

In many diseases with pathological protein aggregates, disordered protein can act like a prion, inducing changes in other normal proteins. A study by Nonaka et al. (2016) investigated if insoluble phosphorylated TDP-43 had a prion-like seeding behavior. The authors created insoluble phosphorylated TDP-43 extracts to act as seeds, and then introduced them to neuroblastoma expressing either wild-type TDP-43 or TDP-43 lacking a nuclear localization signal (NLS)-a well characterized mutation in TDP-43 proteinopathies. The cells lacking an NLS on their own, and wild-type cells treated with the seeds were insufficient at inducing phosphorylated TDP-43 aggregates. Hyperphosphorylated aggregates could only be induced when cells lacking an NLS were exposed to seeds. Taken together, these findings suggest that it is the combination of a malfunctioning localization signaling together with exposure to insoluble phosphorylated TDP-43 aggregates that can cause a prion-like seeding behavior. These findings also provide insight into possible summation of genetic factors and spontaneous or environmental insults that may ultimately combine to play a causative role in the etiology of TDP-43 pathology.

Phosphorylation as a compensatory response

Although insoluble hyperphosphorylated TDP-43 aggregates have been shown to be neurotoxic, this does not necessarily imply that phosphorylation itself is neurotoxic. Indeed, some studies suggest that phosphorylation of TDP-43 may actually be a compensatory response by the cell to halt or prevent TDP-43 aggregation (Brady et al., 2010; Li et al., 2011). For example, Brady et al. (2010) investigated the effect that phosphorylation of TDP-43 at site Ser409/410 in mammalian cell pathology models would have on its propensity to form insoluble aggregates. Modifying Ser409/410 on TDP-43 to a non-phosphorylatable state slightly (by 15%) reduced its tendency to aggregate. Modifying it to mimic its phosphorylated state at this site substantially (by 60%) reduced aggregation and improved TDP-43 solubility. These surprising results suggest that TDP-43 phosphorylation may actually regulate or arrest the development of insoluble TDP-43 aggregates. Brady et al. (2010) proposed that phosphorylation, particularly at Ser409/410 may happen after TDP-43 begins to aggregate, as the cell attempts to reduce further aggregation, possibly by using the electrostatic repulsion incurred by phosphorylation. Other experiments in their study showed that phosphorylation of TDP-43 was also associated with its impaired turnover. Therefore, while hyperphosphorylation at some sites may prevent aggregation by improving TDP-43's solubility and repulsing it from other phosphorylated protein, it could also impair its degradation by protein turn over systems within the cell. A study by Li et al. (2011) reported a similar finding in mammalian cell pathology models and in transgenic *Drosophila melanogaster*. The authors found that both full-length and truncated TDP-43 had a significantly reduced propensity to aggregate when phosphomimetic substitutions were made to sites such as Ser403/404, Ser409/410, with increasing degrees of phosphorylation causing greater reduction of aggregation. They also showed that increased activity of the kinase CK2 could improve the solubility of TDP-43 fragments, a kinase that phosphorylates sites on TDP-43 associated with pathology. The studies of both Brady et al. (2010) and Li et al. (2011) suggest that hyperphosphorylation of TDP-43 at some sites associated with pathology may happen *after* the protein begins aggregating, and that it *slows* progression of the pathology. It is plausible, therefore, that hyperphosphorylation is a compensatory response by the cell to stop the aggregation of TDP-43, at the expense of poor processing by protein turnover mechanisms. So, although hyperphosphorylated TDP-43 inclusions are generally considered a primary hallmark of TDP-43 pathology, the cause and effect relationship between TDP-43 hyperphosphorylation and ultimately neurotoxicity remains unclear.

TDP-43 dysregulation and dysfunction in pathology

There are several different components to TDP-43 pathology besides inclusions in the cytoplasm that are neurotoxic. An investigation by Yang et al. (2022) reported that low-level overexpression (less than 60% above endogenous levels) of wild-type TDP-43 in transgenic mice lead to a variety of phenotypes resembling ALS, such as neuron loss, muscle denervation, astrogliosis, oligodendrocyte injury, demyelination of the spinal cord, neuroinflammation, progressive weakness and paralysis in mid-life. Similar low-level overexpression has been observed in *post mortem* ALS and FTLD neural tissues (Yang et al., 2022). Although cytoplasmic inclusions or nuclear TDP-43 depletion was not observed in the TDP-43 overexpressing mice, the authors reported decreased solubility of TDP-43, suggesting the protein was aggregating modestly. Therefore, the findings from Yang et al. (2022) strongly suggest that pathology and ALS-like symptoms can be caused by an over expression of TDP-43, and can occur independently of the formation of large insoluble phosphorylated aggregates or nuclear depletion.

How might overexpression of TDP-43 mechanistically cause neurotoxicity, even in the absence of cytoplasmic aggregates? One possibility is that disorders of TDP-43's normal functions could serve as a catalyst for TDP-43 pathology. Recall that TDP-43 is auto regulated; i.e., it directly binds and metabolizes TARDBP mRNAs (Wood et al., 2021). A study by Fratta et al. (2018) investigated the effect that a TDP-43 over-functioning mutation had on the transcriptome of transgenic mice. This mutation caused an increase in TDP-43's mRNA splicing activity (i.e., a gain of function mutation (GOF)), which led to a particular set of exons being removed from direct RNA targets of TDP-43 - an event they called "skiptic exons." These exons would normally be left in the mRNA transcripts; but due to the aberrant TDP-43 over activity they were removed. Skiptic exons

caused frameshifts or premature termination codons in 30% of the RNA transcripts that were analyzed, and ultimately reduced levels of the proteins encoded by those mRNAs. The authors observed a progressive neuromuscular phenotype in the mice with the GOF mutation. However, they failed to find insoluble TDP-43 inclusions, suggesting that a GOF alone was sufficient to induce ALS like phenotypes. They also found that TARDBP mRNA levels were substantially upregulated in mice with the GOF mutation, suggesting a GOF in TDP-43's splicing imbalances its autoregulation, although they found protein levels were not changed.

An overexpression and gain of function are not the only components to the disordered TDP-43 activity implicated in neurotoxicity. Nuclear clearance of TDP-43 is also typical of pathology, most likely stemming from decreased function in its normal roles (de Boer et al., 2020). A study by Ling et al. (2015) investigated the effect that a TDP-43 under-functioning mutation had on TDP-43's splicing targets and overall protein expression in transgenic mice and HeLa cells. This mutation caused a decrease in TDP-43's mRNA splicing activity, i.e., a loss of function mutation (LOF). The authors found in cells and in mice, that LOF mutation of TDP-43 resulted in mRNA transcripts containing nucleotide sequences that would normally by removed by splicing, an event called a "cryptic exon." Cryptic exons introduced frameshifts and stop codons to the affected mRNAs.

Furthermore, Fratta et al. (2018) found that both GOF and LOF mutations induce an upregulation in TARDBP gene expression, suggesting that GOF and LOF of TDP-43 may have an effect on its autoregulation. The authors also found that the GOF and LOF mutations on TDP-43 did not act on the same set of genes. Importantly, this suggests that over functioning and under functioning in splicing by TDP-43 has its own independent effects on the transcriptome. TDP-43 GOF and LOF may play distinct roles at different stages in pathogenesis. Moreover, an increase in cryptic exon and skiptic exon splicing events has been observed in human ALS, suggesting these events play some role in full-blown human diseases (Ling et al., 2015; Fratta et al., 2018; Torres et al., 2018; Yang et al., 2022). The importance of these findings cannot be over emphasized, because up to this point the formation of phosphorylated aggregates has been a main focus of characterizing and treating TDP-43 proteinopathies. Phosphorylated aggregates might represent a late step in the pathogenesis, which is preceded by dysfunction in TDP-43 expression and normal function - and therefore suggestive of possible alternate therapeutic interventions.

Disordered autophagy and TDP-43 aggregation

TDP-43 actively binds several thousand mRNA transcripts in its normal function and is known to modify the expression of at least 41 genes (Torres et al., 2018; Prasad et al., 2019). Gene regulation aside, how might disordered mRNA splicing by TDP-43 affect processes in the cell? Torres et al. (2018) found that down-regulating TDP-43 in human neural stem cells and HeLa cells lead to deleterious splicing events in mRNA and decreased protein levels of a critical autophagy enzyme. The authors observed a 20% increase in cryptic exons in *ATG4B* (autophagy related 4B cysteine peptidase) mRNAs, and a 30% decrease in ATG4B protein levels; changes that are consistent with a loss of TDP-43 function. Due to TDP-43's direct binding and splicing of ATG4B mRNA, TDP-43 is considered necessary for autophagy (Torres et al., 2018). Torres et al. (2018) posited that the increase in cryptic exons likely leads to break down of aberrant mRNA's by nonsense-mediated decay, causing the lower protein levels, and subsequent dysfunction in the autophagy response. The authors also quantified the abundance of cryptic exons in ATG4B mRNAs from ALS brain and spinal cord tissues. They found that the amount of cryptic exons in ATGB mRNAs was mainly influenced by ALS status, and that the ALS cases with higher levels of aberrant mRNAs had a more severe disease phenotype in life. TDP-43 knock out studies in mouse neuroblastoma have also reported a decreased expression of the critical autophagy gene *Atg7*, impaired autophagy, and an increase in accumulated polyubiquitinated proteins (Wood et al., 2021). In the case of over functioning, studies with mice overexpressing TDP-43 found inhibited autophagy due to an upregulation of the autophagy regulator Bcl-2 (Wood et al., 2021). Together, these findings suggest that TDP-43 over and under expression lead to a respective over or under functioning, and each on their own is sufficient to inhibit the autophagy response. TDP-43 pathology has been found in an expanding category of neurodegenerative disorders involving protein inclusions, its role in autophagy suggests a possible mechanism for TDP-43 involvement in these conditions (Wood et al., 2021).

The consequence of inhibited autophagy due to TDP-43 dysregulation may have implications for the accumulation of TDP-43 itself. For example, it has been found that TDP-43 is cleared from the cytoplasm by both the ubiquitin proteasome system (UPS) and autophagy (Wood et al., 2021). Additionally, Scotter et al. (2014) investigated the effect that inhibitors of the UPS and autophagy had on TDP-43 accumulation and solubility in human cellular ALS/FTLD models. They found that inhibition of the UPS, but not autophagy, increased levels of insoluble cytoplasmic TDP-43, as long as it began in a soluble form. Furthermore, when they inhibit both the UPS and autophagy, they found increased levels of insoluble TDP-43 macroaggregates, compared to inhibition of the UPS alone. When autophagy was inhibited, TDP macroaggregates could still be disassembled into smaller aggregate particles, although those smaller aggregates persisted in the autophagy inhibited cells, compared to controls. Taken together, Scotter et al.'s (2014) findings suggest that the UPS primarily degrades TDP-43 when it is soluble, but autophagy is required to degrade insoluble aggregate particles. Their findings suggest that inhibited autophagy, which can be caused by dysregulation in TDP-43 itself, could actually prevent the clearance and exacerbate TDP-43 aggregation (Scotter et al., 2014; Torres et al., 2018).

Effect of TDP-43 on mRNA splicing

Other studies have identified potential disease mechanisms in TDP-43 pathology by investigating the direct transcription regulation and mRNA splicing targets of TDP-43, and how its dysfunction affects systems in the cell downstream. For example, Klim et al. (2019) investigated potential mRNA targets of TDP-43 that would be deleteriously affected by TDP-43 knock down in cultured human motor neurons and found 885 mRNA transcripts that required TDP-43 to maintain their normal levels. Of the targets they identified in human motor neurons (hMN), they noted that levels of mRNA encoding protein Stathmin-2 (STMN2) were especially sensitive to abberations

in TDP-43 abundance and function; STMN2 is enriched within the central nervous system, and is essential to axonal growth and regeneration, cytoskeletal regulation, and microtubule stabilization (Klim et al., 2019). Furthermore, hMNs with TDP-43 depletion, and hMNs expressing TDP-43 with mutations commonly associated with disease, showed a significant decrease in STMN2 mRNA expression. More recently, Krus et al. (2022) generated STMN2 knockout mice and observed phenotypes that showed slow progressive, motor-selective neuropathy with functional deficits and neuromuscular denervation. Taken together, these findings emphasize that STMN2 reduction stemming from TDP-43 pathology may contribute to ALS pathogenesis by damaging the integrity of neural circuits and communication between cells, beyond impaired autophagy alone.

Discussion

The literature investigating TDP-43's phosphorylation, prion like seeding activity, over expression, aberrant splicing function, and role in processes like autophagy, axonal regrowth, and neurite branching paints a complex picture of TDP-43 pathogenesis. Interference at each of these components has been shown to ameliorate the accumulation of TDP-43, prevent neurodegeneration, and improve behavioral symptoms in some models. However, these studies suggest that dysfunction in TDP-43 could present itself in many ways outside of the traditional characterization of TDP-43 pathology; it is likely a mosaic of events with several discreet yet interrelated steps. The dysregulation and dysfunction of TDP-43 seems to feedback on itself and further exacerbate its own pathogenesis. Consequently, development of effective therapies for TDP-43-associated diseases may need to focus on interfering with the mechanisms that initiate this dysregulation. Eliminating only one element, for example hyperphosphorylation, may be insufficient or even harmful to disease outcomes, and could fail to overcome the adverse involvement of TDP-43 pathology in full-blown neurodegenerative diseases. These studies, taken together, suggest that the hallmarks we consider to be characteristic or even causative of TDP-43 pathology may only be the end state of a complex cascade of events with likely both environmental and genetic components. Further investigations into the factors that trigger TDP-43 dysregulation and subsequent dysfunction may elucidate more effective therapeutic targets, and enrich our understanding of the mechanisms of pathogenesis in the expanding category of diseases associated with TDP-43.

Author contributions

BIN drafted the current manuscript, with writing and editing contributions from HFU. All authors contributed to the article and approved the submitted version.

Funding

Funding for this article was provided by the National Institutes of Health through grants AG062220, AG066518, and OD011092.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Aging Neuroscience

TYPE Mini Review
PUBLISHED 14 April 2023
DOI 10.3389/fnagi.2023.1109256

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Alzheimer's Disease and Related Dementias, a section of the journal Frontiers in Aging Neuroscience

RECEIVED 27 November 2022
ACCEPTED 13 March 2023
PUBLISHED 14 April 2023

CITATION
Chen C-Y, Yang G-Y, Tu H-X, Weng X-C, Hu C and Geng H-Y (2023) The cognitive dysfunction of claustrum on Alzheimer's disease: A mini-review. *Front. Aging Neurosci.* 15:1109256. doi: 10.3389/fnagi.2023.1109256

The cognitive dysfunction of claustrum on Alzheimer's disease: A mini-review

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Alzheimer's disease (AD) is one of the most common neurodegenerative diseases characterized by cognitive deficits and dementia. AD entails predominant pathological characteristics including amyloid beta (Aβ) plaque formation, neurofibrillary entanglements, and brain atrophy, which gradually result in cognitive dysfunctions. Studies showed that these pathological changes are found in a myriad of brain structures, including the claustrum (CLA), a nucleus that penetrates deeply into the brain and is extensively interconnected to various brain structures. The CLA modulates many aspects of cognitive functions, with attention, executive function, visuospatial ability, language, and memory in particular. It is also implicated in multiple neuropsychiatric disorders, of which one worthy of particular attention is AD-related cognitive impairments. To inspire novel AD treatment strategies, this review has summarized the CLA functionality in discriminative cognitive dysfunctions in AD. And then propose an array of potential mechanisms that might contribute to the cognitive impairments caused by an abnormal CLA physiology. We advocate that the CLA might be a new promising therapeutic target in combination with existing anti-AD drugs and brain stimulation approaches for future AD treatment.

KEYWORDS

claustrum, Alzheimer's disease, cognitive dysfunction, neural circuits, pathology

Introduction

Alzheimer's disease (AD) is a type of ubiquitous neurodegenerative disease characterized by cognitive dysfunction. This kind of neurodegenerative disease deprives individuals of the ability to concentrate and poses challenges to executive functions and can gradually progress to misplacing, narrative incompletion, and further result in delayed recollection as well as false memories in the later stage of AD (El Haj et al., 2020; Knopman et al., 2021). Previous studies identified a myriad of brain areas that are involved in AD development, such as the prefrontal cortex (PFC), entorhinal cortex (EC), and hippocampus. While recently, a nucleus located in the forebrain named claustrum (CLA), has gained increasing popularity due to its functions in attention, executive function and memory (Smith et al., 2020; Nikolenko et al., 2021; Whalley, 2022), which are perceived as an integral part of AD cognitive impairment.

The CLA is a thin sheet of grey matter deeply penetrating into the forebrain and sandwiching between insula and putamen. It is widely interconnected to brain structures, e.g., PFC, anterior cingulate cortex (ACC), EC, hippocampus, amygdala, and insula. The CLA assembles substantial cognitive-relevant cells such as Von Economo neurons (VEN)

and position-responsive cells apart from multitudinous claustral neurons (see Figure 1; Smythies et al., 2014; Jankowski and O'Mara, 2015; Smith et al., 2020). Consequently, the CLA and its related circuitries get involved in several cognitive functions, including attention, executive function (White et al., 2018), visuospatial ability (Gould et al., 2006), language (Van Rinsveld et al., 2017), and memory (Seo et al., 2016), and these cognitive functions achieved by varies brain networks in AD tend to denigrate over the course of the disease.

Prominent pathological alterations are observed in the CLA with its related circuits in AD patients. Both the plaques and the neurofibrillary tangles accumulate in the CLA (Braak and Braak, 1991; Thal et al., 2002). More clearly, the senile plaques exist in the third phase of Aβ deposition in the CLA (Thal et al., 2002), while the mild neurofibrillary tangles occur in the CLA at stage IV, with increasing severity in stage V and VI (Braak and Braak, 1991). AD patients accompanied with delusional symptoms possess a significant grey matter volume reduction in the left CLA (Bruen et al., 2008). Neuronal loss and synaptic pathology happening in the CLA are hallmarks of AD pathology, particularly in the anterior portion (Baloyannis et al., 2013). At the circuit level, the paramygdala part of the CLA connected to the entorhinal cortex suffers the primary deterioration in AD brains (Morys et al., 1996).

This review illustrates the functions of CLA in various cognitive impairments of AD, respectively. And it further elucidates the underlying mechanisms by combining CLA itself with its relevant circuitries in modulating pathological changes of AD in five cognitive perspectives: attention, executive function, visuospatial ability, language, and memory, to demonstrate the feasibility of targeting CLA for future treatment of AD cognitive dysfunction.

Attention

Attention is the first affected non-memory domain in AD. Clinically, at the early stage where there is no or little memory deficit, AD patients are frequently muddled and unable to concentrate on tasks that are effortless to accomplish previously (Schumacher et al., 2019). And they had difficulty in processing attentional information with higher reaction speed and error rate when switching tasks (Hennawy et al., 2019). In mild cognitive impairment (MCI), a neurodegenerative disease indicated an incremental risk for evolving to AD, the functional connectivity of the CLA has increased within the salience network (SN), a brain network highly involved in mediating the attention function of AD (Schultz et al., 2017).

The CLA enables to mediate attention at both cellular and circuit levels. The activities of abundant VEN in CLA promote the interaction between the default mode network (DMN) and the task-related network in attention (Smythies et al., 2014). The CLA has the resilience to distraction when chronic and acute inactivation on claustral Egr2-expressing neurons (CLA_{Egr2+}) in two-alternative forced-choice behavioral tasks by presenting irrelevant auditory distractor simultaneously to mice, which is attributed to the activation of CLA_{Egr2+} neurons modulated cortical sensory processing and suppression on tone representation of the auditory cortex (Atlan et al., 2018). Genetically-assisted silencing of CLA neurons delayed the acquisition of conditioned responses, suggesting that the CLA is essential in acquiring classical conditioning tasks, mainly in attentional processes concerning conditioned/unconditioned stimulus association (Reus-García et al., 2021). Across the claustral pathways, neurons projecting to ACC are more densely and evenly distributed than those to the

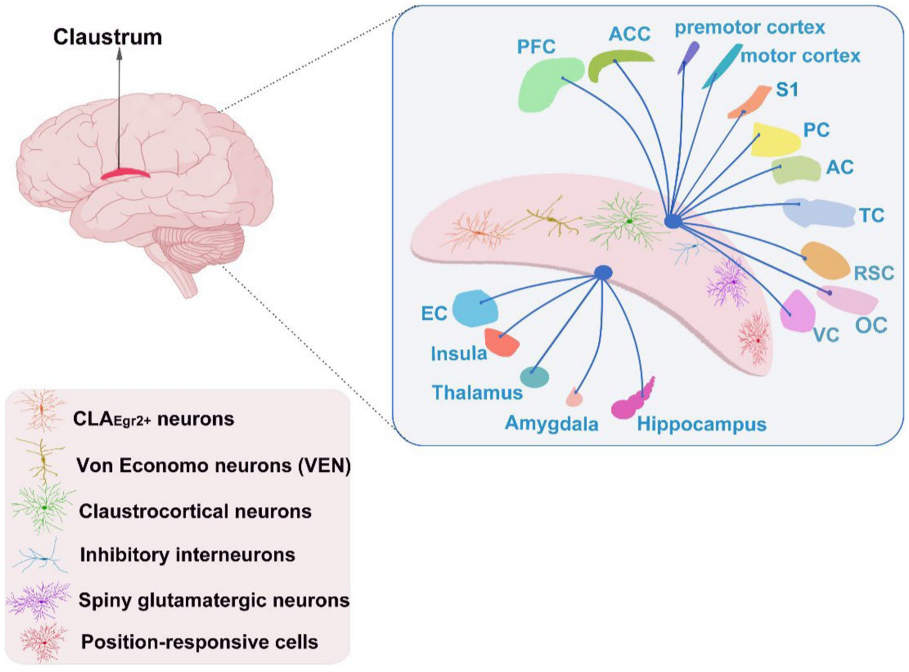

FIGURE 1
The cognitive neuronal types of the CLA and its interconnection with other brain areas. PFC, prefrontal cortex; ACC, anterior cingulate cortex; S1, primary somatosensory cortex; PC, parietal cortex; AC, auditory cortex; TC, temporal cortex; RSC, retrosplenial cortex; VC, visual cortex; EC, entorhinal cortex; OC, occipital cortex.

primary somatosensory cortex (S1), implicating that the CLA may preferentially coordinate attention-relevant functions regulated by ACC (White et al., 2017). An attentional strategy demonstrates that PFC-CLA is mainly achieved through feedforward inhibition imposed by CLA on cortical patterns. These evidences support this hypothesis that the CLA integrates limbic information from the medial PFC, thalamus and amygdala to direct attention relevant sensory events in modality-related areas of motor and sensory cortex (Smith et al., 2019). Although there is a range of evidence supporting the role of CLA in mediating attention at cellular and circuit levels, the neurobiological basis of the attentional deficits in AD remains unclear, yet it is reasonable to assume that the lesions of the CLA occurring at the early stages of AD possibly affect attentional regulation.

Executive function

Executive function is the ability to control or direct behavior from the top to down, like decisions making and motive initiation (Schumacher et al., 2019; Gaubert et al., 2022). Executive dysfunction occurs in early stages of AD (Tort-Merino et al., 2022), and it highly corresponds to the decreasing volumes of central executive network including lateral parietal cortex, dorsolateral frontal cortex and partial premotor area which have dense connections with CLA (Smythies et al., 2014; Miro-Padilla et al., 2020; Fang et al., 2021). It is demonstrated that a negative correlation between the Reading the Mind in the Eyes Test concerning executive function and the functional connectivity of the SN in the CLA in the early stage of AD (Valera-Bermejo et al., 2021). In human imaging, the left CLA was activated in the executive tests covering Stroop, N-back, and Go/No Go (Minzenberg et al., 2009). Likewise, the CLA is engaged in the underlying processes of executive function, i.e., the activation occurs during both the switching and updating tasks (McKenna et al., 2017).

According to a series of studies, together CLA with its pathways is substantiated to affect executive function. A higher error rate of behavioral flexibility shows in rats during the reversal of the excitotoxic anterior CLA group in a water-maze experiment compared to the control (Grasby and Talk, 2013). The cognitive control of action is further uncovered from CLA by manipulating CLA projection neurons during 5-choice serial reaction time task employing optogenetic modulation on claustral Gnb4-cre mice (White et al., 2020). Besides, the claustral circuits mediate executive performance. The claustral spiny glutamatergic neurons and inhibitory interneurons are monosynaptically innervated by the ACC, the former of which has magnified ACC inputs in a way that is suppressed by claustral inhibitory microcircuits, which demonstrates ACC-CLA as a modulator in top-down action control (White et al., 2018). Chemogenetically activating or inhibiting the CLA-PFC, respectively, would intensify or attenuate the impulsive-like behaviors in 5-choice serial reaction time task (Liu et al., 2019), whereas chemogenetic inhibition on the bilateral claustrocortical neurons projecting to S1 decreases the inappropriate lick response (Chevée et al., 2022). Given that CLA suffers a certain executive dysfunction with neuroimaging analysis in the early stage of AD, future attempts might be made to alleviate executive function symptoms in AD by activating CLA and its related cortical circuits.

Visuospatial ability

Patients with AD initially have clinical challenges with visuospatial difficulties, such as spatial disorientation, being trapped in familiar surroundings (Quental et al., 2009). Additionally, AD patients get stuck in face discrimination and struggling to process complicated visual scenes (Quental et al., 2009; Knopman et al., 2021). In an imaging study, the grey matter density fluctuation in the left CLA of AD patients corresponds to scores changes in the visuo-constructional apraxia test (Venneri et al., 2008). The AD patients further suffered claustral inactivity during the visuospatial paired information encoding and retrieval (Gould et al., 2006).

Evidence has identified several possible mechanisms of the CLA in mediating visuospatial disorders in AD. Initially, abundant place-responsive cells with hippocampal and EC characteristics have been observed in the anterior CLA in mice. They display rapid spatial activity when exposed to the environment (Jankowski and O'Mara, 2015). Nevertheless, the lewy body pathology in CLA leads to decreasing neuronal activity and even atrophy in this area, thereby disrupting its spatial response function which has been detected in AD patients with alpha-synuclein immunohistochemistry (Hashimoto and Masliah, 1999). In addition, the impaired integration function of CLA circuits induces visuospatial dysfunction in global aspects. Compared with auditory, somatosensory, or motor areas, the lewy body pathology in the CLA is more closely associated with visual areas, and the damage of the visuo-claustral pathway that connects with insula and EC would result in visual misidentification (Yamamoto et al., 2007). Meanwhile, the CLA has extensive connections with both the hippocampus and EC (Smythies et al., 2014; Smith et al., 2020), and the claustral glutamatergic neurons projecting to limbic cortex were activated during sleep, which powerfully reinforces the function of the CLA in space and navigation (Luppi et al., 2017). Furthermore, it interconnects with the occipital, temporo-parietal, and frontal cortices, a brain network involved in spatial and visual constructive abilities, which can be associated with early mechanisms of cognitive deterioration in the progression to AD (Smythies et al., 2014; Plaza-Rosales et al., 2023). The anatomical changes in the CLA give rise to compromised visuospatial functionality of AD. All this points to CLA as a crucial spot in coordination concerning visuospatial dysfunction owing to its place-responsive cells and interconnections with numerous brain structures in AD patients.

Language

Language dysfunction appears in early AD, showing preliminary difficulty in semantic abilities (Venneri et al., 2008). Mild AD patients are diagnosed to be subject to language obstacles in verbal fluency, auditory perception, reading comprehension, and narrative performance (Tsantali et al., 2013). In a study of nicotinic acetylcholine receptor binding in the preclinical patient group, verbal memory learning in MCI patients was found to be associated with discrete uptake reduction in CLA, which provides evidence that the left CLA might modulate cognitive performance in diagnosed or prodromal AD (Terrière et al., 2010). The semantic abilities deteriorate in the early stage of AD, whereas the volumetric changes in bilateral CLA of AD patients were found prominently associated with confrontational naming tasks and categorization fluency (Venneri et al., 2008).

A series of neuroimaging investigations prove that CLA occupies an essential linguistic role. Combined with fMRI on the brains of proficient bilingual subjects doing simple and complex addition mental arithmetic tasks, the CLA has different levels of evocation in people with different language dominance (Van Rinsveld et al., 2017). The MRI scans of all aphasia patients emerge ischemic lesions in the left hemisphere, and the largest areas of overlapping foci are localized in the CLA and other brain structures (Marangolo et al., 2014). By conducting meta-analysis, the right CLA, bilateral inferior frontal cortex and superior temporal gyrus performed a clear consistent neural motivation pattern in written language and speech processing in the child group (Zhu et al., 2014), while it also engaged in two of thirteen major clusters of insula connections of language function (Ardila et al., 2014). The medial CLA provides a robust contralateral connection between the right subcortex and left PFC, resulting in patients with right subcortical lesions performing worse than the left in cognitive linguistic functions (Girija et al., 2018). Altogether, the language function is obviously modulated by CLA itself and its circuit connections. Thus, an intervention targeting CLA could potentially salvage linguistic dysfunction in AD patients.

Memory

The most severely damaged cognitive deficit in AD patients is mnemonic dysfunction, where they have difficulty not only in the encoding and storage stages but also in the retrieval stage (El Haj et al., 2020). They easily forget familiar faces or things since their brains fail to integrate these memories (Roy et al., 2016). Notable evidence manifests amnesia AD patients have defective functions in episodic memory (Schwindt and Black, 2009), working memory (Stopford et al., 2012), and contextual memory (El Haj et al., 2020). During memory encoding and retrieval paradigms, the CLA exhibits higher activity in healthy controls than in AD patients (Schwindt and Black, 2009). Resting-state fMRI notes that AD patients have weakened functional connectivity between the right CLA and the amygdala, which elucidates the relevancy to memory deficits (Wang et al., 2016).

The CLA has a substantial effect on memory. The neurons of anterior CLA modulate theta rhythm critical to episodic memory impairment in early AD, which requires the synchronized activity of CLA and relevant cortical regions (Jankowski and O'Mara, 2015). The CLA participated in acquiring stable long-term memory for the value of objects in a high-capacity fMRI study (Ghazizadeh et al., 2018). A hypothesis proposes that pathological loss of the VEN in the CLA attenuates task-related brain network functions in the CLA, especially memory functions in AD (Smythies et al., 2014). The posterior CLA projects onto the retrosplenial cortex (RSC), a well-established cortex in mnemonic processing regarding auditory cues, illuminating that the CLA-RSC has a significant influence on the function of remote memory retrieval in rodents (Todd et al., 2016). The CLA-medial EC is activated by new contexts and enables to modulate the function of the medial EC (Kitanishi and Matsuo, 2017), which may in turn influence contextual memory in AD patients. The CLA is further capable of processing working memory by means of its ipsilateral and contralateral connections with PFC, premotor, and motor areas (Smythies et al., 2014; Smith et al., 2020). And this is consistent with the postulation of Gattass et al., that the CLA is the gateway for perceptual information into the memory system, due to its extensive interconnectivity with almost the entire neocortex and its projections to the hippocampus, amygdala and basal ganglia (Gattass et al., 2014). The CLA deficits in AD patients are likely to be interposed in the development of several forms of memory impairments, supposing that intervention in the claustral neurons and CLA memory-related circuits probably adjust memory dysfunction in AD patients.

Future direction

The evidence mentioned above provides an exhaustive account of the relationship between CLA and AD pathology in terms of cognitive functions, including attention, executive function, visuospatial skills, language, and memory (see Figure 2). It has analyzed and summarized the underlying mechanisms by which the CLA and claustral circuits might mediate AD pathological changes in terms of these cognitive functions. Although the CLA has the capability of multimodal information integration and is involved in regulating high-order cognition, more basic researches are required to clarify the relationship between the CLA and AD *via* advanced structural and functional research techniques.

The CLA has widespread interconnections to various brain structures, with a structural basis for the integration of various cognitive functions. In detail, the respective interconnections between CLA and ACC, PFC are engaged in attention and executive function, while the CLA-PFC further regulates language and working memory and the CLA-S1 takes part in executive functions. For visuospatial ability, there are significant connections between the CLA and the visual cortex, insula, hippocampus, EC as well as temporal–parietal lobes. Similarly, the language can be modulated by the pathways of CLA and the inferior frontal gyrus, insula. It is also noted that multiple memories can be mediated by claustral circuits, in which CLA interconnects with a myriad of areas, including RSC, EC, premotor, and motor cortex. Although the CLA has the capability of multimodal information integration and is involved in regulating high-order cognition, the functions of these circuits in mediating distinct cognitive aspects in AD remains to be explored.

Some symptoms of the early stage of AD, such as attention deficit, executive dysfunction, language misinterpretation, and memory impairment, have been found to be associated with early pathological changes in CLA (Venneri et al., 2008; Schwindt and Black, 2009; Valera-Bermejo et al., 2021). Therefore, the therapeutic interventions on the CLA and claustral circuits may alleviate the progression of AD at early stage. For example, the chronic intracerebroventricular administration of AT IV receptors agonists, like norleucine1-Ang IV, remarkably improve the acquisition of spatial memory in AD mice (Prakash et al., 2015), while the high density of AT IV receptors was found in CLA (Chai et al., 2000). Thus, the AT IV receptor agonists in the CLA could serve as a promising target for drug intervention to alleviate spatial memory impairment of AD. It is also found that the left CLA increases glucose metabolism in AD in both one-year and one-month deep brain stimulation (DBS; Laxton et al., 2010), which illustrates the significance of CLA for the improvement of cognitive symptoms in AD. The CLA, meanwhile, is involved in several brain networks that regulate various cognitive functions in AD patients. Considering the potential claustral mechanism in AD, it should be a promising approach to administer drugs or DBS activation to the CLA with its related circuits.

Furthermore, it certainly requires more basic pathological and physiological studies to elucidate the function of CLA in mediating AD. Although many types of cognitive cells that have been identified so far, there might be yet other unknown neurons carrying utterly different cognitive functions. Additionally, despite the great number of circuitries being discerned, the function of specific circuits remains

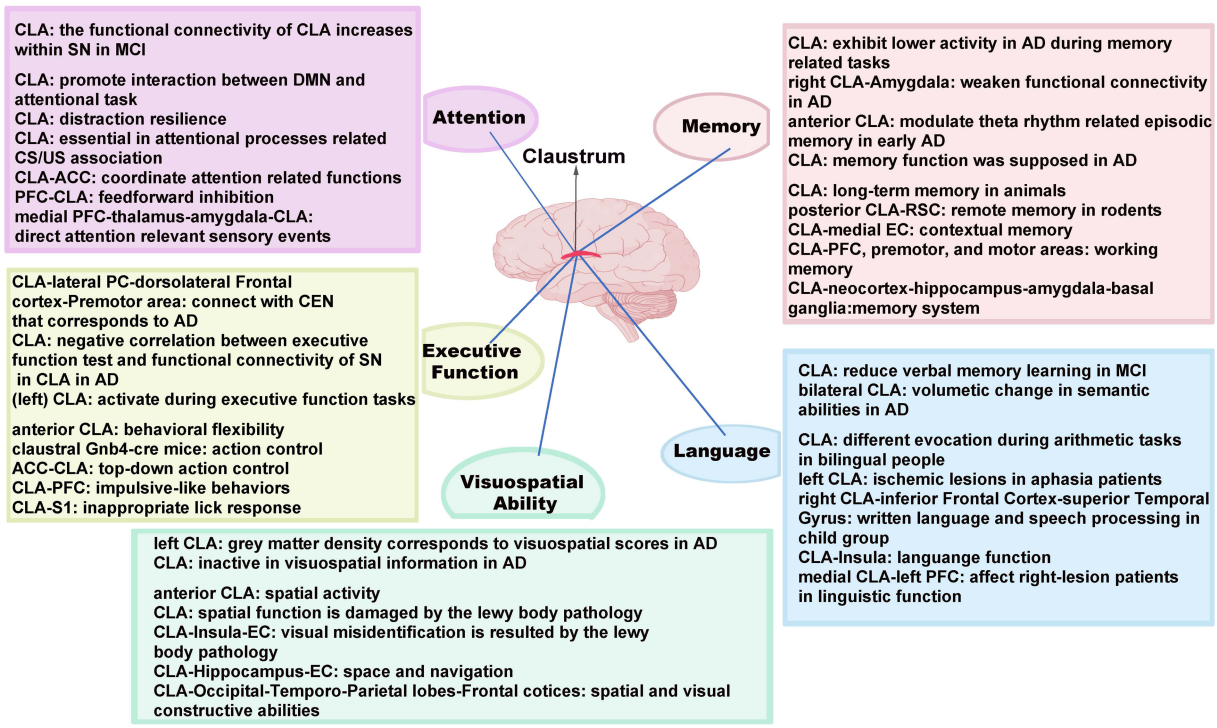

FIGURE 2
Major cognitive functions and the underlying mechanisms mediated by the CLA with its related circuits in AD. SN, salience network; MCI, mild cognitive impairment; DMN, default mode network; CS, conditioned stimulus; US, unconditioned stimulus; CEN, central executive network; ACC, anterior cingulate cortex; PFC, prefrontal cortex; S1, primary somatosensory cortex; PC, parietal cortex; EC, entorhinal cortex; RSC, retrosplenial cortex.

to be resolved, especially that are profoundly implicated in AD etiology. Besides, animal models that could be implemented in AD-CLA studies are still lacking. Given that the CLA and the claustral pathways robustly intermediate multiple cognitive functions, it would be a promising direction for future research to simultaneously monitor the activity of the CLA with its brain networks in AD.

Conclusion

This review highlights a fundamental but previously overlooked brain region, the CLA, and elaborately demonstrates its cognitive function on attention, executive function, visuospatial ability, language, and memory in AD. The claustral pathological changes are often found in structural and functional neuroimaging studies in AD, while the underlying mechanisms behind it are rarely analyzed, or even interpreted in terms of higher-order cognitive functions. We have combined normal physiological functions of the CLA and its pathological changes in AD to provide preliminary insights on the inferential framework of pathogenic mechanisms and attempted to propose certain therapeutic strategies for early-stage AD treatment by targeting CLA with its related circuits.

Author contributions

C-YC and H-YG designed this review framework. C-YC, G-YY, H-XT, and H-YG searched the relevant literature. C-YC, G-YY, H-XT, X-CW, CH, and H-YG wrote the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants from the Key-Area Research and Development Program of Guangdong province (2019B030335001), the National Natural Science Foundation of China (32200815), the National Social Science Foundation of China (20&ZD296), and the China Postdoctoral Science Foundation (2022M721218).

Acknowledgments

Thanks to Mamatsali·Abdurahman for his help in the claustrum related literature collection and discussion. We would like to apologize to our colleagues whose work was not cited here.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Aging Neuroscience

TYPE Perspective
PUBLISHED 15 June 2023
DOI 10.3389/fnagi.2023.1204852

OPEN ACCESS

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RECEIVED 12 April 2023
ACCEPTED 31 May 2023
PUBLISHED 15 June 2023

CITATION
Boukhvalova MS, Kastrukoff L and Blanco JCG (2023) Alzheimer's disease and multiple sclerosis: a possible connection through the viral demyelinating neurodegenerative trigger (vDENT).
Front. Aging Neurosci. 15:1204852.
doi: 10.3389/fnagi.2023.1204852

Alzheimer's disease and multiple sclerosis: a possible connection through the viral demyelinating neurodegenerative trigger (vDENT)

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Alzheimer's disease (AD) and multiple sclerosis (MS) are two CNS disorders affecting millions of people, for which no cure is available. AD is usually diagnosed in individuals age 65 and older and manifests with accumulation of beta amyloid in the brain. MS, a demyelinating disorder, is most commonly diagnosed in its relapsing-remitting (RRMS) form in young adults (age 20–40). The lack of success in a number of recent clinical trials of immune- or amyloid-targeting therapeutics emphasizes our incomplete understanding of their etiology and pathogenesis. Evidence is accumulating that infectious agents such as viruses may contribute either directly or indirectly. With the emerging recognition that demyelination plays a role in risk and progression of AD, we propose that MS and AD are connected by sharing a common environmental factor (a viral infection such as HSV-1) and pathology (demyelination). In the viral DEmyelinating Neurodegenerative Trigger (vDENT) model of AD and MS, the initial demyelinating viral (e.g., HSV-1) infection provokes the first episode of demyelination that occurs early in life, with subsequent virus reactivations/demyelination and associated immune/inflammatory attacks resulting in RRMS. The accumulating damage and/or virus progression deeper into CNS leads to amyloid dysfunction, which, combined with the inherent age-related defects in remyelination, propensity for autoimmunity, and increased blood-brain barrier permeability, leads to the development of AD dementia later in life. Preventing or diminishing vDENT event(s) early in life, thus, may have a dual benefit of slowing down the progression of MS and reducing incidence of AD at an older age.

KEYWORDS

Alzheimer's disease, multiple sclerosis, viral, HSV-1, demyelination, trigger, vDENT

Introduction

MS pathogenesis, models, and treatment approaches

Multiple sclerosis (MS) is a demyelinating disorder of CNS affecting 2.3 million people worldwide (Wallin et al., 2019). It is most often diagnosed in individuals between 20 and 40 years of age (Howard et al., 2016). Historically, clinical subtypes of MS include clinically isolated syndrome, relapsing-remitting MS (RRMS), and primary and secondary progressive MS (Thompson et al., 2018). RRMS is the most common presentation of MS and is characterized by days to weeks of increased inflammation and demyelinated lesions in the white matter (Lassmann and Bradl, 2017). Depending on their location in the CNS, the lesions can lead to visual, sensory, motor, incoordination, neurocognitive, and bladder and bowel symptoms (Khan and Amatya, 2017). The acute clinical attack is followed by complete or partial recovery in patients, resulting from the resolution of inflammation and remyelination. Accumulating evidence suggests that relapsing vs. progressive MS phenotype is driven by "host factors," most notably patient's age, with younger patients displaying greater frequency of relapses and older patients more prone to having progressive phenotypes (Waubant et al., 2019).

The pathogenesis of MS includes attacks on myelinating glia [oligodendrocytes (OL)] in the CNS resulting in myelin degradation, axonal dysfunction, and neurodegeneration. The attack is thought to be immune-mediated, and is the basis for most disease modifying therapies (DMTs). Examples of approved treatments for MS include peptides found in myelin basic protein acting as a decoy for the attacking immune cells, a sphingosine-1-phosphate receptor modulator sequestering lymphocytes in lymph nodes, therapeutics preventing immune cell infiltration into the CNS, and β-interferon drugs (Derwenskus, 2011). While these treatments can slow progression of the disease, they are not capable of curing MS. Recently, remyelination-promoting therapies became a major focus of MS pharmacotherapy [reviewed in Melchor et al. (2019)].

There are 4 different animal models of demylination: (1) genetic/transgenic, (2) viral, (3) toxin-induced, and (4) autoimmunity-driven (Gudi et al., 2014; Boukhvalova et al., 2019; Torre-Fuentes et al., 2020). The latter two are most commonly used for the evaluation of MS therapeutics (Melchor et al., 2019). Toxin-induced demyelination is induced by feeding animals cuprizone, a copper chelator, or by injecting toxins like ethidium bromide or lysolecithin into the CNS. The autoimmunity-driven models (e.g., the model of Experimental Autoimmune Encephalomyelitis, or EAE) involve immunizing animals with myelin components to induce autoimmune attacks on myelin, or by passively transferring myelin-specific activated lymphocytes. These models have been very useful for understanding mechanisms of re-myelination and dissecting the role of various cell types in the process. However, neither toxin models nor EAE models reproduce MS as observed in humans, and may explain in part the failure of many immunomodulatory and neuroprotective treatment strategies in MS [reviewed in Rolfes et al. (2020) and Huntemann et al. (2021)].

The role of viral infections in MS pathogenesis

The involvement of viral infections in triggering an acute attack in RRMS, potentially through a non-specific effect, has been suggested decades ago (Andersen et al., 1993; Panitch, 1994). A number of viruses including Epstein-Barr virus (EBV) and human herpes virus 6 (HHV-6) have been implicated in MS pathogenesis (Lindeberg et al., 1991; Haahr et al., 1992, 1995; Soldan et al., 1997; Munch et al., 1998; Virtanen and Jacobson, 2012; Bjornevik et al., 2022). However, how specific the role of these viruses is in acute attack of RRMS remains to be determined. A longitudinal study of 26 RRMS patients and 20 healthy controls that quantified EBV, HHV-6, cytomegalovirus (CMV) and herpes simplex virus 1 (HSV-1) DNA by PCR in PBMCs, showed that EBV and HHV-6 were detected in MS patients during acute attack and periods of remission, but also in healthy controls, with no significant differences between the MS patients and controls (Ferrante et al., 2000). In contrast, CMV and HSV-1 were detected only in MS patients, with HSV-1 DNA showing up only during an acute MS attack (Ferrante et al., 2000). This finding, together with the earlier suggestions (Lycke et al., 1996; Bergstrom, 1999; Ferrò et al., 2012), highlight HSV-1 as an important etiologic factor in triggering an acute attack in MS.

The role of HSV-1 in MS is difficult to model in laboratory animals. Prior to our recent work in cotton rats *S. hispidus*, multifocal demyelination, the main pathophysiologic feature of MS, could be induced by lip HSV-1 infection only in murine strains that carry inherent defects in complement system, macrophage function, and/or muscle repair (strains A/J, SJL/J, and PL/J) (Kastrukoff et al., 1987, 2012). These strains are used to study developmental defects, epilepsy, spontaneous tumorigenesis, myopathy, and/or autoimmunity, all of which may affect CNS manifestations. Cotton rats *S. hispidus* are not prone to these disorders and, instead, have proven to be a reliable translational model of human viral diseases (Boukhvalova et al., 2009, 2015, 2018, 2022). The lip HSV-1 infection in *S. hispidus* delivered by abrasion caused multifocal demyelination in the CNS, followed by remyelination and formation of MS-like plaques (Boukhvalova et al., 2019). Virus antigens were detected in association with demyelinated lesions, suggesting a direct effect of viral infection/presence in the brain. Involvement of thalamus was noted, with perivascular cuffing and potential demyelination developing in the area. In human MS cases, involvement of the thalamus has been associated with a variety of clinical manifestations, including fatigue, movement disorders, pain, and cognitive impairment (CI) (Amin and Ontaneda, 2020). A recent study of brain samples from chronic progressive MS cases showed that active MS lesions were populated by CD8 + tissue-resident memory T cells with signs of reactivation and infiltration into the brain parenchyma (Fransen et al., 2020), possibly as a recall response to viral infection/reactivation in the CNS. Accumulating evidence, therefore, points to an important role of viral infections/reactivations in MS pathogenesis and etiology.

AD pathogenesis and current treatment approaches

Alzheimer's disease (AD) is a disorder that affects cognitive function and memory that can lead to dementia. Dementia caused by AD is diagnosed usually in people age 65 and older, and affects an estimated 6.7 million Americans (Alzheimer's disease facts and figures, 2023). The main pathologic findings in AD are the extracellular amyloid plaques and the intracellular Tau neurofibrillary tangles (Yiannopoulou and Papageorgiou, 2020). AD pathophysiology is based on the "amyloid hypothesis," where cleavage of the large amyloid precursor protein (APP) into protease-resistant peptide fibrils results in formation of beta amyloid (Aβ) plaques. The process triggers neurotoxicity, local inflammation, oxidation, excessive glutamate (excitotoxicity), and Tau hyperphosphorylation. Tau is a microtubule-associated protein that helps neuronal transport system and stabilizes growing axons. Abnormally hyperphosphorylated Tau forms intra-neuronal tangles composed of insoluble fibrils (Anand et al., 2017). Accumulating neuronal damage leads to deficiencies and imbalance between different neurotransmitters (e.g., acetylcholine, dopamine, serotonin) and associated cognitive deficiencies (Yiannopoulou and Papageorgiou, 2020). Treatments approved for AD have historically been purely supportive and aimed at counterbalancing the neurotransmitter imbalance. They include acetylocholinesterase inhibitors and an NMDA-receptor open-channel blocker that affects glutamatergic transmission (Yiannopoulou and Papageorgiou, 2013; Cummings et al., 2019). Multiple clinical trials of disease modifying treatments (DMT) with drugs that target amyloid-related mechanisms or associated inflammation have met with mixed results (Yiannopoulou and Papageorgiou, 2020). In the past 2 years, the FDA has approved two drugs for AD treatment: aducanumab and Leqembi (lecanemab-irmb). Both are monoclonal antibodies targeting Aβ, shown to reduce appearance of amyloid plaques, and both have advanced through the FDA accelerated approval system. However, there are concerns over efficacy and serious adverse events. One study of aducanumab identified cerebral edema or hemorrhage in 41% of patients in the study (Salloway et al., 2022). The process of accelerated approval does indicate a dire need for effective AD therapeutics at the time when the elderly population is increasing worldwide (Owolabi et al., 2023). The lack of success of a number of amyloid- and immune-targeting AD therapeutics in recent years (reviewed Mullane and Williams, 2020) argues for a better understanding of AD etiology and pathogenesis.

New developments in the AD field: the role of viral infections, myelin damage, and immune response

The number of publications supporting a role for HSV-1 in pathogenesis of AD has steadily increased and has recently been reviewed (Itzhaki, 2017, 2021). In brief, HSV-1 can enter the CNS and reside there in latent form. Individuals with the type 4 allele of the apolipoprotein E gene (APOE-ε4) are at increased risk of AD development after HSV-1 infection (Wu et al., 2020). In a Taiwanese study of 8,362 subjects aged ≥ 50 years, newly diagnosed with HSV (HSV-1 or HSV-2), and exhibiting severe symptoms of herpes labialis and/or genitalis, an increased risk of 2.56-fold of developing dementia in a 10-year follow up compared to controls was identified. The risk was reduced in patients who received antiherpetic medications (Tzeng et al., 2018). Further support comes from *in vitro* studies where HSV-1 was reported to induce accumulation of Aβ in cultured neurons (De Chiara et al., 2010; Piacentini et al., 2011) and to promote Tau hyper-phosphorylation (Zambrano et al., 2008; Wozniak et al., 2009). A recent study in mice infected with HSV-1 by lip abrasion showed that repeat reactivation of virus following thermal stress led to progressive accumulation of AD biomarkers, including Aβ and abnormal Tau, and development of cognitive deficits (De Chiara et al., 2019). Apart from HSV-1, other viruses, including varicella zoster virus (VZV), EBV, CMV, and HHV-6, have been linked to dementia, but for at least some of them it is not clear whether neurodegeneration develops as a result of direct virus involvement or an indirect effect on inflammation that reactivates HSV-1 (Cairns et al., 2022).

Although AD has long been considered a disease of gray matter, recent neuroimaging studies have identified micro- and macro-structural changes in the white matter that could contribute to risk and progression of AD, resulting in a shift of focus in AD research toward myelin and oligodendrocytes [reviewed in Nasrabady et al. (2018)]. It has also been shown that several AD-relevant pathways overlap significantly with remyelination pathways that contribute to myelin repair by encouraging oligodendrocyte proliferation. Importantly, amyloid, Tau, and ApoE, previously defined as therapeutic targets of AD, contribute to both remyelination and AD progression (Papuć and Rejdak, 2018). Aggregated Aβ 42 and neurofibrillary tangles may not only be responsible for neuronal loss but can also induce myelin damage and oligodendrocyte death (Papuć and Rejdak, 2018). The impairment in the formation of myelin sheath can even precede Aβ and Tau pathologies in AD (Couttas et al., 2016; Papuć and Rejdak, 2018). The contribution of immune-mediated mechanisms to pathogenesis of AD is also gaining increased recognition. Dysregulation of monocyte subsets, accumulation of neutrophils in the CNS, depleted and/or dysfunctional regulatory T cells (Tregs), and brain damage mediated by CD8 + T cells have now been documented in both AD and MS cases [reviewed in Rossi et al. (2021)].

The vDENT model

The scientific fields of MS and AD appear to be rapidly changing, in part because of a lack of success of a number of immune- or amyloid-targeting therapeutics developed on the basis of an earlier understanding of the pathogenesis of these diseases (Mullane and Williams, 2020; Rolfes et al., 2020; Huntemann et al., 2021). It is becoming clear that MS and AD, albeit disparate in regard to the timing of their diagnosis and the extent of cognitive impairment, share a number of important similarities, such as the contribution of herpesvirus infections, demyelination, and immune dysregulation. The potential role of an infectious etiology in MS and AD is becoming more focused. Members of the family Herpesviridae including HSV-1, EBV, CMV, HHV-6, VZV (and others) have long been suspected of playing a role, but their involvement has never been proven. Recently, a contribution

of HSV-1 to AD has been acknowledged, while a similar interest in the contribution of herpesviruses to MS is increasing. We would like to propose that MS and AD are connected, share a viral infection as an environmental trigger, and demyelination as a common factor in pathogenesis. We propose the viral DEmyelinating Neurodegenerative Trigger (vDENT) model of AD and MS (**Figure 1**) where the initial viral infection (e.g., HSV-1) and ensuing demyelination provoke the first episode of MS-like disease early in life, with subsequent viral reactivations and associated immune/inflammatory attacks leading to appearance of RRMS-like disease, with periods of symptomatic disease coinciding with virus reactivation/demyelination episodes and remission brought on by remyelination and resolution of immune/inflammatory reaction. The CNS damage accumulating during the repeated reactivation episodes would lead to amyloid dysfunction, which, combined with the potential virus progression deeper into the CNS, inherent remyelination defects developing in older age (Barbosa et al., 2019; Dimovasili et al., 2023), and altered immune and blood-brain barrier function (Mooradian, 1988; Ransohoff, 2023), would bring on AD-like cognitive defects. It is also possible that neurodegenerative damage accumulates in the absence of symptomatic reactivation episodes (MS forms other than RRMS), that demyelination becomes less pronounced with subsequent reactivation events, and/or that immune dysfunction plays a bigger role during the later stages of MS that occur at an older age, manifesting the prevalence of progressive MS form over RRMS in the elderly (Waubant et al., 2019; Ransohoff, 2023).

The vDENT model of MS/AD stipulates that developing MS after viral infection early in life can lead to symptomatic AD in old age, and that preventing/lessening MS can reduce incidence of AD. More intricately, it suggests that the pre-symptomatic phase of AD, which may span decades and appear well before the cognitive defects develop (Braak et al., 2011; Braak and Del Tredici, 2014, 2015), may overlap with the mid- or late- stages of MS and represent a progression of the same pathophysiologic mechanism initiated by viral infection. The recent demonstrations that HSV-1 can directly cause Tau pathology [reviewed in Harris and Harris (2018) and Duarte et al. (2019)], and that Tau defects appear during the first decades in life, while amyloid abnormalities occur at an older age (Braak and Del Tredici, 2015), support the progressive nature of viral-induced CNS neurodegeneration. The connection of both AD and MS to demyelination, the critical role demyelination can play in initiation (and potentially relapsing nature) of MS, and overlap of demyelination and AD-critical pathways, further support the link between AD, MS, and viral infections that can cause demyelination. Importantly, during the earlier stages of AD, Tau defects are found not in the cortex but in the neurons of the brainstem (BST) (Braak and Del Tredici, 2015), the same place where the first demyelinating lesions appear after the lip HSV-1 infection. In both HSV-1 infected cotton rats and in susceptible murine strains, demyelinated lesions after the initial HSV-1 infection progress in the sequence BST > cerebellum > cerebral hemispheres (Kastrukoff et al., 1992, 2012; Boukhvalova et al., 2019).

Multiple sclerosis is very heterogeneous in its clinical course, clinical severity and outcome, pathological appearance, MRI appearance, and response to therapy. It is possible that vDENT model applies only to a subset of MS cases. It is also likely that the model applies to a small fraction of all herpesvirus infections, as seroprevalence of some of them (e.g., HSV-1) can be as a high as 90% in developed countries (Roizman and Knipe, 2001; Whitley and Roizman, 2001). The selection may depend on the

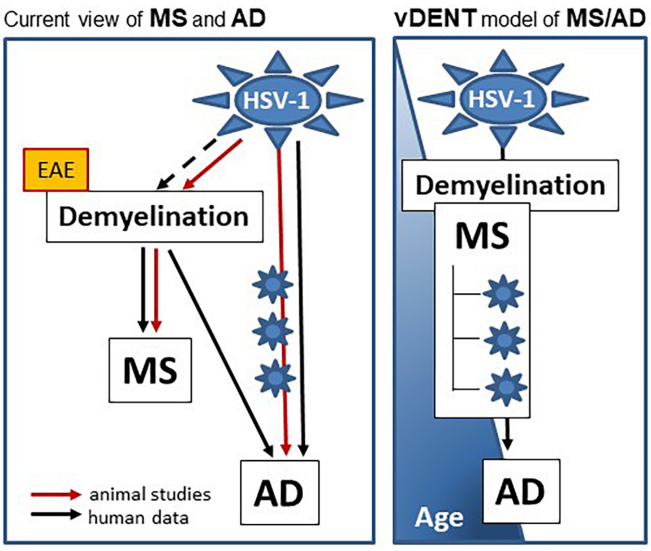

FIGURE 1
vDENT (viral demyelinating neurodegenerative trigger) model of AD and MS. vDENT model of MS/AD (on the **right**) is based on the current view of MS and AD (on the **left**). In this current view, HSV-1 contributes to AD in humans and animal models through repeated reactivation of virus in the nervous system (blue star symbols on the red line). Contribution of HSV-1 to MS in humans is not entirely clear (dashed black line), however, it's been demonstrated in animals (cotton rats, solid red line). Although demyelination is central to the pathogenesis of MS in both humans and animals, many therapies tested in the non-infectious EAE models (yellow box) have failed to show efficacy in humans. Not only is demyelination central to MS, it is also recognized as being important for risk and progression of AD in humans. A model is proposed on the right in which MS and AD are linked to the same vDENT event early in life, which can lead to development of AD later on.

ability of herpesviruses to induce CNS demyelination under certain conditions. One example here may include a specific age at which the first (acute) infection occurs, and whether it happens in a susceptible child/adolescent or an adult. Our studies in cotton rats indicate that demyelination in the CNS after lip HSV-1 infection occurs prevalently in young animals, when brain plasticity is still high, and that demyelination and disease in animals infected with HSV-1 for the first time as "adults" are less pronounced (Boukhvalova et al., 2019, 2022). This finding is important as it may indicate that vDENT hypothesis of MS/AD connection applies specifically to select pediatric-onset MS cases (Thompson et al., 2018). It is also possible that the model applies to a subset of MS patients with detectable lesions in trigeminal root entry zone (TREZ) [about 10% (Sugiyama et al., 2015)], as TREZ is a portal often utilized by herpesvirus infections. Overall, only a fraction of herpesvirus-infected individuals may go on to develop CNS demyelination, MS, and subsequently AD.

The direct progression from MS to AD has not been proposed before, possibly because of the reduced life expectancy in MS patients in the past compared to the general population (Lunde et al., 2017; Leadbetter et al., 2023), because of so many diverse forms/manifestations of MS, because remyelinated lesions are often difficult to image (potentially precluding detection of both MS and AD pathology in the same autopsy samples), and/or because of the lack of systematic studies searching for the causative association between MS and AD. It is known, however, that cognitive dysfunction develops in about half of MS patients (Sumowski et al., 2018), potentially influenced by genetics and lifestyle. As the survival gap between MS patients and general population appears to be receding due to progress in disease management (Leadbetter et al., 2023), detection of MS to AD progression could become easier in future studies designed to detect markers of both diseases in respective patient cohorts of all ages, taking into account the evolving nature of these diseases. The overlap may be easier to correlate to viral markers during the late MS - early (preclinical) AD in patients who are younger, as the disease may progress to the more immune-mediated mechanisms and the frequency of MS relapses (and coincidentally detectable viral markers) may reduce with advancing age (Waubant et al., 2019).

It is possible that in those individuals who are genetically susceptible to developing MS (with or without influence of additional environmental factors), the initial demyelinating event and later reactivations of virus can trigger a complex abnormal immune reaction directed at myelin and myelinating cells (Miller et al., 2001; Vanderlugt and Miller, 2002). With repeated viral reactivation and damage to the CNS, breaks in tolerance, epitope spread, bystander activation, and molecular mimicry will evolve and begin to take over from viral reactivation as the driving force behind the disease (Miller et al., 1997, 2001). Eventually MS can be established as an autoimmune disease. In those individuals who are genetically susceptible to developing AD, the initial demyelinating event and later reactivations of virus can trigger an abnormal immune reaction directed at neuronal cells (Jamieson et al., 1991; Itzhaki et al., 1997; Mori, 2010; Rossi et al., 2021). It can be a secondary event with the primary event being virus taking over neuronal function and giving rise to the toxins that eventually result in abnormal Tau proteins and amyloid bodies (Duarte et al., 2019). The proposed connection between MS and AD through the common viral demyelinating trigger, therefore, may be complicated, but is nevertheless important as it suggests that therapeutics capable of slowing down progression of MS may also be able to reduce incidence of AD at an older age.

Conclusion

Recently, a theory that Tau pathology is an initiating event leading to sporadic Alzheimer's disease has been proposed (Arnsten et al., 2021). This theory is partly based on the fact that Tau abnormalities are first detected in childhood, while amyloid abnormalities do not show up until an older age (Braak and Del Tredici, 2015). vDENT theory, and the fact that HSV-1 infection itself can cause Tau abnormalities, fits this "Tau-first" hypothesis very well and takes it one step further by suggesting that the first Tau abnormalities in children and/or young adolescents are caused by the first encounter with HSV-1 (or other demyelinating viruses) at an age when the brain is more susceptible to virus-induced demyelination and when the immune system is still naïve to these viruses. vDENT theory of MS/AD connection suggests that, in some cases, as the child/adolescent becomes an adult, and then an elderly, inherent aging-related deficiencies may contribute to the transition from MS to AD, including defects in remyelination mechanisms (Barbosa et al., 2019; Dimovasili et al., 2023), increased permeability of blood-brain barrier (Mooradian, 1988), and propensity for autoimmunity (Ransohoff, 2023). Historical arguments of immune and inflammatory mechanisms contributing to AD and MS pathogenesis, therefore, are not excluded by the vDENT theory. On the contrary, they are a crucial part of it that should be incorporated through the lenses of antigen-specific local mechanisms in brain parenchyma that may not have been considered before.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MB conceptualized the model and performed the literature review and information interpretation. LK provided a critical revision. MB, LK, and JB were involved in manuscript preparation. All authors contributed to the article and approved the submitted version.

Conflict of interest

MB and JB were employed by Sigmovir Biosystems, Inc.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TYPE Mini Review
PUBLISHED 15 June 2023
DOI 10.3389/fnagi.2023.1191729

OPEN ACCESS

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RECEIVED 22 March 2023
ACCEPTED 30 May 2023
PUBLISHED 15 June 2023

CITATION
Buele J and Palacios-Navarro G (2023) Cognitive-motor interventions based on virtual reality and instrumental activities of daily living (iADL): an overview. *Front. Aging Neurosci.* 15:1191729. doi: 10.3389/fnagi.2023.1191729

Cognitive-motor interventions based on virtual reality and instrumental activities of daily living (iADL): an overview

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Non-invasive, non-pharmacological interventions utilizing virtual reality (VR) represent a promising approach to enhancing cognitive function in patients with degenerative cognitive disorders. Traditional "pen and paper" therapies often lack the practical engagement in everyday activities that older individuals encounter in their environment. These activities pose both cognitive and motor challenges, underscoring the necessity of understanding the outcomes of such combined interventions. This review aimed to assess the advantages of VR applications that integrate cognitive-motor tasks, simulating instrumental activities of daily living (iADLs). We systematically searched five databases—Scopus, Web of Science, Springer Link, IEEE Xplore, and PubMed, from their inception until January 31, 2023. Our review revealed that motor movements, coupled with VR-based cognitive-motor interventions, activate specific brain areas and foster improvements in general cognition, executive function, attention, and memory. VR applications that meld cognitive-motor tasks and simulate iADLs can offer significant benefits to older adults. Enhanced cognitive and motor performance can promote increased independence in daily activities, thereby contributing to improved quality of life.

KEYWORDS

cognitive disorders, daily living, instrumental activities, motor intervention, virtual reality

1. Introduction

Human life expectancy has seen a significant increase in recent decades (van Leeuwen et al., 2019). However, aging is accompanied by notable physical and cognitive changes that necessitate consideration (Elliott et al., 2021). Emerging technologies, including artificial intelligence, robotics, big data, telematics, and virtual and augmented reality, offer promising tools in health sciences to enhance individuals' quality of life (Palacios-Navarro et al., 2016; Baig et al., 2019; Wildenbos et al., 2019; Hülür and Macdonald, 2020). VR systems have been leveraged for diagnosing age-related diseases and abnormalities in older adults (Varela-Aldás et al., 2022). Beyond diagnosis, VR has revolutionized therapeutic, training, and rehabilitation processes by providing immersive three-dimensional experiences aimed at

restoring or maintaining a wide range of cognitive functions often compromised in older adults (Appel et al., 2020).

Executive functions (EF) are responsible for mental manipulation of information, concept formation, problem solving, and cue-directed behavior (Weintraub et al., 2012). They entail advanced cognitive skills such as working memory, inhibitory control, cognitive flexibility, planning, reasoning, and problem-solving (Cristofori et al., 2019). Reduced performance of these functions is quite evident when Mild Cognitive Impairment (MCI) is already present. Alzheimer's disease (AD) in its early phase is particularly characterized by a diminished ability to mentally manipulate information (Elosúa et al., 2021). EF, related to working memory and attention, develop fully in adulthood and have direct links to cognitive efficiency, knowledge acquisition, academic performance, and autonomy (Baragash et al., 2022).

The reduction of autonomy generates problems in the person as it limits their ability to carry out their activities of daily living (ADL) (Tornero-Quiñones et al., 2020). EF interact with long-term memory in the episodic buffer, enabling the retrieval of previously learned information essential for problem-solving and new information processing for long-term storage (Oosterman et al., 2021). iADL demand greater effort from older adults, requiring continuous problem-solving related to their self-care (Cornelis et al., 2019). Key iADLs include meal preparation, budget planning, basic mathematical operations, and transportation use, necessitating active phonological loops to maintain auditory information in consciousness for immediate use (Weintraub et al., 2012). Patients with MCI or AD show significant impairments in long-term memory, EF, and spatial orientation (Murman, 2015).

Older adults often face physical limitations due to reduced motor and sensory system functionality (Khan et al., 2022), complicating both self-care activities (basic ADL or bADL) and mobility exercises such as walking, marching, or maintaining balance (Osoba et al., 2019). Research indicates that aerobic and balance physical training can increase muscle strength, thus reducing falls (Sherrington et al., 2019). It is important to note that while young and cognitively healthy adults generally do not exhibit postural and gait control problems, older adults or those with cognitive issues are vulnerable to cognitive distractions (dual or additional tasks) that may compromise postural control (Zhang et al., 2019). Studies like that of Sato (2017) have shown that EF partly governs the motor and sensory system, meaning that its malfunctioning is linked to falls. These findings underscore the need for cognitive interventions that also incorporate physical exercises, aiming for a comprehensive approach (Tromp et al., 2015).

Conventional cognitive therapies, or "paper and pencil" therapies, have long been used to treat cognitive impairments in older adults. These cost-effective, easily accessible, and clinically validated therapies include tabletop activities like puzzles, wooden blocks, card games, and mazes (Bernini et al., 2019). However, these therapies often struggle to assess patients' cognitive levels systematically and keep them engaged. Computer-based cognitive interventions, on the other hand, have emerged as a promising alternative, demonstrating effectiveness in improving cognitive function in both healthy older adults and those with neuropsychological disorders (Thapa et al., 2020; Zuschnegg et al., 2023). Unlike conventional therapies, these computer-based interventions are capable of systematically adjusting task difficulty according to the individual's cognitive level, offering a more diverse and engaging range of programs and activities (Wollesen et al., 2020). These interventions surpass static and straightforward training, providing interactive and immersive experiences.

While computer-based cognitive interventions offer many advantages, it is crucial to establish specific guidelines to assist healthcare professionals in determining the appropriate activities and clinical conditions for implementation (Goldstein and McNeil, 2012). Standardizing these guidelines can enhance the effectiveness and efficiency of computer-based interventions in clinical practice. Given the existing digital divide between younger and older adults, it's vital to consider how this might impact older individuals' access to modern technologies like VR. VR-based cognitive interventions, leveraging advancements in information technology, have shown great promise (Liao et al., 2020). While some older adults have successfully used these technologies for social interaction and cognitive enhancement (Gao et al., 2020), others may face social exclusion due to a lack of necessary skills and equipment. Addressing this digital divide is essential to ensure older individuals can fully benefit from VR/AR-based interventions for cognitive enhancement and overall wellbeing.

Research shows that VR can significantly enhance cognitive-motor interventions in older adults (Kwan et al., 2021). For instance, the study of Pichierri et al. (2012) incorporated traditional physical exercise and dance video games into cognitive-motor training. This dual-task exercise led to VR system users taking quicker steps than the passive control group, potentially preventing falls in real-life situations. Another study (Torpil et al., 2021) featured various serious games, including activities such as a boxing trainer, a running game controlled by jumping and body movements, a penalty kick game, and a skydiving game controlled by body and shoulder movements. The results showed improvements in visuospatial perception, organization, orientation, attention, and concentration compared to the control group. The study of Cameirão et al. (2016) demonstrated how mood and cognitive functioning can supplement physical rehabilitation, as post-stroke participants had to locate a target image within a set of 15 distractors for attention and memory training.

Several reviews have analyzed VR's effect on cognitive and motor functions. A systematic review conducted by Zhu et al. (2021) included 11 randomized controlled trials (RCTs), revealing a moderate impact of VR interventions on cognitive and motor function, including attention/execution, memory, global cognition, and balance in patients with mild cognitive impairment (MCI) and dementia. Gao et al. (2021) analyzed six VR interventions combined with traditional rehabilitation, showing significant improvements in general cognition, attention, and mood, though not in global cognition, motor function, and ADLs. In the review of Pichierri et al. (2011) computerized interventions (mostly VR) showed positive effects on various physical abilities in older adults with TBI and stroke compared to non-VR proposals. Participants displayed greater motivation and compliance with the computerized environment compared to regular physical training programs. A similar approach was used in the study of Schoene et al. (2014), where the use of technological tools in cognitive-motor rehabilitation was analyzed. The two studies that used a VR environment with a treadmill reported improvements in balance and mobility.

The benefits of VR in training older adults are evident based on the existing evidence. However, the heterogeneity of activities simulated in VR environments makes analysis challenging. Therefore, this review focuses solely on VR applications in which participants perform iADLs and motor tasks (iADL-m) to assess their impact on the cognitive functions of older adults.

2. Methods

2.1. Eligibility criteria

This review adheres to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for systematic reviews. Inclusion criteria encompass: (i) articles published in English; (ii) studies without temporal or spatial restrictions; (iii) interventions employing VR-iADL and motor applications; (iv) clinical trials and pilot studies; (v) studies involving healthy older adults with MCI or dementia; (vi) immersive and non-immersive systems; and (vii) studies both with and without a control group.

2.2. Exclusion criteria

Exclusion criteria include: (i) theoretical or descriptive studies; (ii) non-peer-reviewed articles and preprints; (iii) studies not employing VR; (iv) applications that do not simulate an iADL; (v) interventions solely cognitive in nature; (vi) literature reviews; (vii) interventions for disorders other than those specified; (viii) diagnostic or screening investigations; and (ix) interventions without a pretest and posttest.

2.3. Data sources and search strategy

Relevant articles were identified in Pubmed, Scopus, IEEE Xplore, Apa PsycNet, and the Web of Science databases, from their inception until January 2023. The search terms included keywords relating to virtual reality (e.g., "virtual," "computer"), cognitive-motor interventions (e.g., "cognitive," "motor," "memory," "executive," "rehabilitation," "training," "stimulation"), iADL (e.g., "daily," "ADL," "iADL," "store," "shopping," "supermarket," "cook," "cooking," "kitchen"), and cognitive disorders [e.g., "mild," "Alzheimer," "dementia," NOT ("stroke," "brain injury," "TBI")].

2.4. Study selection

Search terms were tailored to each database. The titles and abstracts of articles in each database were screened independently by two authors (JB and GP-N) in line with the specified inclusion and exclusion criteria. Duplicate studies were removed, and additional studies cited in the identified articles were included. The selected articles were then stored, organized, and assessed using the Mendeley bibliographic manager v1.19.8 (Mendeley Ltd., Elsevier, Netherlands).

3. Results

Upon identifying articles that met the inclusion and exclusion criteria, data were extracted from each article. This included the authors, the study design, the sample, the motor and cognitive intervention applied, and the main findings. **Table 1** presents the characteristics of each study.

4. Discussion

With advancing age, the ability to perform motor-related activities becomes increasingly challenging. As noted by Muir et al. (2012), elderly individuals with MCI demonstrate a reduction in gait speed and an elongated stride completion time when transitioning from a single task to a double one. Older adults with cognitive difficulties are at a higher risk of falls compared to their healthy counterparts, and this risk escalates when the walking speed drops below 1 m/s (Abellan Van Kan et al., 2009). Furthermore, elderly people with MCI are likely to make risky decisions when crossing streets (Rizzo et al., 1997). An increase in latency at the onset of a journey and a slower pace are also reported (Bahureksa et al., 2016), indicating a correlation between gait issues and the onset of Alzheimer's Disease (AD) due to associated visuospatial deficits (Fukui and Lee, 2009; Rosso et al., 2019). A reduction in walking speed is perceived as an indicator of cognitive frailty that impacts wellbeing and survival (Duan-Porter et al., 2019; Van Schooten et al., 2019; Beltz et al., 2022). From a cognitive standpoint, memory and executive functions (EF) are most frequently impacted by AD.

4.1. Benefits in cognitive functions

Cognitive-motor interventions have demonstrated potential as an effective method to boost cognitive functions and alleviate frailty. Evidence indicates that these interventions can enhance physical performance, brain functionality (as determined by resting functional magnetic resonance imaging), and cognitive capacities (Raichlen et al., 2020; Yue et al., 2020). The use of VR for such interventions has been successfully demonstrated in both healthy elderly individuals and those suffering from dementia (Yi et al., 2022).

A recent review highlighted that VR cognitive training can exert moderate to large effects on global cognition, attention, memory, and motor performance in individuals with Mild Cognitive Impairment (MCI), with additional benefits for executive function seen in people with dementia (Papaioannou et al., 2022). The VR-integrated ADL motor studies explored in our review have successfully motivated individuals to utilize learned skills in real life, with encouraging knowledge transfer outcomes (McDaniel et al., 2014). Several studies (Healy et al., 2005; Dahlin et al., 2008) propose that transferable skills are only developed through practice, suggesting that other non-iADL applications may not yield the same benefits. More specifically, evidence suggests that practicing an activity can facilitate the transfer of coordination skills in dual tasks, as demonstrated in the study by Schubert et al. (2017). The review conducted by Joubert and Chainay (2018) indicated

TABLE 1 Characteristics of the included studies.

References	Design	Sample	VR intervention motor	Cognitive	Major findings
Liao et al., 2020, Taiwan	RCT	34 MCI patients (23F/11M)	Aerobic and resistance exercises, cleaning windows, tai chi, walking, bending and lifting objects at home	Shopping, preparing food, managing finances and transportation	Decreased activation in prefrontal areas indicating increased neural efficiency. Dual VR tasks (physical and cognitive) could have positive effects on several cognitive functions
Liao et al., 2019, Taiwan	RCT	34 MCI patients (23F/11M)	Aerobic and resistance exercises, walking, getting on and off a stool	Shopping, preparing food, managing finances and transportation	The training improved divided attention (cognitive and motor at the same time) and cognitive flexibility (aspects of EF). VR was able to increase motivation
Park et al., 2020, Republic of Korea	RCT	35 MCI patients (17F/18M)	Moto Cog: personal hygiene, driving, door opening, shampoo, use of handles	Card game, puzzle, construction activity with sticks and mazes	The VR group improved in the MoCA, TMT and DST tests performance. Motivation improved with positive effects on attention and short-term visuospatial memory
Doniger et al., 2018, Israel	RCT	34 healthy older adults with a history of Alzheimer's disease	Walking on a treadmill	View a virtual shopping list and pick up items, plan purchases with 100 shekels (Israel currency)	Shopping tasks are very important to maintain and/or regain independence. There was a neuroplastic change in DTI measures of the hippocampus in just 2 h of training
Mrakic-Sposta et al., 2018, Italy	Pilot Study	10 MCI and MD patients (6F/4M)	Cycling in a park, cross the road by bike avoiding cars	Virtual shopping: List of five items, choose the aisle and the product	Improvements in the MMSE, ROCFT, FAB and AM tests performance. Increased antioxidant capacity and reduction of lipid peroxidation and DNA damage. Better performance in real life thanks to self-perceived improvement and motivation
Arlati et al., 2017, Italy	Pilot Study	10 patients with MCI	Cycling in nature, cross and avoid cars by bike	buy five items	Patients showed better performance in real life (less forgetfulness). The trick words (distractors) did not change the results. Patients exhibited high levels of commitment and motivation
Kwan et al., 2021, China	RCT	17 MCI patients (15F/2M)	Bicycle exercise on an ergometer	Shopping, transportation, cooking, bird watching, reporting lost items	Patients reported better performance in real life because of self-perceived improvements. The intervention could improve cognition and frailty, reducing the risk of falls, disability and mortality.
McDaniel et al., 2014, United States	RCT	96 healthy older adults (61F/35M)	Setting the table with cutlery, flexibility exercises (aerobics)	Prepare breakfast: five foods, board game and remember health facts	Participants' performance did not improve in the kitchen task. Aerobic exercises did not show significant changes. Cognitive training did not transfer to other tasks.

AM, attentional matrices test; DST, digit span test (forward/backward); DTI, diffusion tensor imaging; F, female; FAB, frontal assessment battery; M, male; MMSE, mini-mental state examination; MoCA, montreal cognitive assessment; Moto cog, VR training program focused on improving upper extremity ADL performance; ROCFT, Rey-Osterrieth complex figure test; TMT, trail making test (A/B).

10.3389/fnagi.2023.1191729

a slight superiority for combined physical and cognitive training over training conducted separately. However, separate training also influences different cognitive functions, warranting further research. The links between cognitive and motor processes are not new, and they likely share a similar evolutionary history (Leisman et al., 2016).

The study carried out by Liao et al. (2020) reported that the stimulation of dual tasks (physical and cognitive) simulating ADL in virtual environments can impact various cognitive functions, notably executive functions (EF) and memory (Lauenroth et al., 2016). In previous work, the authors (Liao et al., 2019) created a VR application simulating iADL-m, which aided in training divided attention and cognitive flexibility (aspects of EF), targeting individuals to achieve between 50 and 75% of their maximum heart rate. Concurrently, the results of the study of Mrakic-Sposta et al. (2018) revealed improvements in attention, EF, and memory in patients with MCI. Similar improvements in EF and walking speed were also observed in Kwan et al. (2021)'s study, consistent with a recent review (Papaioannou et al., 2022). These applications provide real-time feedback, leading to long-term benefits, such as the transfer of knowledge to the real world (Ross et al., 2016).

McDaniel et al. (2014) combined virtual food preparation, table setting, and flexibility exercises, showing benefits for prospective memory. This involves spontaneous recovery and care processes that enable defining the actions to be carried out based on the place and situation. High levels of physical activity correlated directly with the proper functioning of EF, suggesting a potential palliative measure (Galle et al., 2022). The study of Galle et al. (2023) showed that those who increased their physical activity by more than 30% displayed improvements in gait speed, aerobic capacity, EF, and global cognition compared to those who did not. Significant enhancements in spatial cognition were also reported, implying that orientation practice could potentially forestall the cognitive decline of the elderly. Applications simulating a virtual city and requiring street crossings could be beneficial to users (Waddington and Heisz, 2023).

According to the study of Doniger et al. (2018), dual processing speed (mobility) training offered protection against dementia. As demonstrated in the longitudinal study carried out by Edwards et al. (2016) cognitive-motor training reduced the experimental group's chances of developing dementia after 10 years by 33%. Although this study primarily aimed to improve cognitive function with simultaneous walking being an incidental action inherent to the shopping task, the results indicated that cognitive training benefited physical performance (PE) while physical training benefited memory. The study of Kwan et al. (2021) reported improvements in cognitive function as a result of virtual cognitive-motor training, which can be attributed to neural plasticity. This effect could be due to the super additive synergistic effects created by the multitasking requirement of simultaneous physical and cognitive exercises. This aligns with the findings of Herold et al. (2018), who suggested that motor training incorporating a cognitive task has the highest ecological validity. Interventions that encourage significant physical exercise, offer variable levels of difficulty, and maintain a task-focused approach have shown to be more effective in adapting to related tasks (Stanmore et al., 2019; Wollesen et al., 2020). This suggests that a comprehensive, multifaceted approach can be more beneficial for cognitive health and physical function.

4.2. Changes in brain function

Numerous research studies have underscored the advantages of physical exercise as a complementary approach in cognitive rehabilitation. Liao et al. (2020) reported that such exercise promotes the release of brain-derived neurotrophic factor, enhancing blood flow and exerting beneficial metabolic effects. Park et al. (2020) further emphasized this in a virtual cognitive-motor intervention study, indicating that physical exercise stimulates the hypothalamic-pituitary-adrenal axis, thereby increasing cortisol levels and enhancing learning and memory (Luger et al., 1987). Doniger et al. (2018) observed that groups engaged in cognitive-motor training demonstrated increased cerebral blood flow in the prefrontal, middle, and posterior cingulate cortices. This could be indicative of heightened brain activity, even though the motor task was mild, potentially sparking neuroplastic changes given the brain's cognitive reserve (Esiri and Chance, 2012; Chapman et al., 2015). This hypothesis aligns with animal studies demonstrating new neuronal and synaptic connections in advanced age, increased cortical thickness, enhanced brain weight, and changes in blood flow (Mora, 2013). Contrastingly, groups engaged solely in motor exercise exhibited changes in the hippocampus without modifications in cerebrovascular reactivity (Chapman et al., 2016).

Theories of brain plasticity have been at the forefront of recent research (Chiu et al., 2017; Yamada and Sumiyoshi, 2021). The combination of increased cerebral blood flow and its synergistic response on global cognitive function could foster the nervous system's ability to reorganize neuronal activity and function, a process known as neuroplasticity, thereby enhancing cognitive learning (Kwan et al., 2021). Diminished activation of prefrontal areas is linked with greater neural efficiency, while reduced activation of frontoparietal areas suggests improved cognitive performance post-training (Schättin et al., 2016; Vermeij et al., 2017). In a similar vein, Park et al. (2020) asserted that cognitive-motor interventions stimulate brain neurotransmitters, particularly the cholinergic and dopaminergic systems, thereby bolstering concentration and memory in older adults (Hwang et al., 2021; Yang et al., 2022). The literature consistently highlights the impact of physical exercise on cognitive functions, particularly executive functions, due to the release of brain-derived neurotrophic factor and increased hippocampal blood flow, both of which result in favorable metabolic effects (Liao et al., 2020).

4.3. Implications for practice

Traditional cognitive tests, primarily pencil-and-paper based, have received criticism for their inherent limitations, including the omission of key factors such as an individual's education level (Kessels, 2019; Palacios-Navarro et al., 2022). However, the emergence of VR and ecological momentary assessments through wearable devices present innovative alternatives capable of enhancing precision and sensitivity in cognitive assessments (Chan et al., 2018; Hartle et al., 2021). These methods not only supplement traditional tests but also pave the way for a new direction in rehabilitation interventions. The landscape of cognitive treatment methodologies is evolving, with both traditional and VR-based techniques demonstrating efficacy. Both conventional cognitive

training programs and VR-based interventions have induced improvements in cognition and executive functions among older adults. Specifically, VR interventions shine in their capacity to simulate ADLs, thereby emerging as a promising tool for cognitive rehabilitation in early stage cognitive disorders (Wollesen et al., 2020; Matsangidou et al., 2023).

Immersive VR offers a stimulating and engaging experience for seniors, enhancing their motivation and enjoyment. Besides its adaptability and high level of automation, these features can alleviate the workload for caregivers and medical professionals (Bauer and Andringa, 2020). Immersive VR also fosters a sense of autonomy in older adults, which is vital for their emotional and cognitive wellbeing. The current review and recent studies suggest that older adults can tolerate and significantly benefit from immersive VR regarding cognitive and physical health (Yi et al., 2022; Matsangidou et al., 2023), as highlighted by Słyk et al. (2019) in their systematic review. However, it is of utmost importance to tailor these interventions to the individual needs and capabilities of participants, necessitating adjustments in task difficulty, session duration, and supervision during training.

Virtual reality, particularly when simulating iADLs, is carving a niche in cognitive-motor rehabilitation (Arlati et al., 2017). Such training programs are well received by patients and can be applied across various clinical environments, including community centers and senior care facilities (Kwan et al., 2021). Patient safety is paramount, requiring careful evaluation before inclusion in these programs and vigilant monitoring for symptoms of VR-induced dizziness post-training (Kwan et al., 2021). VR exhibits significant flexibility in its implementation, suitable for a range of clinical contexts from neurology clinics and rehabilitation centers to home care settings (McDaniel et al., 2014). Successful implementation, however, hinges on the availability of appropriate equipment and trained personnel. In conclusion, VR holds immense potential to revolutionize the treatment of cognitive disorders, offering a personalized and motivating approach to rehabilitation.

4.4. Future implications

When designing future studies that utilize iADL-m based VR interventions, it is imperative to consider the sociodemographic characteristics of participants. Factors such as age, education level, family history, and cognitive disorders should be accounted for, as these variables could potentially influence the results. Moreover, interventions need to be tailored to each participant's physical condition to avoid injury or loss of motivation. To this end, maintaining a heart rate between 50 and 75% of the maximum is suggested, which some may perceive as moderately intense. Notably, most participants in the reviewed studies were primary-educated women, highlighting the need to consider these variables when designing effective interventions for older adults.

The duration of interventions also requires careful consideration. The systematic review conducted by Kelly et al. (2014) evaluated training and cognitive stimulation in older adults and their influence on cognition and daily functioning. They identified that studies lasting at least 10 sessions and whose exercises are adapted to the conditions of the population using level advancements or hints have higher skill maintenance effects. It is important to consider that a high number of sessions could generate a repeated learning effect that promotes disinterest and unreliable results, as mentioned by Cooley et al. (2015). Furthermore, McDaniel et al. (2014) suggested that, although aerobic exercise can enhance certain tasks, repeating the same exercise for an extended period might decrease interest and motivation.

In terms of experimental design aimed at improving cognitive and physical health, the inclusion of an active control group is recommended for more accurate comparisons. It is also important for participants to follow similar training routines, either through comparable interactive applications or by conducting physical and cognitive exercises at home using accessible interactive headsets. Ensuring that the application is specially designed for the study population and adapts the difficulty levels to each individual's characteristics is crucial. Strategies such as incorporating clues or positive feedback in the systems, as suggested by Arlati et al. (2017), can help maintain participants' motivation. In the same vein, including distractors, like presenting several brands of the same product in a simulated supermarket task, can test the participants' concentration. However, it is essential to consistently use and position the same elements to prevent information bias (Arlati et al., 2017).

As mentioned by Wollesen et al. (2020), traditional interventions that combine cognitive and motor aspects, along with technology-based exercise games, have shown favorable impacts on general cognition and inhibitory capacity in older adults. However, due to the heterogeneity of studies concerning interventions, measurements, and results, caution is needed when interpreting these results. Future research may explore the benefits and challenges of a hybrid approach that combines "pencil and paper" activities with an exercise program, enhanced by interactive technology. Some proposals have suggested a training program that merges both real and virtual environments (Foloppe et al., 2018). This approach could potentially be replicated in a more diverse and representative sample. These integrated approaches have the potential to optimize cognitive and physical outcomes in older adults by leveraging the benefits of conventional therapies–which are accessible, affordable, easy to use, and clinically validated–and the personalization and motivation offered by interactive-based interventions.

By considering the unique needs and capabilities of older individuals, comprehensive interventions that combine physical and cognitive exercises can be developed. This holistic approach optimizes the potential for cognitive function improvement, promotes independence, and enhances older adults' overall quality of life. In particular, new technologies can supplement unsupervised home training methods, providing older individuals with a handy tool for conducting appropriate training sessions independently. By offering immersive and stimulating experiences, interactive technology can boost older adults' motivation and engagement, which may, in turn, positively impact their training outcomes and quality of life.

5. Conclusion

This review provides compelling evidence that iADL-based VR cognitive-motor interventions can notably enhance both

cognitive function and motor skills in individuals with Mild Cognitive Impairment (MCI) and dementia. These interventions hold significant promise, particularly in enhancing independence, functional ability in ADL, cognitive functions, and reducing frailty among older adults. Moreover, these VR-based interventions potentially offer a more engaging and motivational alternative to conventional therapies, which could improve treatment adherence and outcomes.

The literature suggests that the relationship between cognitive exercise and motor functions is bidirectional–cognitive training can positively impact motor performance, and conversely, motor training can have beneficial effects on cognitive function. Moreover, practicing specific activities can enhance coordination skills in dual tasks, contributing to the training of divided attention and cognitive flexibility. Thus, VR cognitive-motor interventions centered on iADLs can effectively aid in the transfer of acquired skills to the performance of daily activities. However, the choice of the appropriate intervention should be tailored to each individual, considering their needs, personal goals, and physical and motor conditions. Combining physical and cognitive training may yield slightly better results than training these areas separately. Nonetheless, further research is needed to deepen our understanding of how each training type affects different cognitive domains.

Author contributions

JB and GP-N contributed to conception, design of the study, and wrote the first draft of the manuscript. JB organized the database. Both authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Aging Neuroscience

TYPE Review
PUBLISHED 16 June 2023
DOI 10.3389/fnagi.2023.1209115

OPEN ACCESS

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RECEIVED 20 April 2023
ACCEPTED 31 May 2023
PUBLISHED 16 June 2023

CITATION
Liang T, Wu Z, Li J, Wu S, Shi W and Wang L (2023) The emerging double-edged sword role of exosomes in Alzheimer's disease. *Front. Aging Neurosci.* 15:1209115. doi: 10.3389/fnagi.2023.1209115

The emerging double-edged sword role of exosomes in Alzheimer's disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease characterized by progressive loss of memory and cognitive dysfunction. The primary pathological hallmarks of AD are senile plaques formed by deposition of amyloid β (Aβ) protein, intracellular neurofibrillary tangles resulting from hyperphosphorylation of microtubule-associated protein tau, and loss of neurons. At present, although the exact pathogenesis of AD is still unclear and there is a lack of effective treatment for AD in clinical practice, researchers have never stopped exploring the pathogenic mechanism of AD. In recent years, with the rise of the research of extracellular vesicles (EVs), people gradually realize that EVs also play important roles in neurodegenerative diseases. Exosomes, as a member of the small EVs, are regarded as carriers for information exchange and material transport between cells. Many cells of the central nervous system can release exosomes in both physiological and pathological conditions. Exosomes derived from damaged nerve cells can not only participate in Aβ production and oligomerization, but also disseminate the toxic proteins of Aβ and tau to neighboring neurons, thereby acting as "seeds" to amplify the toxic effects of misfolded proteins. Furthermore, exosomes may also be involved in the degradation and clearance process of Aβ. There is increasing evidence to suggest that exosomes play multiple roles in AD. Just like a double-edged sword, exosomes can participate in AD pathology in a direct or indirect way, causing neuronal loss, and can also participate in alleviating the pathological progression of AD. In this review, we summarize and discuss the current reported research findings on this double-edged role of exosomes in AD.

KEYWORDS

Alzheimer's disease, exosomes, pathogenesis, amyloid β, tau

1. Introduction

Alzheimer's disease (AD), also known as senile dementia, is one of the most prevalent central neurodegenerative diseases. AD mainly shows the gradual loss of self-care ability, progressive memory decline and behavioral cognitive impairment, accompanied by neuropsychiatric abnormalities, which seriously affect the quality of life of AD patients (Si et al., 2023). With the aging of the global population becoming increasingly prominent, the number of cases of AD is increasing year by year, which has become a major public health problem in front of us, and brought a heavy burden to individuals, society and families. Although the researchers have invested a great deal of financial resources and manpower to explore the pathogenesis of AD, it has not been fully elucidated, and to date, there is still no effective treatment available to stop the development of AD. Currently, with the rising and deepening of the research of extracellular vesicles (EVs), people have gradually realized that a kind of small EVs called exosomes to play a crucial role in AD pathogenic process (Gomes et al., 2022).

Exosomes are EVs with a phospholipid bilayer membrane structure. Exosomes can be released from most cell types and are widely present in biological fluids. Although exosomes containing specific cargoes are closely related to their parent cells of origin, they mainly include proteins, lipids, and nucleic acid molecules. Exosomes transport these cargoes from the donor cells to neighboring or more distant recipient cells, which can internalize exosomes from the extracellular space via several mechanisms including phagocytosis, pinocytosis, endocytosis or plasma membrane fusion (Zhang et al., 2021). In addition, exosomes are considered as a carrier tool that can move dynamically between cells and play an important role in material transfer and information exchange. Studies have shown that many cells in the central nervous system, including neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells, can release exosomes and play both beneficial and pathogenic roles in physiological and pathological conditions (Kanninen et al., 2016). It has been recognized that the two typical pathological features of AD are senile plaques formed by the deposition of extracellular amyloid β (Aβ) protein and intracellular neurofibrillary tangles formed by the hyperphosphorylation of microtubule-related protein tau (d'Errico and Meyer-Luehmann, 2020). There is increasing experimental evidence showing that exosomes play indispensable roles in the formation and dissemination of these two major pathological hallmarks (Soliman et al., 2021). More importantly, studies have found that exosomes can play a double-edged role in AD. On the one hand, exosomes derived from damaged nerve cells can transfer amyloid precursor protein (APP), γ/β-secretase, Aβ peptide, C-terminal APP and tau protein to adjacent healthy neurons to accelerate the death of peripheral neurons, thus leading to the spread of pathological features of AD (Perez-Gonzalez et al., 2012; Sardar Sinha et al., 2018). On the other hand, exosomes also have a positive role in promoting Aβ clearance. For example, neuron-derived exosomes (NDEs) can transport Aβ to the lysosomes of microglia and degrade in the lysosomes (Yuyama et al., 2012). In short, the roles of exosomes have been attracted much attention in AD. Many previous reviews have mainly illustrated the clinical value of exosomes in serum, plasma, urine or cerebrospinal fluid as a diagnostic tool in the early diagnosis of AD. However, the main focus of our study is to summarize the multiple roles of exosomes in the production, transport, dissemination and clearance of AD toxic proteins in order to provide new ideas for the pathogenesis, targeted therapy and early diagnosis of AD.

2. Biological characteristics of exosomes

Exosomes are small EVs with a diameter of 30-150nm. They can be widely isolated from a variety of body fluids, such as blood, cerebrospinal fluid, saliva, thoracic and abdominal fluids, urine, semen, breast milk, etc (DeLeo and Ikezu, 2018; Pascual et al., 2020). Exosome membranes are mainly composed of phospholipids and proteins. The surface of exosomes contains specific marker molecules (CD9, CD63, CD81, CD82, adhesion proteins, integrins, glycoproteins, etc.), and exosomes can pack a wide variety of cargoes, including but not limited to nucleic acids (microRNAs, mRNA, DNA, ribosomal RNA, long non-coding RNAs, etc.), proteins (Alix, tumor susceptibility gene 101 protein, heat shock proteins, lipid-associated proteins, cytoskeletal proteins, etc.) and lipids (lipid raft-associated lipids, ceramides, sphingolipids, phospholipids, glycerol phospholipids, etc.) (Song et al., 2020; **Figure 1**). Although the cargoes in exosomes are similar to some extent, they also have some cell specificity, which is related to the specific substances contained in the parent cells of their origins and the physiological or pathological conditions of exosome production. Additionally, exosome cargoes can change under different stimulus factors, and can be detected by proteomics technology, lipidomics technology, nucleic acid sequencing and digital PCR (Kanninen et al., 2016).

In view of the biological characteristics of exosomes, the value of exosomes as biomarkers to distinguish healthy and disease states has attracted more and more attention. As a tool for disease diagnosis, exosomes have many unique advantages. Firstly, exosomes can be extracted from majority of body fluids in a convenient and non-invasive way, thus avoiding the damage to the organism caused by sampling. Secondly, exosomes are rich in cargoes, and their membrane structure can protect the cargoes from degradation by external factors, thereby maintaining their integrity and biological activity. Moreover, the exosome cargoes vary with the disease state and are closely related to the process of disease. Remarkably, exosomes can appear in peripheral blood by crossing the blood-brain barrier via bilayer lipid structure. Considering the prevalence of blood samples, researchers pay more attention to search for disease-specific biomarkers from blood exosomes. However, due to the widespread and complex sources of blood exosomes, the extracted total exosomes can not accurately reflect the disease status of the nervous system, and brain-derived exosomes (BDEs) need to be further isolated from blood exosomes.

3. Brain-derived exosomes

BDEs are a group of exosomes secreted by central nervous system cells, including neuron-derived exosomes (NDEs) and astrocyte-derived exosomes (ADEs). By detecting the changes of BDEs contents, the intrinsic pathological changes of brain

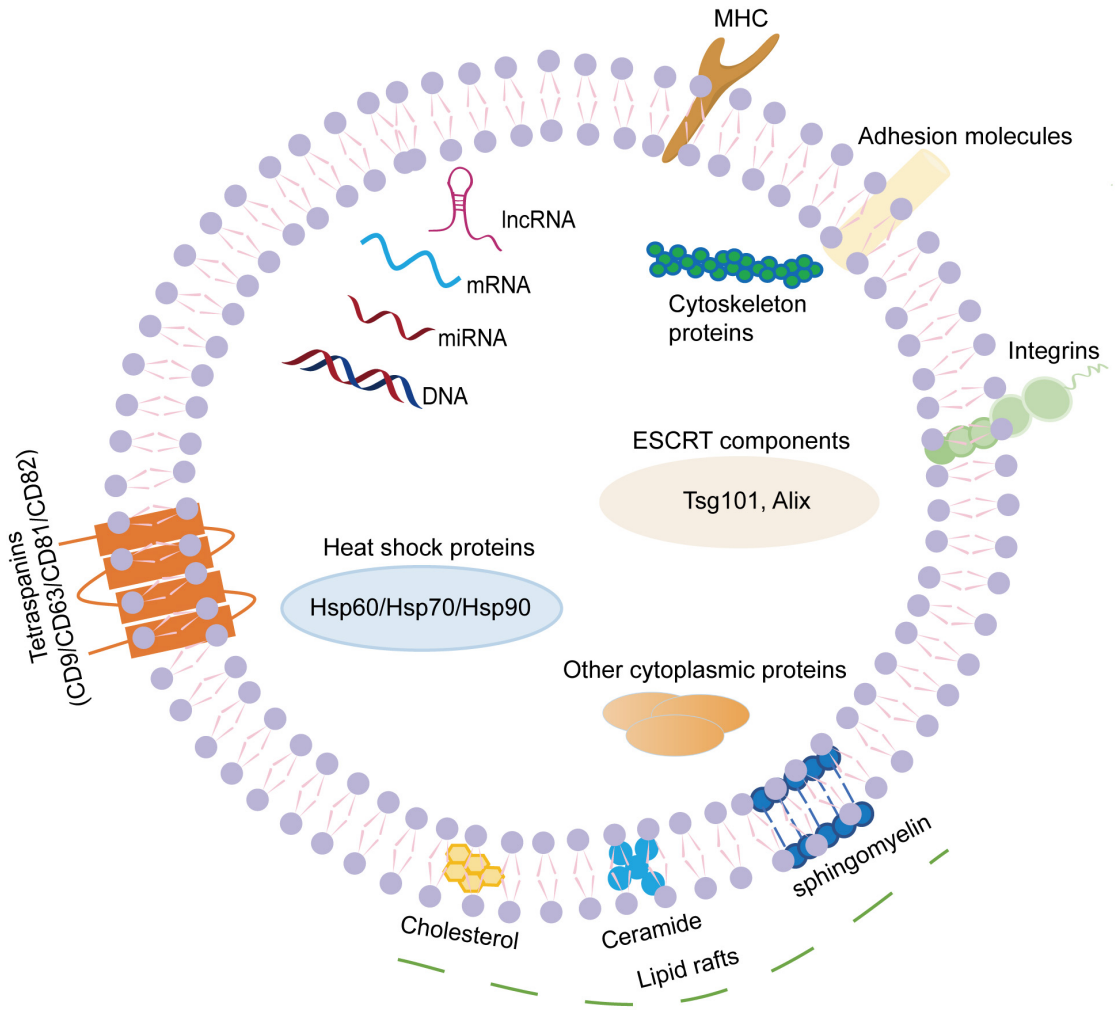

FIGURE 1
The composition of exosomes. Exosomes are small extracellular vesicles with a diameter of 30–150 nm. The exosome membranes are mainly decorated with various lipids and proteins. The lipids mainly present in the lipid raft regions, including ceramide, cholesterol, sphingomyelin, phospholipids, glycerol phospholipids, etc. The surface of exosome contains specific transmembrane molecules (CD9, CD63, CD81, and CD82), adhesion proteins, integrins, MHC, etc. In addition, exosomes can pack a wide variety of cargoes, including nucleic acids (miRNAs, mRNA, DNA, lnc RNA, etc.), proteins (Alix, TSG101, heat shock proteins, cytoskeletal proteins, etc.). MHC, major histocompatibility complex; mRNA, messenger RNA; miRNA, microRNA; lnc RNA, long non-coding RNA; TSG101, tumor susceptibility gene 101.

can be indirectly reflected. This is not only to better explore the pathogenesis of exosomes in AD, but also to provide a minimally invasive method for the early diagnosis of AD, which is considered as a form of "liquid biopsy" (Li et al., 2019). A precipitate/immunoaffinity system has been developed at an earlier stage for the isolation of NDEs from peripheral blood. NDEs were first described in 2015. After extracting total plasma exosomes using ExoQuick exosome precipitation solution, NDEs are further isolated using antibodies against neuronal cell adhesion molecules (Fiandaca et al., 2015). Neuronal L1 cell adhesion molecule (L1CAM) or neural cell adhesion molecule (NCAM) can be used as a biomarker for isolating BDEs. This BDEs isolation technique has also been verified and used in other study (Goetzl et al., 2016a). In the same year, their experimental team took a similar approach with antibodies against glutamine aspartic acid transporters to enrich ADEs in peripheral blood (Goetzl et al., 2016b). The above innovative isolation methods of BDEs subsets have greatly triggered a research upsurge in the pathogenesis and biomarkers of central nervous system diseases. Subsequently, due to the development of experimental techniques, some other BDEs capture techniques have been gradually developed. For instance, a two-step immunocapture technique using immunomagnetic beads is established to isolate specific NCAM/amphiphysin 1 or NCAM/ATP-binding cassette transporter A1 (ABCA1) NDEs from total plasma exosomes (Li et al., 2022a,b). At present, most research strategies are to use L1CAM or NCAM antibody combined with magnetic beads to capture NDEs. Although earlier literatures have shown that L1CAM is an exosome surface marker molecule specifically derived from neurons (Fauré et al., 2006), there are some other studies have suggested that L1CAM is not only expressed in neurons, but also in other peripheral tissue cells (Fowler, 2019). Surprisingly, L1CAM has a soluble variant, which can exist in a free form in body fluids (Angiolini et al., 2019). A more recently reported study indicates that L1CAM mainly exists

in the form of free protein in cerebrospinal fluid and plasma, and it may not be an ideal biomarker of NDEs (Norman et al., 2021). Thus, the extraction purity of NDEs or ADEs is crucial for the subsequent experimental results. This requires better isolation and purification techniques and further needs to discover higher specificity of BDEs marker molecules.

4. Exosomes: a double-edged sword in Alzheimer's disease

Although the understanding of exosome function in AD has not been fully elucidated, with the deepening and extensive research, increasing evidence supports that exosomes play multiple roles in AD. Just like a double-edged sword, exosomes can not only participate in the pathological process of AD in a direct or indirect way, causing neuronal loss, but also help in alleviating the progression of AD pathology. Based on the current research literature, we speculate that exosomes may be involved in the pathogenesis of AD in several ways. One way is that exosomes involve in the formation, oligomerization, plaque formation and clearance of Aβ. Another way is that exosomes can act as constantly moving carriers to transport toxic cargoes (such as Aβ, tau, inflammatory molecules, etc.) or beneficial cargoes (such as enkephalins, insulin-degrading enzymes, etc.) in the brain at short or long distances. Its dissemination mechanism is similar to that of prions. Additionally, both neurons and glial cells can release and take up exosomes. As a carrier of cell-to-cell communication, exosomes can mediate the interregulation between neurons and glial cells, thus participating in the development process of AD (**Figure 2**).

4.1. The pathogenic role of exosomes in AD

4.1.1. Exosomes and Aβ

4.1.1.1. Exosomes participate in the APP metabolic process

Aβ is a product of the sequential cleavage of the transmembrane APP by β- and γ-secretase. Normally, intracellular Aβ can be degraded through the endosomal-lysosomal pathway. However, once the impairment of this pathway (especially the dysfunction of key molecules involved in the Aβ degradation process, such as metalloproteinase endothelin-converting enzyme), it can lead to the intracellular accumulation of Aβ, thereby making it easier for Aβ and APP metabolites to be encapsulated in exosomes and released into the extracellular space via exosomes (Pacheco-Quinto et al., 2019). Many earlier reports have described the presence of APP-associated proteins and their metabolites during Aβ production in exosomes of AD cell models and AD patients. Rajendran et al. first reported the existence of APP in exosomes, and the cleavage of β-secretase occurs in the early endosome. A minute fraction of Aβ can be secreted from the cells in association with exosomes and released from APP-transfected cells into the culture medium. Furthermore, they found that the brain slices of all AD patients show the enrichment of exosome marker Alix around small neuritic plaques, thus confirming the accumulation of exosomes around the amyloid plaques (Rajendran et al., 2006). Subsequently, Vingtdeux et al. also observed the presence of APP-related metabolites APP-carboxyl-terminal fragments (CTFs) and amyloid intracellular domains (AICDs) in multivesicular bodies (MVBs) of differentiated neuroblastoma cells transfused with human APP. Their data showed that MVBs are essential organelles for APP metabolism, and all APP metabolites can be secreted into the extracellular space (Vingtdeux et al., 2007). More importantly, several key members of the secretase family of proteases (β-site APP cleaving enzyme 1, presenilin 1, presenilin 2, and disintegrin and metalloprotease 10) can also be localized in exosomes (Sharples et al., 2008). APP-related metabolites in NDEs are also toxic and exhibit similar pathological features of AD in healthy neurons. Zheng et al. injected exosomes harvested from the conditioned medium of HEK293-APP Swe/Ind cells into the hippocampal dentate gyrus via a stereotactic approach. They found that exosomes containing pathogenic proteins (full-length APP and APP metabolites) showed higher neurotoxicity and could impair neurogenesis in the hippocampus (Zheng et al., 2017a). In conclusion, considering the process of exosome formation, combined with the metabolic site and process of APP, it is not surprising that these endosome-associated protein products can be detected in neuronal exosomes under the pathological conditions of AD (**Figure 2A**).

In addition to the direct involvement of exosomes in APP metabolism through the above-mentioned ways, exosomes can also participate in indirect ways. A recent study reported a novel mechanism to regulate APP expression in different cells via the exosome-mediated miR-185-5p delivery. Exosomes isolated from AD mouse brains and APP-overexpressed N2a cell cultures significantly increased APP expression levels in recipient cells. Surprisingly, the effects of exosomes on APP expression in recipient cells are not mediated by the direct transferring of APP gene products. Instead, it is mediated by the reduction of the expression levels of miR-185-5p in exosomes (Ding et al., 2022). This indirect regulation has increased the complexity of exosomes involved in APP metabolism, which still needs more evidence to confirm.

4.1.1.2. Exosomes promote Aβ aggregation and plaque formation

Emerging evidence suggests that exosomes can promote Aβ aggregation and then accelerate the formation of amyloid plaques. The correlation between exosomes and Aβ fibrosis is first reported in the study of Yuyama et al. In their study, they found that the assembly of Aβ is markedly accelerated when incubates with exosome portions prepared from the culture medium of PC12 cells treated with chloroquine and KCl. The formation of extracellular amyloid fibers is associated with GM1 gangliosides on exosomes, which is blocked by antibodies that recognize the GM1-Aβ complex (Yuyama et al., 2008). Moreover, it was Yuyama and his colleagues who revealed that exosomes isolated from both N2a and primary neurons promote fibrillization of Aβ40 and Aβ42 with Aβ42 aggregation occurring more rapidly. Using cholera toxin B subunit blocking of ganglioside GM1 and endoglycoceramidase-treated glycosylysis *in vitro* cell experiments, they demonstrated that glycosphingolipids (GSLs) glycochains on the surface of exosomes play an important role in inducing the Aβ fibril formation (Yuyama et al., 2012). GSLs are a group of glycochain membrane lipids that are localized on the outer

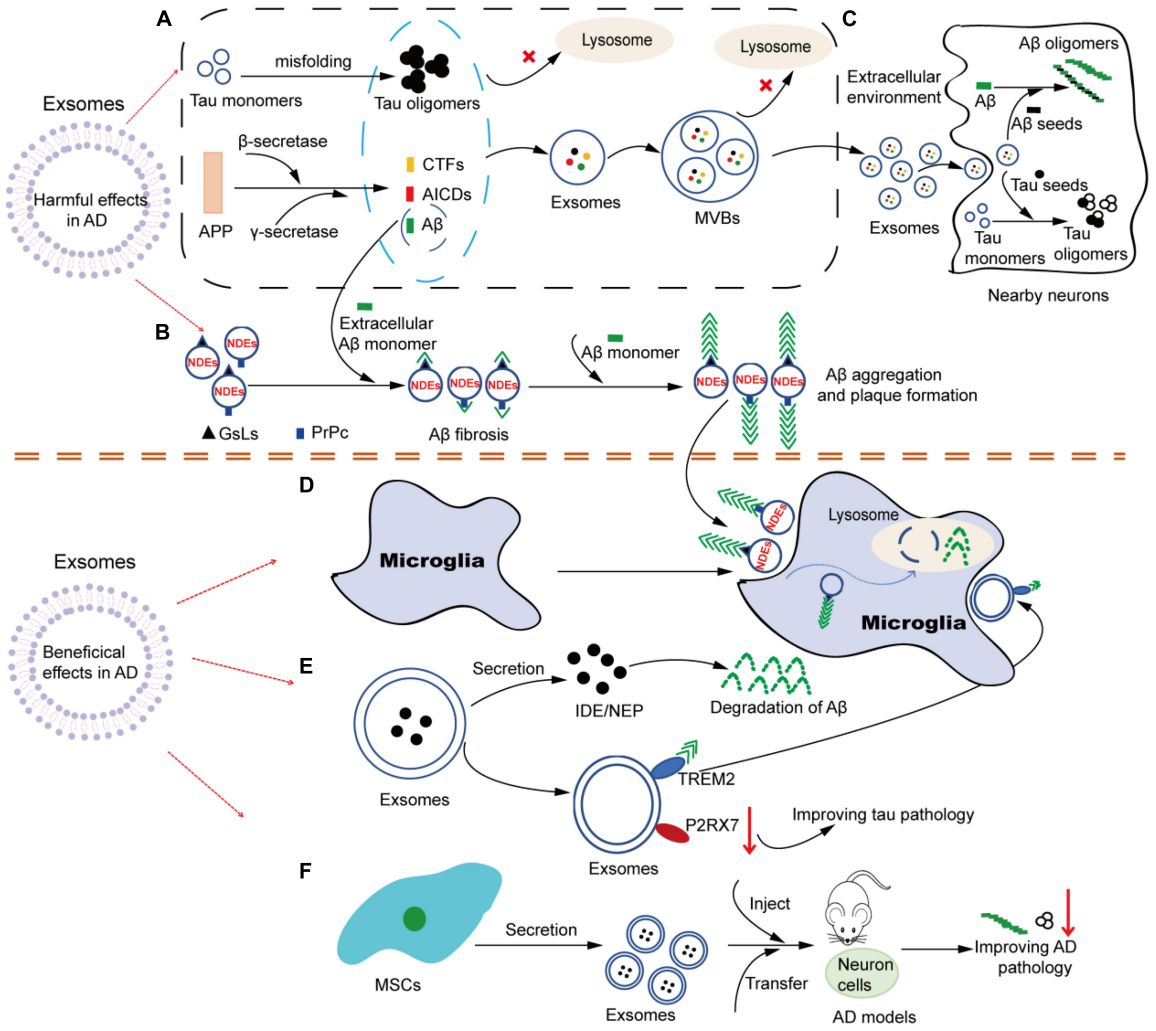

FIGURE 2
The multiple roles of exosomes in AD. **(A)** Tau and APP-related metabolites accumulate intracellular and are encapsulated into exosomes. Under pathological conditions, soluble Tau monomers can be misfolded into Tau oligomers after hyperphosphorylation in neurons. In addition, APP can be continuously cleaved by β-secretase and γ-secretase to produce APP-related products such as CTFs, Aβ and AICDs. When lysosome function is impaired, these Tau and APP-related metabolites accumulate in the cytoplasm and are easily encapsulated in exosomes. Similarly, due to dysdegradation of Tau- and Aβ-containing exosomes in lysosomes, exosomes in MVBs are filled with Tau- and APP-related products, which are released into the extracellular environment as exosomes are transported. **(B)** NDEs are involved in the oligomerization of Aβ. The surface of NDEs is enriched with GSLs and PrPC, and both GSLs and PrPC can bind to Aβ, thereby mediating the involvement of exosomes in the fibrosis and oligomerization of Aβ. Therefore, NDEs can capture Aβ via GSLs and PrPC in a single or synergistic manner, thus accelerating Aβ aggregation and amyloid plaque formation. **(C)** Exosomes in Tau and Aβ spread. Exosomes containing Tau-and APP-related metabolites released into the extracellular environment can be used as pathologic seeds to be captured by adjacent neuronal receptor cells and participate in Tau and Aβ oligomerization in the recipient cells. Similarly, infected recipient cells can further spread the pathology to other previously unaffected cells, causing the proliferation of pathological proteins from cell to cell. **(D)** Microglia are involved in NDEs-dependent Aβ clearance. NDEs-dependent Aβ oligomers can be captured by microglia and degraded in lysosomes. **(E)** Exosomes may be involved in the improvement of Aβ and Tau pathological features through the release of contents (IDE, NEP, etc.) or specific molecules on the surface (TREM2, P2RX7, etc.). **(F)** Exosomes from different sources of MSCs can be used in AD models, showing therapeutic value and alleviating AD pathology. AD, Alzheimer's disease; APP, amyloid precursor protein; CTFs, carboxyl-terminal fragments; AICDs, amyloid intracellular domains; Aβ, amyloid β; MVBs, multivesicular bodies; NDEs, neuron-derived exosomes; GSLs, glycosphingolipids; PrPC, cellular prion protein; IDE, insulin degrading enzyme; NEP, neprilysin; TREM2, triggering receptor expressed on myeloid cells-2; P2RX7, P2X purinoceptor 7; MSCs, mesenchymal stem cells.

layer of cells and exosomal membranes, and their glycans are exposed to the external environment. GSLs laterally traverse the cell membrane and form clusters at high densities, which monomeric Aβ is able to recognize and bind (Yuyama and Igarashi, 2022). Many studies have documented that the rich lipid rafts in GSLs (including GM1 ganglioside) can bind to Aβ and promote its aggregation (Ariga et al., 2001; Hayashi et al., 2004). Exosomes, especially NDEs, enrich GSLs. Therefore, it is speculated that exosomes may indeed act as seeds for Aβ aggregation and plaque formation.

In addition to GSLs, cellular prion protein (PrP(C)) is also highly enriched in exosomes. PrP(C) is a glycosylphosphatidylinositol-anchored surface glycoprotein that is localized on the outer leaflet of the membranes of neurons and exosomes. Studies have proved that exosomes can also bind to Aβ via PrP(C), which has the highest binding affinity for dimeric,

pentameric and oligomeric Aβ species, and accelerates the fibrosis of Aβ, thereby reducing the neurotoxic effects of oligomeric Aβ (Falker et al., 2016). Taken together, these findings suggest that NDEs can capture Aβ via GSLs and PrP(C) in a single or synergistic manner, thus accelerating Aβ aggregation and amyloid plaque formation (**Figure 2B**).

4.1.1.3. Exosomes contribute to the spread of Aβ

On the one hand, NDEs, as described above, carry proteins associated with the Aβ generation pathway, such as APP, β-site APP cleaving enzyme 1, γ-secretase and their pyrolysis products β soluble APP, α soluble APP, CTFs and Aβ (Goetzl et al., 2016b). On the other hand, exosomes isolated from the brains of APP transgenic mice show higher levels of flAPP and APP CTFs than those of wild-type mice, suggesting that APP-related metabolites can accumulate in exosomes under the pathogenic conditions of AD, thus contributing to the spread of amyloid protein between cells (Perez-Gonzalez et al., 2012). The above two factors provide some theoretical basis for the pathological propagation of exosomes involved in AD. Accumulating evidence that Aβ can be transmitted in the brain from the source cells to the recipient cells by means of exosomes as vectors, in a way similar to prion diseases (**Figure 2C**). Research by Sinha et al. showed that exosomes can mediate the pathologic proliferation of Aβ between cells for the first time. NDEs have been demonstrated to mediate Aβ oligomers (oAβ) diffusion between neurons by co-localization of oAβ with exosomes in cells. Most importantly, exosomes carrying oAβ can be internalized in cultured neurons and spread their toxic contents to nearby cells. Blocking exosome formation, secretion, or uptake has been found to reduce oAβ diffusion and associated toxicity (Sardar Sinha et al., 2018). Besides, exosomes isolated from the cerebrospinal fluid and plasma of AD patients, or from the medium of neural cells expressing AD presenilin 1 mutations may mediate transcellular spread of pathogenic Aβ species, disrupt neuronal Ca^{2+} homeostasis, impair mitochondrial function, and induce neuronal apoptosis (Eitan et al., 2016). Another more convincing study is that Zheng et al. injected exosomes isolated from peripheral plasma into the hippocampus of AD mouse models in order to investigate the diffusion process of exosomes, and observed that exosomes can spread from the dentate gyrus to other regions of the hippocampus and cortex, and to the entire brain (Zheng et al., 2017b). Another study showed that exosomes harvested from the conditioned medium of HEK293-APP Swe/Ind cells contain APP and are able to efficiently transfer APP to normal nerve cells, which also provides evidence for direct intercellular diffusion of amyloid proteins via exosomes (Zheng et al., 2018).

4.1.2. Exosomes and tau pathology

It is known that intracellular neurofibrillary tangles formed by hyperphosphorylated tau protein are one of the typical pathological features of AD, and the pathological proliferation of tau is also a hallmark of AD. Although the toxic effects of tau occur primarily inside the cell, tau can be released into the extracellular space as a "seed". The tau "seeds" can be taken up by other healthy recipient cells and transferred from one cell to another (**Figure 2C**). Hence, tau pathology is spread through different regions of the brain in a manner similar to prions. This proliferative effect significantly promotes the pathological process of tau. However, in earlier times, investigators believe that tau is passively released into the extracellular space only through cell death, and then these membrane-free tau "seeds" spread to neighboring nerve cells (Gómez-Ramos et al., 2006). On the contrary, in recent years, with the discovery of EVs, people gradually realize that exosomes can also serve as an important vehicle to actively secrete tau "seeds" into the extracellular environment. Recently, the role of exosomes in the spread of tau pathology has gradually become one of the hot issues concerned by many researchers.

Tau oligomers first pass through the endoplasmic reticulum and Golgi apparatus, then become part of vesicles and subsequently enter exosomes. Under physiological conditions, exosomes containing tau are degraded by lysosomes. However, once the lysosome is damaged, it contributes to tau accumulation in exosomes. Earlier studies have reported that some forms of tau exist in the EVs (Dujardin et al., 2014), and these EVs isolated from neuronal culture can induce abnormal tau phosphorylation in the brain of wild-type mice, showing significant neurotoxic effects (Aulston et al., 2019). Moreover, another study revealed that most of the intracellular tau is full-length, while the bulk of the extracellular tau is free-floating, unaggregated and C-terminal truncated, lacking the microtubule binding regions necessary for aggregation. Only a small number of tau is encapsulated in exosomes (Kanmert et al., 2015). These tau proteins packed in exosomes contain the microtubule binding regions and have the ability to aggregate. Furthermore, it has been confirmed that there are small amounts of full-length tau in neuronal exosomes (Guix et al., 2018). In summary, the detailed mechanisms of tau encapsulated in exosomes still need further study.

Evidence from some studies illustrates that tau aggregates can spread and replicate in the brain in a prion-like manner via exosomes. Tau oligomers delivered by exosomes may act as "seeds", and the uptake of pathological tau "seeds" leads to tau misfolding into a toxic conformation in recipient cells (Jackson et al., 2022). Exosomes isolated from the brains of tau transgenic rTg4510 mice carry a large number of tau "seeds", thereby inducing endogenous tau aggregation in the recipient cells and increasing tau phosphorylation and oligomer formation. This evidence confirms that EVs are the carriers of tau pathology (Baker et al., 2016; Polanco et al., 2016). Many *in vivo* experiments have demonstrated that tau-containing neuronal exosomes from AD patients can induce the formation of neurofibrillary tangles (NFT) in rodents, exhibit tau neurotoxic effects, and thus reproduce the disease characteristics triggered by the original exosome contents. Winston et al. found that NDEs extracted from the plasma of patients with mild cognitive impairment and AD are able to seed p-tau pathology and induce AD-like neuropathology in the brains of normal mice (Winston et al., 2016). In addition, another study has shown that neuronal exosomes derived from human tau have toxic effects on recipient mouse neurons *in vivo* and cause long-distance propagation of tau pathology and neurodegeneration (Winston et al., 2019). A similar phenomenon has also been observed in the study of Reilly et al. (2017). Surprisingly, further research by Polanco et al. showed that a simple neuronal circuit model was built to observe the diffusion of exosomes in the interconnected neurons using a microfluidic culture system. The findings suggest that exosomes can spread the tau protein over long distances through a novel hijacking mechanism of endosomes, thereby increasing the pathogenic potential and radius of action of the exosomes (Polanco et al., 2018). In a recent study, to reveal

how tau seeds contained within internalized exosomes exploit mechanisms of lysosomal degradation to escape the endosome and induce tau aggregation in the cytoplasm, their research team also found that the enzymatic activities of lysosomes can penetrate the exosomal and endosomal membranes, thereby promoting the entry of exosomal tau seeds into the cytoplasm and inducing its aggregation (Polanco et al., 2021). In earlier studies on the relationship between exosomes and tau, several studies described that the spread of tau pathology is achieved by the direct transmission of exosomes across synapses between interconnected neurons, and the depolarization of neurons faciliates the release of tau-containing exosomes (Wang et al., 2017). Recent literatures have also reported that only exosomes and vesicle-free tau seeds are shown to propagate across synapses along neural networks (Polanco and Götz, 2022). Most of the exosomal tau released from AD synapses is C-terminal-truncated and oligomeric, and with seeding activity that is enhanced by Aβ (Miyoshi et al., 2021). These results also support the ideas that Aβ-induced pathology may directly or indirectly drive tau-mediated neurotoxicity and NFT formation (Blurton-Jones and Laferla, 2006).

It is becoming increasingly clear that microglia may play a critical role in the interneuronal transmission of tau pathology promoted by exosomes. It has been shown that microglia can spread tauopathy by internalization and secretion of exosomes. Microglia propagates tau pathology via secretion of tau-containing exosomes. The depletion of microglia or the inhibition of exosome synthesis significantly reduces tau propagation *in vitro* and *in vivo*. Surprisingly, tau propagation mediated by microglia can occur not only through trans-synaptic transmission, but also in non-trans-synaptic pathways (Asai et al., 2015). Most importantly, several reports have illustrated that some genes closely related to the risk of AD morbidity can interfere with the spread of tau pathology by influencing the production of exosomes in microglia. Bridging integrator 1 is a gene associated with late-onset AD. Overexpression of bridging integrator 1 promotes the release of tau-enriched EVs from microglia, and contributes to exacerbate tau pathology in P301S tau transgenic PS19 mice, thus promoting the spread of AD-related tau pathology (Crotti et al., 2019). Triggering receptor expressed on myeloid cells 2 (TREM2) is a transmembrane protein produced by microglia in the brain. Variations in TREM2 have been shown to increase the risk of late-onset AD (Ulland and Colonna, 2018). It has been demonstrated that Trem2 deletion can enhance the transport, distribution and seeding of tau by microglial exosomes (Zhu et al., 2022).

4.1.3. Exosomes and inflammation

Increased research has focused on exosomes as important communication mediators between neurons and glial cells. Exosomes induce neuroinflammation by acting as inflammatory mediators via carrying inflammation-causing cargoes (Weng et al., 2022). The accumulation of Aβ and hyperphosphorylation of tau have been shown to continuously activate microglia and astrocytes, and promote inflammatory responses (Novoa et al., 2022). Aβ or tau can be effectively encapsulated in exosomes, and activated glial cells or neuronal cells can release exosomes into the extracellular space, thus amplifying the neuroinflammatory effects caused by toxic proteins (Gupta and Pulliam, 2014). Additionally, microRNAs, as an important nucleic acid cargo in exosomes, have been found to be involved in the induction of neuroinflammation. It has been reported that NDEs containing miR-21-5p can be phagocytosed by microglia and induce microglia M1 polarization, which leads to increased release of neuroinflammatory factors, inhibition of neurite outgrowth, increased accumulation of P-tau, and increased the apoptosis of PC12 cells (Yin et al., 2020). Another study from Wei et al. has shown that miR-182-5p delivered by plasma exosomes can target brain-derived neurotrophic factor (BDNF) and activate the nuclear transcription factor-κB pathway, thereby promoting sevoflurane-induced neuroinflammation and cognitive dysfunction in aged postoperative cognitive dysfunction rats (Wei et al., 2022). In addition to enhancing and spreading inflammation in the extracellular microenvironment, exosomes can also play an anti-inflammatory role. Recent studies have reported the anti-inflammatory therapeutic value of exosomes due to their excellent properties, such as carrier transport, ease of modification and encapsulation of therapeutic agents. Related studies have also demonstrated that the activation of nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) inflammasome is closely associated with the occurrence of AD (Liang et al., 2022). By blocking the assembly of NLRP3 inflammasome, the exosome-like nanoparticles from ginger rhizomes strongly inhibit the downstream pathways of NLRP3 inflammasome activation, including caspase1 autocleavage, interleukin 1β and interleukin 18 secretion, and pyroptotic cell death (Chen et al., 2019). Under some specific conditions, exosomes released from microglia can also exert an anti-inflammatory role. For instance, the increased miR-124-3p in microglial exosomes promotes the anti-inflammatory M2 polarization of microglia, inhibits neuronal inflammation, and transfers into neurons to promote neurite outgrowth during traumatic brain injury (Huang et al., 2018). Taken together, whether exosomes promote or inhibit the inflammatory response may be related to the different stimulants and the cell types that produce exosomes, and further research is needed to explore the potential mechanism.

4.2. The protective role of exosomes in AD

4.2.1. NDEs contribute to the Aβ clearance process mediated by glial cells

In contrast, while accumulated evidence has demonstrated that NDEs can be involved in the formation and spreading of the pathological features of AD, some studies have confirmed that NDEs also exert a protective role in the progression of AD. Therefore, NDEs play a dual role. Growing evidence indicates that NDEs and glial cell-derived exosomes may participate in Aβ clearance through independent or synergistic action and transfer neuroprotective substances between cells to alleviate the nervous system injury (**Figure 2D**). Earlier studies have shown that exosomes released from neuroblastoma N2a can capture and bind to Aβ via GSLs on their surface and be transported into microglia for degradation. Moreover, *in vivo* studies further provide evidence that the infusion of NDEs into the brains of APP mice can reduce Aβ levels and ameliorate Aβ-related pathologies (Yuyama et al., 2014). The next year, further research demonstrated that neuronal exosomes, but not glial exosomes, have abundant GSLs

and can capture Aβ. Infusion of neuronal exosomes into the brains of APP transgenic mice can reduce Aβ and amyloid deposition, and these findings highlight the role of neuronal exosomes capable of capturing Aβ as messengers for Aβ clearance (Yuyama et al., 2015). All the above evidence have clearly demonstrated that intracerebral NDEs administration can improve the Aβ-related pathogenesis, which may provide a new direction for the treatment of AD. Furthermore, Yuyama et al. investigated that NDEs can drive the conformational changes of Aβ through GSLs on their surface. The changes in Aβ conformation can serve as seed on which other Aβ combines to form Aβ oligomers, and then form amyloid fibrinates. The Aβ-bound exosomes are endocytosed into endosomal-lysosomal system by microglia in a phosphatidylserine-dependent manner and promote the degradation of Aβ. Moreover, Yuyama et al. further demonstrated that the secretion of NDEs is modulated by the activity of sphingomyelin metabolic enzymes, including nSMase2 and sphingomyelin synthase 2. Inhibition of nSMase2 prevents exosome production, while inhibition of sphingomyelin synthase 2 promotes exosome release (Yuyama and Igarashi, 2022). In the co-culture experiment of N2a cells transfected with human APP and microglia cells, inhibition of sphingomyelin synthase 2 activity to improve the secretion of neurons' exosomes can enhance the uptake of Aβ by microglia cells, and significantly decrease the level of extracellular Aβ (Yuyama et al., 2012). However, contrary to the results of this study, Dinkins et al. revealed that ADEs can also promote Aβ accumulation, but interfere with the uptake of Aβ by glial cells, thus promoting the formation of plaques *in vivo*. Inhibition of SMase2 activity by GW4869 or 5 × FAD mouse model targeted at nSMase2 gene deletion blocks exosome synthesis *in vivo* and *in vitro*, decreases the levels of Aβ1-42, alleviates amyloid plaque load in the brain of mice, and improves the cognitive deficits (Dinkins et al., 2014, 2016). These results suggest that neurons and astrocyte-derived exosomes may differ in glial Aβ clearance, but the underlying mechanisms remain unclear.

4.2.2. Microglia-derived exosomes are involved in the remission of AD pathology

The evidence suggests that microglia and microglia-derived exosomes also play active roles in the mechanisms of Aβ clearance or tau pathologic protection. Earlier researches have shown that microglia exosomes contribute to the secretion of insulin degrading enzyme, which is an important enzyme for the extracellular degradation of Aβ (Tamboli et al., 2010). According to a recent study, triggering receptor expressed on myeloid cells-2 (TREM2), expressed on the membrane of microglia exosomes, can mediate the secretion of exosomes. Free microglia exosomes can bind to Aβ through TREM2, releasing chemokines to alter the inflammatory levels surrounding Aβ and promote the recognition and phagocytosis of Aβ by microglia cells (Huang et al., 2022). In addition to its roles in Aβ clearance, TREM2 can also affect tau pathology. Trem2 deletion, as previously described, can enhance tau trafficking, distribution, and pathological spread through microglia exosomes (Jain and Ulrich, 2022; Zhu et al., 2022). Conversely, upregulation of TREM2 in microglia inhibits the inflammatory response and ameliorates the pathological effects of activated microglia on neuronal tau hyperphosphorylation (Jiang et al., 2018). These evidence confirm that TREM2 can be involved in protecting tau pathology via microglia exosomes. P2X purinoceptor 7 (P2RX7) is an ATP-gated cationic channel, and its enrichment in microglia promotes exosome secretion. Administration of the P2RX7-specific inhibitor GSK1482160 to P301S tau mice significantly reduces the number of exosomes and accumulation of tau in the hippocampus, thereby improving working and contextual memory of model mice (Ruan et al., 2020). Inhibition of P2RX7 to down-regulate exosome expression can also be regarded as a novel pathway to improve tau pathology (**Figure 2E**).

4.2.3. The therapeutic role of stem cell-derived exosomes in AD

It is necessary to take into consideration that recent studies have focused on the therapeutic effects of exosomes in AD, which further demonstrates the beneficial effects of exosomes. In this review, the therapeutic values of exosomes from different sources in AD are summarized in **Table 1**. However, it should be noted that exosomes that play protective roles in these studies are mainly from healthy cells. At present, numerous reports have described that stem cell-derived exosomes may play a positive role in alleviating the pathological features of AD (**Figure 2F**). Research by Lee et al. showed that exosomes secreted by adipose-derived stem cells reduce β-amyloidosis and neuronal apoptosis in AD transgenic mouse models and enhance the axon growth in the brain of AD patients (Lee et al., 2018). Further study indicates that mesenchymal stem cell (MSC)-derived exosomes can also significantly improve the pathological and cognitive deficits of AD (Chen et al., 2021). Exosomes derived from bone-MSCs alleviate cognitive decline in AD-like mice by improving BDNF-associated neuropathology (Liu et al., 2022). In addition, double transgenic APP/PS1 mice injected with bone-MSCs can activate the sphingosine kinase-1/sphingosine-1-phosphate signaling pathway to reduce Aβ deposition and promote cognitive function recovery in AD mice (Wang and Yang, 2021). Exosomes isolated from human umbilical cord MSCs (hucMSCs) have been shown to have therapeutic effects in many inflammation-related diseases. Ding et al. observed that hucMSC-exosomes injection contributes to the removal of Aβ deposition, alleviates cognitive dysfunction in AD model mice, and regulates the activation of microglia cells, thus alleviating neuroinflammation (Ding et al., 2018). Katsuda et al. also found that human adipose tissue-derived MSCs (ADSCs) secrete exosomes carrying the enzyme activity neprilysin (NEP). NEP is an enzyme that is important for the extracellular degradation of Aβ. The ADSCs-derived exosomes are transferred into N2a cells and reduced intracellular Aβ levels in N2a cells (Katsuda et al., 2013, 2015). In addition to stem cells, some other cell-derived exosomes or bioengineered exosomes also play beneficial roles in AD. Pan et al. used human brain microvascular endothelial cells derived exosomes inheriting p-glycoprotein as an Aβ cleansing system to remove Aβ peptides from the brain by specific capture between p-glycoprotein and Aβ, which can facilitate the clearance of Aβ and effectively ameliorate the cognitive dysfunction of AD mice (Pan et al., 2020). Moreover, M2 microglia-derived exosomes may also play a protective role in the pathogenesis of AD by improving PINK1/Parkin-mediated mitophagy (Li et al., 2022a). Based on bioengineering technology, microglia-targeting exosomes and targeted drug delivery can be

TABLE 1 Protective roles of exosomes from different sources in AD.

Source of exosomes	Investigation model	Mechanism	References
ADSC	NSCs from the brains of TG2576 AD mice	Reducing Aβ42, Aβ40 levels, the cell apoptosis of AD neuronal cells and promoting the neurite growth.	Lee et al., 2018
	N2a cell line	Carrying enzymatically active neprilysin to decrease Aβ levels.	Katsuda et al., 2013, 2015
MSC	Human neural cell culture model with FAD mutations and AD transgenic mice	Reducing Aβ expression, restoring the expression of neuronal memory/synaptic plasticity-related genes in the cell model and improving brain glucose metabolism and cognitive function in AD mice.	Chen et al., 2021
BMSCs	A sporadic AD mouse model	Improving AD-like behaviors, inhibiting the hyperactivation of microglia and astrocytes, and improving BDNF-related neuropathology.	Liu et al., 2022
	APP/PS1 mice	Improving spatial learning and memory ability of APP/PS1 mice, enhancing the expression of SphK1 and S1P, inhibiting the levels of amyloid and promoting the expression of NeuN.	Wang and Yang, 2021
HucMSCs	AβPP/PS1 transgenic mice	Repairing cognitive disfunctions, clearing Aβ deposition, and alleviating neuroinflammation.	Ding et al., 2018
HBMVECs	Aβ-induced AD mice model	Facilitating the cerebral clearance of Aβ and ameliorating cognitive dysfunction.	Pan et al., 2020
M2 microglia	Neuronal HT-22 cells and APP/PS1 mice	Ameliorating PINK1/Parkin-mediated mitophagy	Li et al., 2022a
MExo-Gem	BV2 cells and $A\beta_{1-42}$-induced AD mice	Binding with Aβ and specifically target microglia, thus promoting lysosome-mediated clearance of Aβ and improving the learning and memory ability of AD mice.	Hao et al., 2022

AD, Alzheimer's disease; Aβ, amyloid beta; ADSC, adipose-derived stem cells; NSCs, neuronal stem cells; MSC, mesenchymal stem cell; FAD, familial AD; BMSCs, bone-marrow mesenchymal stem cells, BDNF, brain-derived neurotrophic factor; SphK1, sphingosine kinase-1; S1P, sphingosine-1-phosphate; HucMSCs, human umbilical cord mesenchymal stem cells; HBMVECs, human brain microvascular endothelial cells, PINK1, PTEN-induced putative kinase1; MExo-Gem, mannose-modified exosomes laden with Gem.

designed. Mannose-modified exosomes containing gemfibrozil can not only bind with Aβ, but also specifically target microglia, thereby promoting the entry of Aβ into microglia, activating lysosome activity by exosome gemfibrozil, and accelerating lysosome-mediated clearance of Aβ in microglia (Hao et al., 2022).

5. Conclusions and future perspectives

In recent years, the research of exosomes is gradually becoming a new hotspot and receiving more and more attention. As a kind of widespread EVs, exosomes carry a variety of cargoes and are involved in the transport of substances, information transmission and cell-to-cell regulation, playing key roles in physiological and pathological conditions. Exosomes are also now known to play a critical role in the occurrence and development of AD. This review focuses on summarizing the "double-edged sword" role of exosomes in the pathogenesis of AD. In AD, exosomes can not only promote the production of pathological proteins, the formation of aggregates and the diffusion in the brain, but also enhance the inflammatory response to accelerate the pathological process. Meanwhile, exosomes can also alleviate the pathological process by promoting the clearance of Aβ or tau. In particular, given the complexity and multiplicity of exosome interactions between cells, more evidence is needed to reveal the roles of exosomes in AD in the future, especially imaging labeling techniques that provide dynamic real-time visualization of the pathogenesis of exosomes in cells or in animal models. In addition, exosomes may serve as potential biomarkers for AD due to their unique biological characteristics. Moreover, the regulation of exosome production or the modification of exosomes as biological carriers of specific molecules may become a new therapeutic measure for AD. However, the important factors limiting the basic research and clinical application of exosomes are the lack of more specific BDEs isolation and extraction technologies, the long time consumption and lack of unified and standardized extraction process, which requires extensive and in-depth researches in these aspects in the future. Last but not least, although it is a great interest to research the detrimental or beneficial roles of exosomes in the progression of AD, the current literature has generally avoided the potential mechanisms by which exosomes exert these varying functions. For example, is it specific surface proteins that prompt exosomes to spread Aβ or tau seeds between neuronal cells, rather than carrying them to microglia for degradation? In addition, the relationship between NDEs and Aβ shows multiple functions, including participating in the oligomerization of Aβ and playing a role in the clearance of Aβ via microglia cells. Whether there is a potential regulatory role in the seemingly contradictory relationship between them remains unknown. These questions may be a new direction to explore the roles of exosomes in AD in the future, which also requires further study by researchers.

Author contributions

TL designed, collected literatures, and wrote the manuscript. JL, WS, and SW collected some literatures. ZW and LW revised

the article. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Natural Science Foundation Program of Hubei Province (Grant number 2021CFB579 and 2022CFB181), the Special Fund of Union Hospital of Tongji Medical College, Huazhong University of Science and Technology (Grant No. 02.03.2018-130).

Acknowledgments

We are grateful to the editors and reviewers for giving valuable advice and important comments in the review.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Aging Neuroscience

TYPE Systematic Review
PUBLISHED 21 June 2023
DOI 10.3389/fnagi.2023.1206123

OPEN ACCESS

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RECEIVED 14 April 2023
ACCEPTED 31 May 2023
PUBLISHED 21 June 2023

CITATION
Vandersteen C, Plonka A, Manera V, Sawchuk K, Lafontaine C, Galery K, Rouaud O, Bengaied N, Launay C, Guérin O, Robert P, Allali G, Beauchet O and Gros A (2023) Alzheimer's early detection in post-acute COVID-19 syndrome: a systematic review and expert consensus on preclinical assessments.
Front. Aging Neurosci. 15:1206123.
doi: 10.3389/fnagi.2023.1206123

Alzheimer's early detection in post-acute COVID-19 syndrome: a systematic review and expert consensus on preclinical assessments

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Introduction: The risk of developing Alzheimer's disease (AD) in older adults increasingly is being discussed in the literature on Post-Acute COVID-19 Syndrome (PACS). Remote digital Assessments for Preclinical AD (RAPAs) are becoming more important in screening for early AD, and should always be available for PACS patients, especially for patients at risk of AD. This systematic review examines the potential for using RAPA to identify impairments in PACS patients, scrutinizes the supporting evidence, and describes the recommendations of experts regarding their use.

Methods: We conducted a thorough search using the PubMed and Embase databases. Systematic reviews (with or without meta-analysis), narrative reviews, and observational studies that assessed patients with PACS on specific RAPAs were included. The RAPAs that were identified looked for impairments in olfactory, eye-tracking, graphical, speech and language, central auditory, or spatial navigation abilities. The recommendations' final grades were determined by evaluating the strength of the evidence and by having a consensus discussion about the results of the Delphi rounds among an international Delphi consensus panel called IMPACT, sponsored by the French National Research Agency. The consensus panel included 11 international experts from France, Switzerland, and Canada.

Results: Based on the available evidence, olfaction is the most long-lasting impairment found in PACS patients. However, while olfaction is the most prevalent impairment, expert consensus statements recommend that AD olfactory screening should not be used on patients with a history of PACS at this point in

time. Experts recommend that olfactory screenings can only be recommended once those under study have reported full recovery. This is particularly important for the deployment of the olfactory identification subdimension. The expert assessment that more long-term studies are needed after a period of full recovery, suggests that this consensus statement requires an update in a few years.

Conclusion: Based on available evidence, olfaction could be long-lasting in PACS patients. However, according to expert consensus statements, AD olfactory screening is not recommended for patients with a history of PACS until complete recovery has been confirmed in the literature, particularly for the identification sub-dimension. This consensus statement may require an update in a few years.

KEYWORDS

Alzheimer's disease, post-acute COVID-19 syndrome, biomarkers, early diagnosis, olfactory disorders

1. Introduction

Since the beginning of the COVID-19 pandemic, many patients remain impaired in their daily life, long after the infection. In a study based upon an international cohort (Davis et al., 2021), cognitive, sensory-motor, memory, and speech or language symptoms persisted in an average of 30% (Ceban et al., 2022; d'Ettorre et al., 2022; Han et al., 2022; Nehme et al., 2022) of patients up to 7 to 12 months after SARS-CoV-2 infection (COVID-19). These symptoms are grouped under the term of Post-Acute COVID-19 Synonym (PACS) as defined by an OMS Delphi consensus[1]. Morphological MRI changes in brain structure have also been observed for approximately 141 days after the infection (Douaud et al., 2022) including primarily in global brain size and, secondarily in a decrease of the olfactory cortex thickness. Major changes in tissue damage markers in brain areas functionally connected to the primary olfactory cortex were also observed (Douaud et al., 2022), which could explain why 29.8% of PACS patients complain of persistent dysosmia, or a change in the sense of smell, more than 24 months after COVID-19 (Lechien et al., 2023). The point is that much of the recent literature focuses on the emerging risk of neurodegenerative disease and more precisely on AD (Luukkainen et al., 2018; Heneka et al., 2020; Rebholz et al., 2020; Verkhratsky et al., 2020; Erausquin et al., 2021; Mahalaxmi et al., 2021; Beauchet and Allali, 2022; Chen et al., 2022) after contracting COVID-19.

Worldwide, Alzheimer's disease (AD) is the main neurodegenerative disease leading to dementia, and it is responsible for an increase in morbidity (Scheltens et al., 2021) affecting more than 50 million people, two-thirds living in low- and middle-income countries (Scheltens et al., 2021). The prevalence of AD is estimated to triple in 2050 (Scheltens et al., 2021). Preclinical and prodromal AD respectively lasts on average for 10 and 4 years (Vermunt et al., 2019) before becoming dementia. The median survival rate for dementia is approximately about 3–6 years (Mayeda et al., 2017; Rhodius-Meester et al., 2019) after diagnosis. AD early diagnosis, followed by non-pharmacological interventions and pharmacological treatment (Scheltens et al., 2021), could potentially stall the rapid cognitive decline associated with dementia. However, early diagnosis remains a real challenge for clinicians as preclinical AD screening tests are still debated.

Current conventional and preclinical AD screening markers, such as neuropsychological assessments, brain morphological (MRI) or metabolic (PET), or a lumbar puncture for example (Drago et al., 2011; Scheltens et al., 2021), are not equally available worldwide. They are expensive, time-consuming, and depend on the availability of both technological platforms and human assistance. Remote digital Assessments for Preclinical Alzheimer's disease (RAPAs) could be an alternate solution that is relatively easy to implement and which might reduce delays in preclinical AD diagnoses. During the COVID-19 pandemic, remote assessments became increasingly common in daily medical practice with telemedicine enabling patients to benefit from continuous remote monitoring through a variety of digital technologies, such as video conferencing tools or symptom tracking applications (Beauchet et al., 2020). Remote assessments, both to provide cognitive assessment and plan treatment interventions, allow patients to have easier access to specialists and highly skilled healthcare professionals—even if those patients are located in remote regions—in a feasible, effective, and acceptable way (Poon et al., 2005; Sekhon et al., 2021). Furthermore, telemedicine is part of an approach to technology use that is intergenerational and has included a growing number of older adults (Fraser et al., 2020) which increased during the pandemic. Telemedicine has been found to help patients to avoid unnecessary travel and limit hospitalizations, which may be desired by some patients and reduce the costs of managing diseases. However, telemedicine is also a challenging process based on a number of different factors including access and ownership of the appropriate digital tools, the ability to use these tools, the physical affordances of the devices and the mobility of the patient, as well as interactional barriers in communicating digitally with someone in a health crisis (Dassieu et al., 2022).

A group of AD remote and digital evaluation platform experts from France, Switzerland, and Canada (IMPACT project) under the leadership of the French National Research Agency, were invited to develop evidence-based recommendations and expert consensus

1 https://apps.who.int/iris/rest/bitstreams/1376291/retrieve

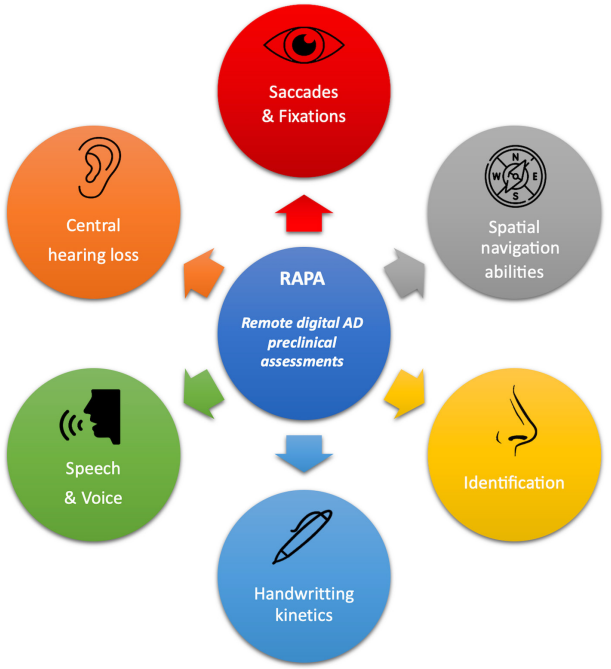

FIGURE 1
Overview of all RAPAs and their main clinical target assessments. Every detail of these RAPAs and the literature review process we used to summarize them is provided in Supplementary Data Sheet 2.

on items related to AD early diagnosis in the post-COVID-19 era. The IMPACT project aims to: 1- review RAPAs potentially impaired in PACS patients which could become unusable in AD early screening in case PACS last a long or a lifetime; 2- describe evidence-based recommendations according to the review; 3-inform people and policymakers of the recommendations. The first and the second items are the primary and secondary objectives of this work.

2. Methodology

2.1. Search strategy

2.1.1. Selection of the remote digital assessments for preclinical Alzheimer's disease

An initial research stage allowed authors to identify Remote digital Assessments for Preclinical AD (RAPAs) in PubMed and Embase Databases which were easily usable, non-expansive, quick, and widely available: vocal, graphical, eye tracking, central auditive impairments, olfactory disorders, and spatial navigation abilities markers were all assessed. A complete process is reported in Supplementary Data Sheet 2 and all selected RAPAs are illustrated in Figure 1.

2.1.2. Data sources

A search request command on PubMed, Cochrane database, and Embase was entered on 31/11/2022. This search included "*keywords*" through VOCAL "speech" OR "language" OR "language tests" OR "voice"; GRAPHICAL "Psychomotor Performance" OR "writing" OR "handwriting" OR "psychomotor performance" OR "mouse movements" OR "patterns" OR "drawing" OR "keystroke"; EYE TRACKING "eye movement" OR "eye-tracking technology" OR "saccades" OR "ocular motility"; CENTRAL AUDITIVE IMPAIRMENTS "Auditory system dysfunction" OR "central auditory function" OR "central auditory deficit"; OLFACTORY DISORDERS "Olfaction Disorders" OR "anosmia" OR "hyposmia" OR "dysosmia" OR "olfactory loss" OR "parosmia"; SPATIALIZATION "Virtual reality" OR "spatial navigation". PACS included "long covid", "post covid", "post-covid, "post-covid-19", "long-covid-19", "long-covid" or "post-acute covid-19 syndrome". The search request strategy is provided in Supplementary Data Sheet 1.

2.2. Inclusion criteria

2.2.1. Types of studies

Systematic reviews with or without meta-analyses and observational studies (only those in peer-reviewed journals) were included. We excluded retrospective studies, meeting abstracts, conference presentations, book reviews, news items, and corrections. Every study in English, relative to humans since 2020, was included if they were a clinical trial, a meta-analysis, a randomized controlled trial, a review, or a systematic review. Studies in languages other than English or French, older than 2020, or without abstract were not included as the COVID-19 pandemic began that year. The electronic database search was supplemented by screening the reference lists of the included studies and relevant reviews.

2.2.2. Types of participants

Only adult (≥18 years old) patients with post-acute COVID-19 syndrome (PACS) were included, but this term is not always called PACS but sometimes "long-COVID-19" or "post-COVID-19". These terms were included in the search strategy protocol. Exclusion criteria were patients previously impaired with neurologic, neurodegenerative, or neuromuscular diseases; speech, voice, or language impairments; psychomotricity, writing- or handwriting-related diseases; abnormal eye-movement related diseases; anterior reported hearing loss; anteriorly reported olfaction disorders or spatial navigation incapacities. All types of intervention were included.

2.2.3. Types of outcomes

We determined that outcome measures must include one or more of the RAPA previously identified among vocal, graphical, eye tracking, central auditive impairments, olfactory disorders, or spatial navigation impairment.

2.2.4. Study selection and evaluation

For the first step, two reviewers (CV, AP) assessed the title/abstract of each result following inclusion and exclusion criteria. In case of conflict, a second review was scheduled with both reviewers (CV, AP) and a third (AG) until a consensus was reached.

Individual clinical research studies were evaluated in accordance with the French HAS criteria.

2.2.5. Quality assessment

The quality of the studies reported was assessed based on a systematic review of methodological quality assessment tools (Zeng et al., 2015). Systematic reviews were assessed using the AMSTAR 2 tool (Assessment of Multiple SysTemAtic Reviews) (Shea et al., 2007, 2017), cohort and observational studies using the Observation Study Quality Evaluation tool (OSQE) (Drukker et al., 2021). Concerning AMSTAR 2, 16 items were evaluated and of these 7 were critical (N°2, 4, 7, 9, 11, 13, 15). A review was assessed as high quality if none or one non-critical weakness was noticed (the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest). A review was assessed as moderate quality when more than one non-critical weakness was noticed (the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review). Reviews were assessed as low quality when one critical flaw with or without non-critical weaknesses were noticed (the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest). Finally, reviews were assessed as critically low-quality when more than one critical flaw with or without non-critical weaknesses (the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies) or multiple non-critical weaknesses were noticed (may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence). For the OSQE evaluation tool, 15 items were evaluated with different evaluation weights explaining why authors (Drukker et al., 2021) did not provide any cut-off score to discriminate good from poor quality studies. Different forms were used, provided by authors in their original work (Drukker et al., 2021), given depending on the observational study type. No meta-analysis was done, so the risk of bias associated with the included studies was not assessed. Ethical clearance from the institutional ethical committee was not required as all the data extracted was from already published studies and no patients or the public were directly interviewed or involved in the present research.

2.3. Consensus process

The EU Joint Program—Neurodegenerative Disease Research (JPND) initiative initiated a call for expert working groups on 1 November 2021, to investigate the impact of COVID-19 on research related to neurodegenerative diseases. In response to the program's call, various national funding organizations were asked to participate based on the country's response. The Funding organization from France, for example, was the French National Research Agency. Our working groups answered this call, which focused on the COVID-19 pandemic and its impact on Alzheimer's care. This included setting up an expert board based on past collaborations in this field of expertise. Talking about digital and clinical distance evaluation platforms required bringing together other specialists in the field of digitalization and digital support explaining working with physicians (CV, OR, CyLa, OG, PR, GA, OB) neuroscientists (AP, VM, KG, NB, OG, PR, GA, OB, AG), speech therapists (AP, AG), communication and age studies experts (CoLa and KS) and a social media research director (KS). VM and AG developed the research topics using the population, intervention, comparator, and outcome (PICO) framework and created the initial recommendation statements. In the first round, a group of 12 experts from the IMPACT project reviewed and provided feedback on the questionnaire using a 5-point scale (ranging from "strongly agree" to "strongly disagree") (Bossard et al., 2018). Responses with a score of 1–2 were considered as indicating agreement. During the second round, the recommendation statements that did not achieve agreement were discussed further. If a consensus agreement of 75% was not reached after discussion, a third round of rating was conducted (Sanz-Paris et al., 2017). Finally, the grades of recommendation were assigned based on the strength of evidence and a consensus discussion of the results from the Delphi rounds.

3. Results

3.1. Literature search results

The initial research team (CV, AP, AG) reviewed 738 articles. Twenty studies met the inclusion criteria after evaluation of titles, abstracts, and full contents of the relevant studies of which four were systematic reviews, seven systematic reviews with meta-analysis, two narrative reviews, six observational cohorts, and one case-control study. The entire selection process is reported in a flowchart (Figure 2). The reviews and observational studies' level of quality are reported in Tables A, B, and C in the Supplementary Data Sheet 3. Based on AMSTAR 2 scores 69.2% (n = 9), 23.1% (n = 3), and 1.8% (n = 1) reviews had respectively critically low, low, and high quality. Based on OSQE scores, 14.3% (n = 1), 28.6% (n = 2), 42.9% (n = 3), and 28.6% (n = 2) of observational studies were, respectively, scored with 14, 13, 12, and 8 stars out of 15.

3.1.1. Demographical data

Demographics are reported in Table 1. When it was reported (90%; n = 18) population size ranged from 34 (Vandersteen et al., 2021) to 178 496 (Parker et al., 2021) people with an average of 24 031 ± 54,301 patients in reviews papers and 638 ± 1,379 in cohort observational studies papers. Patients' ethnic groups were reported to be from all over the world apart from five (38.5%) reviews (Deer et al., 2021; Bertuccelli et al., 2022; De Luca et al., 2022a; Jamoulle et al., 2022; Premraj et al., 2022) and five (71.4%) observational studies (Vandersteen et al., 2021; Girón Pérez et al., 2022; Mendes Paranhos et al., 2022; Michelutti et al., 2022; Ser et al., 2022) where patients where reported to come from only one country depending on teams origins. When it was clearly reported in 50% of studies (n = 10), the average patient ages were 40- and 50-years-old. Only 12 studies clearly reported gender impairment differences with women preferentially impaired in 6/12 studies. The

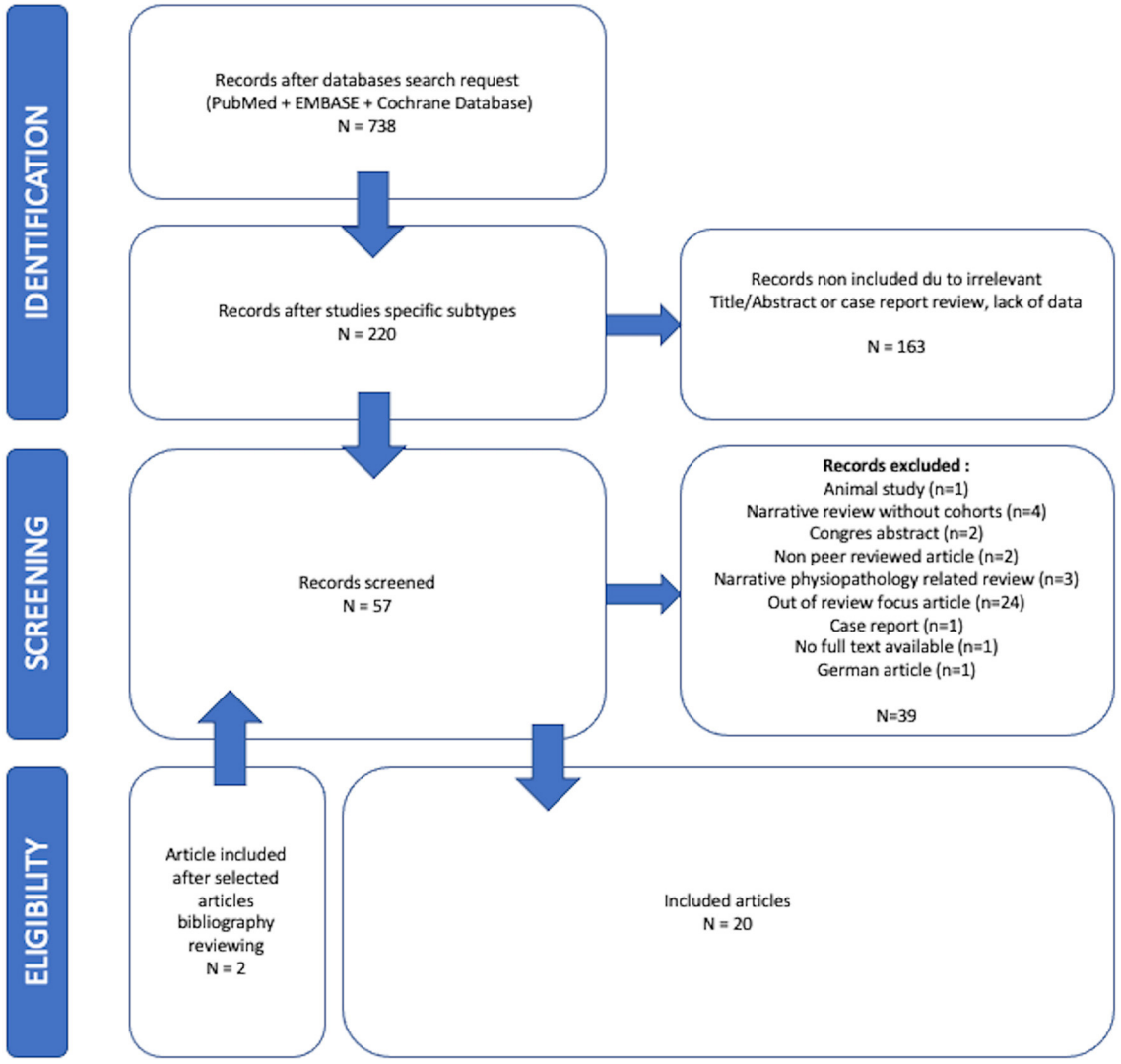

FIGURE 2
Overview of the screening process. PRISMA flow diagram of the studies selection process.

definition of long-COVID-19 has changed a lot in the past 2 years and so heterogeneous assessment time from COVID-19 onset was reported in Table 1.

3.1.2. Impairments observed in the RAPA patients

The summary results of RAPAs review were reported in Table 2. We independently analyzed RAPA impairments in 20 studies and reported direct or indirect impairment for each RAPA (summarized in Table 3) as RAPA could have been directly impaired (for example hand shaking in handwriting assessments) or indirectly impaired (like visual hallucinations in eye-tracking assessments). The most often-reported RAPA impairment was the olfactory function occurring in PACS patients in all but two studies. The second most frequently impaired biomarkers were graphical and eye-tracking ones. The third was central hearing and finally vocal and spatial navigation abilities were reported very rarely.

Summary of the expert' recommendations for the use of every RAPA in PACS are reported in Table 3.

3.2. Consensus recommendations

Many RAPAs were reported as impacted in PACS patients but olfaction was the most impaired. Graphical and eye-tracking assessments were fewer but still reported as impacted. Consensus recommendations were discussed based on these reports.

3.2.1. Consensus recommendation: olfaction-related remote digital assessments for preclinical Alzheimer's disease

Olfaction was impacted in all but two studies (Bertuccelli et al., 2022; Jamoulle et al., 2022). Direct involvement included a persistent dysosmia in 11–57.6% of PACS patients (Ahmad et al., 2021; Davis et al., 2021; Parker et al., 2021; Silva Andrade et al., 2021; Girón Pérez et al., 2022; Michelutti et al., 2022; Tan et al., 2022) related to an anosmia (Ahmad et al., 2021; Fernández-de-Las-Peñas et al., 2021; Malik et al., 2022; Mendes Paranhos et al., 2022; Michelutti et al., 2022; Premraj et al., 2022; Tan et al., 2022),

10.3389/fnagi.2023.1206123

TABLE 1 Main demographic data included in the selected articles.

Authors	Time from COVID-19 onset	*N* (patients)	*N* review (studies)	Type	Age [years ± SD; (min-max)] ~in average	Women *N* (%)
(Ahmad et al., 2021)	2 weeks to 6 months	14,056	20	SR	(18–60)	-
(Parker et al., 2021)	2 weeks to 6 months	178,496	272	SR	(17–93)	-
(Ser et al., 2022)	4 weeks to 3 months	106	-	CCS	39.4 ± 12.5	47 (44.3)
(Deer et al., 2021)	17 days to 4,7 months	NP	59	SR/MA	(12–73)	-
(Bertuccelli et al., 2022)	3–6 months	1,940	25	SR	42.57 ± 7.23 to 79 ± 8; ~60	873 (45)
(Dirican and Bal, 2022)	23 days to 12 months	7,546	20	SR/MA	53.4 ± 8.2; (34–68.8)	1,671 (46.8)
(Jamoulle et al., 2022)	3–18 months	55	-	CS	42,9 ± 15,6	40 (72.7)
(De Luca et al., 2022a)	1 month to 10,6 months	5,582	16	SR	-	-
(Davis et al., 2021)	0–7 months	3,762	-	CS	(30–60)	2,969 (78.9)
(Silva Andrade et al., 2021)	NP	NP	62	NR	-	-
(Premraj et al., 2022)	3–6 months	10,530	18	SR/MA	52 ± 10	6,213 (59)
(Pinzon et al., 2022)	Until 6 months	9,944	36	SR/MA	(17–81)	-
(Malik et al., 2022)	30–180 days	4,828	12	SR/MA	~58.75	2,481 (45,5)
(Girón Pérez et al., 2022)	More than 3 months	76	-	CS	~45 (20–70)	36 (47.4)
(Xydakis et al., 2021)	47 days to 6 months	3,691	-	NR	-	-
(Fernández-de-Las-Peñas et al., 2021)	0–3 months	24,225	33	SR/MA	47.8 ± 16.6	52.26
(Tan et al., 2022)	0–6 months	3,699	18	SR/MA	(30–55.8)	-
(Michelutti et al., 2022)	More than 3months	213	-	CS	53 ± 14	151 (73)
(Mendes Paranhos et al., 2022)	221–264 days	219	-	CS	(18–60)	164 (74.9)
(Vandersteen et al., 2021)	5 ± 2,8 months	34	-	CS	41.6 ± 12.9	16 (47)

SD, Standard deviation; SR, systematic review; CCS, case control study; SM/MA, systematic review and meta-analysis; NR, narrative review; CS, cohort study.

explicitly reported in 12.8% (Deer et al., 2021), 19.3–21.4% (Ahmad et al., 2021), 32.2% (Michelutti et al., 2022), 44% (Ser et al., 2022), or 55.9% (Vandersteen et al., 2021) of cases or hyposmia (Mendes Paranhos et al., 2022; Michelutti et al., 2022) explicitly reported in 14.7% (Vandersteen et al., 2021), 15.3% (Deer et al., 2021), or 33.1% (Michelutti et al., 2022)of cases. Assessment time from COVID-19 onset was extremely variable. Only two studies were over 10 to 12 months of follow-up (De Luca et al., 2022a; Dirican and Bal, 2022) but only De Luca et al. (De Luca et al., 2022a) report a 6-month recovery rate of 95.3% in a 16 study review on PACS persistent chemosensory dysfunction. One study (Vandersteen et al., 2021) reported olfaction subdimensions precisions related to a prevalent identification impairment significantly related to subjective olfactory recovery (VAS; $p = 0.034$) compared to threshold and discrimination scores. According to WHO clinical management of COVID-19,[2] Dirican and Bal (2022) did not find any difference in the persistence of anosmia between severe and non-severe survivors of COVID-19 with a global pooled odds ratio of 1.22 (95%CI 0.69 to 2.16) in a meta-analysis of 20 relevant observational studies. Parosmia was explicitly reported in 23.2% (Davis et al., 2021) and frequently described as "smoke," "burning," "cigarette," and an altered "meat" smell. Phantosmia was reported in 23.2% (Deer et al., 2021). Indirect involvement included dysgeusia (Ahmad et al., 2021; Fernández-de-Las-Peñas et al., 2021; Pinzon et al., 2022; Premraj et al., 2022), which was frequently reported associated with olfaction disorders in 19.3–38.5%of the studies (Davis et al., 2021; Deer et al., 2021; Silva Andrade et al., 2021). Davis et al. (2021) found no significant differences between loss of smell [35.9%, (34.4–37.5%)] vs. loss of taste [33.7%, (32.2–35.2%), $p > 0.1$] in an online questionnaire observational study on 3762 PACS patients 7 months after COVID-19 onset. More precisely, parageusia and phantageusia, similar to qualitative olfactory dysfunction, were reported respectively in 16.4 and 9% (Deer et al., 2021) of PACS patients up to ~5 months after COVID-19 onset.

Considering above discussion, the expert consensus does not recommend the use of olfaction as a RAPA when patients complain of a COVID-19 PACS history (level II, grade B). Many PACS patients continue to complain of olfactory disorders 1 year after the COVID-19 onset, however, to date, not enough high-quality studies report a complete recovery amongst those undergoing either subjective testing or psychophysical olfactory testing (mainly on identification).

2 https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2

10.3389/fnagi.2023.1206123

TABLE 2 Remote digital Alzheimer's disease preclinical assessments (RAPA) impairments related to every study included in the review.

Authors	RAPA					
	Vocal	Graphical	Eye tracking	Central hearing	Olfactory disorders	Spatial navigation
(Ahmad et al., 2021)	X	X	X		X	
(Parker et al., 2021)				X	X	
(Ser et al., 2022)		X			X	
(Deer et al., 2021)	X	X	X	X	X	
(Bertuccelli et al., 2022)						X
(Dirican and Bal, 2022)					X	
(Jamoulle et al., 2022)		X				
(De Luca et al., 2022a)				X	X	
(Davis et al., 2021)	X	X	X	X	X	
(Silva Andrade et al., 2021)	X	X	X	X	X	
(Premraj et al., 2022)					X	
(Pinzon et al., 2022)		X	X	X	X	X
(Malik et al., 2022)					X	
(Girón Pérez et al., 2022)					X	
(Xydakis et al., 2021)					X	
(Fernández-de-Las-Peñas et al., 2021)			X		X	
(Tan et al., 2022)					X	
(Michelutti et al., 2022)			X		X	
(Mendes Paranhos et al., 2022)					X	
(Vandersteen et al., 2021)					X	
Total number of studies	4	7	7	6	18	2

TABLE 3 Recommendations summary related to Remote digital Alzheimer's disease preclinical assessments (RAPA) evaluated in the review.

Assessed items	A	B	C	Level of evidence	Grade of recommendation
	AD early diagnosis RAPA interest	AD RAPA specificity loss in PACS patients	RAPA interest in early diagnosis of AD in PACS patients		
Vocal markers	**4.3 ± 0.7**	3.7 ± 0.9	3.9 ± 0.9	II	B
Graphical markers	**4.1 ± 0.8**	3.9 ± 1	3.9 ± 0.6	II	B
Eye-tracking	2.7 ± 0.7	3.3 ± 0.7	3.3 ± 0.9	II	B
Central hearing	2.6 ± 0.5	3.1 ± 0.8	3 ± 0.5	II	B
Olfactory disorders	**4 ± 0.9**	1.6 ± 1.4	1.4 ± 0.7	II	B
Spatial navigation abilities	3.7 ± 1	3.7 ± 1.3	3.7 ± 1.5	II	B

AD, Alzheimer's disease; RAPA, Remote digital Assessments for Preclinical AD; PACS, post-acute COVID-19 syndrome. Likert scale for items A and C are reported as 1 for not agreeing at all to 5 for completely agreeing. For item B (biomarker specificity loss in PACS patients), Likert scale was inverted. Results in bold are related to impacted likert results for Delphi methodology (≥4).

3.2.2. Consensus recommendation: graphical marker-related remote digital assessments for preclinical Alzheimer's disease

Only one review (Deer et al., 2021) reported a study with 4% of hand muscle weakness in PACS patients that directly involve graphical markers. However, many indirect symptoms were reported (Ahmad et al., 2021; Davis et al., 2021; Deer et al., 2021; Silva Andrade et al., 2021; Jamoulle et al., 2022; Pinzon et al., 2022; Ser et al., 2022) with potential impacts on graphical capacities such as pins and needles and numbness in hand (2%) (Ahmad et al., 2021), and fatigue or muscle weakness (63%) (Ahmad et al., 2021). From a physiological point of view, even if cutaneous sensitivity and conductance parameters were significantly measured as abnormal in PACS patients reporting autonomic complaints, no nerve conduction abnormalities were reported in the literature (Ser et al., 2022). In parallel, many symptoms were reported that could indirectly influence graphical markers such as abnormal exteroceptive sensation (13.8%), abnormality of movements (2%), and dysmetria (2.8%) (Deer et al., 2021); muscle spasms (22%), tremors (28%), vibrating sensations (18%), and tactile hallucinations (3.1%) (Davis et al., 2021); or skeletomuscular global impairment (Davis et al., 2021; Deer et al., 2021; Silva Andrade et al., 2021) with pain (Pinzon et al., 2022) (27.8%), paresthesia (Pinzon et al., 2022) (33.3%), or movement disorders (Pinzon et al., 2022) (3.6%). In a cohort study, Jamoulle et al. (2022) reported the case of a man infected with COVID-19 three times who developed anosmia, dysgeusia, severe cognitive and memory problems, and alteration of cerebral perfusion on SPEC-CT: he complained about paraesthesia in his fingertips, lateral hand tremors, and instances when his hands opened by themselves when doing specific tasks, which caused him to spontaneously drop objects he was carrying.

Considering the above discussion, the expert consensus is to continue using graphical markers in RAPA studies. Rarely did the research report hand skeletomuscular impairments that could lead to graphical marker abnormal results. No PACS studies reported kinetic results and no nerve conductivity abnormalities were reported in this review (level II, grade B).

3.2.3. Consensus recommendation: eye-tracking-related remote digital assessments for preclinical Alzheimer's disease

Three studies (Deer et al., 2021; Silva Andrade et al., 2021; Pinzon et al., 2022) spotted ocular complications in PACS patients described as visual impairments, arterial thrombosis, or ophthalmoplegia, but only one review reported a case of a 28-year-old man with thalassemia minor complaining of gaze-evoked nystagmus and intermittent diplopia on lateral gaze that persisted 10 days after hospital discharge. Five other studies (Ahmad et al., 2021; Davis et al., 2021; Deer et al., 2021; Fernández-de-Las-Peñas et al., 2021; Michelutti et al., 2022) reported indirect potential impairment of eye-tracking tests results mainly the 6 first months after COVID-19 onset: "eyes problems" 79 ± 17 days after COVID-19 onset (Ahmad et al., 2021); visual loss 10–14 weeks after COVID-19 onset (Ahmad et al., 2021); blindness in one study (Deer et al., 2021); blurred vision (9.7–35.7% 7 months after COVID-19 onset) (Davis et al., 2021; Deer et al., 2021); conjunctivitis (8.9%) (Deer et al., 2021); diplopia (6.9%) (Deer et al., 2021) and keratoconjunctivitis (28.6%) (Deer et al., 2021); visual hallucinations (10.4%) (Davis et al., 2021) or finally persistence of visual disturbance in 3.3–8% (Michelutti et al., 2022).

Considering the above discussion, the expert consensus is to continue using eye-tracking markers in RAPA studies as few studies report direct vision and/or oculomotor impairment that could lead to abnormal eye-tracking assessment results (level II, grade B).

3.2.4. Consensus recommendation: central hearing-related remote digital assessments for preclinical Alzheimer's disease

In this review, 4 studies (Deer et al., 2021; Parker et al., 2021; Silva Andrade et al., 2021; Pinzon et al., 2022) reported direct persistent hearing impairment (Silva Andrade et al., 2021) with 6.6% (Deer et al., 2021) to 15% (Parker et al., 2021) persistent sensorineural hearing loss (before 6 months) (Pinzon et al., 2022) without precision on the follow-up and recovery. In parallel, indirect persistent hearing impairments were related to persistent tinnitus and earache (2.5 to 3.6%) (Ahmad et al., 2021; Deer et al., 2021), hyperacusis (34.7%), pulsatile tinnitus (19%), or tinnitus (29%) (Deer et al., 2021; Pinzon et al., 2022). In a systematic review (De Luca et al., 2022a) reported in this work, the authors reported a controlled study of 27 PACS patients (Vs 20 control) 3.81 ± 2.11 months after COVID-19 onset where speech audiometry showed small but significant impairment in PACS correlated in auditory brainstem response to a lengthening of waves III-V interpeak latencies. However, in the same work (De Luca et al., 2022a) the authors report other studies that failed to show any differences in vestibular or cochlear, even retro cochlear, function (auditory brainstem responses).

Considering the above discussion, the expert consensus is to still use central hearing markers in RAPA studies as few works report the possibility that PACS may cause damage to the hearing system and so lead to long-lasting abnormal central hearing results (level II, grade B).

3.2.5. Consensus recommendation: vocal and speech test-related remote digital assessments for preclinical Alzheimer's disease

Three studies (Ahmad et al., 2021; Davis et al., 2021; Deer et al., 2021) reported indirect impairment of speech and language in 49% of PACS patients. Seven months after the onset of COVID-19, 22 % reported difficulty speaking, 47% reported difficulties finding the right word, 30% had difficulties communicating verbally, 17% were slurring words, and 9% reported speaking unrecognizable words. Problems swallowing were reported in a 39 PACS patient cohort study, although no specifics were given (Ahmad et al., 2021). Different types of aphasia were reported in an 81-cohort systematic review (Deer et al., 2021) [anomic in one study (46.3%), bilingual in one study (28.9%), expressive in one study (22.2%), receptive in one

study (23.8%)] with the possibility that COVID-19 could lead to vocal and spontaneous speech impairments (flow rate, hesitations). Only 3 studies (Davis et al., 2021; Deer et al., 2021; Silva Andrade et al., 2021) underlined a direct speech impairment with 7 months after COVID-19 onset 38% speech and language issues (Davis et al., 2021) like slurred speech were reported for 15.8% of patients in a review of 59 PACS papers (Deer et al., 2021). In a narrative review of vocal and speech tests (Silva Andrade et al., 2021), the authors reported the case of a 49-year-old woman with COVID-19 infection who exhibited no flu symptoms but suddenly presented speech disorder and left-side hemiparesis related to a couple of small acute cerebral infarctions in the right prerolandic cortex, which is a rare complication of COVID-19. However, no follow-up data were included.

Considering the above discussion, the expert consensus is to continue to use vocal markers in RAPA studies as few studies reported the possibility that COVID-19 infection may cause significant modifications to vocal performances and lead to abnormal vocal assessments results (level II, grade B).

3.2.6. Consensus recommendation: spatial navigation abilities test-related remote digital assessments for preclinical Alzheimer's disease

Only 2 papers (Pinzon et al., 2022) [Bertuccelli et al. (2022)], included in this work, reported PACS patients with symptoms related to spatial navigation ability impairments. In the first paper (Pinzon et al., 2022) authors reported 2.6% of persistent spatial disorientation and/or confusion in a 697 PACS patient cohort of 63 ± 14.4-year-olds on average, 6 months after hospital discharge. In the second paper [Bertuccelli et al. (2022)], authors analyzed MoCA visuo-spatial subitems and reported the mean score of a sample of 29 non-ICU-admitted subjects, 0–3 months after symptoms onset: they revealed impaired spatial navigational functions (2.50 ± 1.34;max score:4). Moreover, in the same review [Bertuccelli et al. (2022)], five other studies assessed visuo-spatial abilities with visual reproduction of the Wechsler Memory Scale, the Rey-Osterrieth Complex Figure, and the Corsi Test, none of which found relevant deficits.

Considering the above discussion, the expert consensus is to keep using spatial navigation RAPAs, as few studies in the literature are controversial. This indicates that there is a weak possibility that COVID-19 infection may cause significant modifications to the performance of spatial navigation (level II, grade B).

4. Discussion

This study of the literature has aimed to assess the potentially impacted RAPAs in a PACS situation, and to assess the expert consensus or recommendations when considering PACS medical history for each RAPA. The recommendations, based on expert consensus, are directed by physicians, neuroscientists, clinicians, or students working on AD early diagnosis and indicate the importance of keeping in mind COVID-19′s potential influence on results. Clearly, PACS-reporting patients may not be able to be screened for AD efficiently and special attention must be paid to the choice of which early markers to use in making assessments.

A total of 20 studies met our inclusion criteria. The main finding concerns the presence of olfaction persistent impairments, which might seriously affect the validity of olfactory screening for neurodegenerative diseases. This scoping review raises two questions: First, the similarities between PACS and AD. The second is relative to the impact of PACS on RAPA targets, which could potentially hinder any AD screening due to the biased results produced by PACS outcomes.

Since the beginning of the pandemic, many authors have drawn attention to the similarity and connection between COVID-19 and AD. While the cerebral invasiveness of COVID-19 is still being investigated, the inflammatory consequences of COVID-19 on the brain have been demonstrated. Furthermore, many arguments link COVID-19 infection and AD (Verkhratsky et al., 2020; Mahalaxmi et al., 2021; Chen et al., 2022; Li et al., 2022a). The trans-endothelial mechanism is highly discussed as the main way of systemically spreading COVID-19 (Chen et al., 2022). However, olfactory neuroepithelium and olfactory neurons could be an alternative means of transmission. (Meinhardt et al., 2021; Ziuzia-Januszewska and Januszewski, 2022). Viruses, like HSV or EBV infection or reactivation, might play an important role in AD genesis (Ou et al., 2020) and could be self-sustained, for example by the fourth isoform of apolipoprotein E genotype (APOE4). APOE4 is a well-known AD risk factor and has been reported to facilitate HSV1 reactivation in the brain through many events such as immunosuppression, peripheral infection, or inflammation (Abate et al., 2020). Many authors speculate on long-lasting inflammation in PACS patients with astrocytes and microglia brain activation polarized in a facilitating way (M1 phenotype) of ß-amyloid and Tau phosphorylation levels increase (Abate et al., 2020; Chen et al., 2022). Moreover, APOE4 may facilitate the infectivity of COVID-19 by regulating intracellular levels of cholesterol and increasing the S-protein binding to ACE2 (Chen et al., 2022) but its PACS role and staying power are debated in clinical trials (Tavares-Júnior et al., 2022). Wide ACE2 binding during COVID-19 infection could downregulate the ACE2 receptor (Chen et al., 2022) for a while, which has been reported to be decreased in post-mortem brain tissue of AD patients, and inversely is correlated to ß-amyloid levels and Tau phosphorylation (Kehoe et al., 2016). Finally, ß-amyloid, a peptide with antimicrobial properties, may be an innate immune system actor (Soscia et al., 2010) but could be theoretically and ironically over-produced in PACS patients. Given that ∼659 million people have so far been infected by COVID-19, more follow-up with PACS patients and more powerful, high-quality studies need to be undertaken.

4.1. Olfaction RAPAs are no longer recommended

RAPA target assessments could interfere with PACS outcomes, and as such, this type of assessment may complicate potential AD early screenings. As the experts' conclusions (Table 3) underline, olfaction could be an early AD marker. An identification impairment without any other etiology is an early symptom of phosphorylated Tau protein neurofibrillary tangles (NFTs) and ß-amyloid plaques accretion in olfactory bulbs and entorhinal

cortex (De Luca et al., 2022b), which is the main cortex gate between a smell and its memory and one of the first brain-impaired regions in early AD (Saramago and Franceschi, 2021), with the hippocamp and amygdala. Olfactory Identification subdimension is impaired in PACS and reflects the olfactory subjective (visual analogic scale) and patient quality of life impairment (Vandersteen et al., 2021). Almost 2 years (Lechien et al., 2023) after the onset of COVID-19, 29.8% of PACS patients still complain of olfactory disorders (0.6% of hyposmic and 2.3% anosmic on identification psychophysical test results) with 13.4% of parosmia. Parosmias are one of the main olfactory-persistent symptoms of PACS patients (Davis et al., 2021) and are only predictive of a threshold impairment (Menzel et al., 2022). Therefore, just as we see in older patients, there will be a global olfactory score improvement but not an olfactory identification score improvement (Gary et al., 2023; Lechien et al., 2023). Our results indicate the presence of more hyposmia, anosmia, and parosmia from the time of COVID-19 onset. As reported in this review, the lack of psychophysical olfactory tests in the included studies (mainly subjective assessments) seems to overestimate, from a quantitative perspective, olfactory disorders for more than 40% of patients (Nørgaard and Fjaeldstad, 2021). Dysgeusia was frequently reported in PACS in similar proportion to dysosmia. As retro-olfaction is often confused with taste in 50% of people (Nørgaard and Fjaeldstad, 2021), clinicians have to pay attention to "dysgeusia" as it could be an olfaction impairment because gustatory functions are rarely impacted during COVID-19 onset (Hintschich et al., 2020) and when they are, they are short-lived (Chiesa-Estomba et al., 2020). Lack of psychophysical olfactory testing, frequent long-lasting dysosmia, and risk of dysosmia misdiagnoses because of false dysgeusia in the PACS literature prevent us from specifying with precision PACS-persistent olfactory disorders and features and therefore potential long-lasting identification impairment. This is why experts recommend, for the moment, not to trust olfactory identification impairments for RAPA in PACS patients until more high-quality studies are published. Only then will researchers be able to assert if there is complete olfaction recovery.

4.2. Graphical marker RAPAs are still recommended

As the experts conclude, graphical markers are widely studied in RAPA, as AD patients report a decline in fine motor control, coordination, and writing or drawing impairments that compromise daily life activities (Yan et al., 2008). AD hand movements become slower, less fluid, and less consistent due to reduced precision in wrist and finger positioning (Impedovo and Pirlo, 2018). Handwriting pressure decreases in patients with AD when cognitive tasks are performed (Plonka et al., 2021)allowing physicians to differentiate them from healthy controls. Moreover the increase of writing time between two strokes [known as pen-up time (Alfalahi et al., 2022)] is reported to be a key discriminator (Delazer et al., 2021) between AD and Mild Cognitive Impairment (MCI) patients compared to healthy individuals when performing tasks that involve visuospatial construction, cognitive writing, or the Clock Drawing Test (Werner et al., 2006; Müller et al., 2017a,b). For MCI and AD screening, pooled sensitivity and specificity of kinetics are respectively 0,85 and 0,82 in a Scientific Report study (Alfalahi et al., 2022) and allow, specifically for drawing tasks (spiral, crossed pentagons, 3D house, clock drawing test), a high specificity to screen MCI or AD patients (Garre-Olmo et al., 2017). In this research, few symptoms were reported in PACS patients that interfere with direct kinetic assessments [such as tremors and hand muscle weakness Deer et al., 2021] or could influence indirectly the way the patient writes or draws [such as vibrating sensations, tactile hallucinations, abnormal exteroceptive sensation or paresthesia Davis et al., 2021; Deer et al., 2021]. The literature reports upper extremity plexopathy (Li et al., 2022b; Michaelson et al., 2022) in severe COVID-19 (requiring mechanical ventilation) between 1 to 3 months after infection onset. However, the responsibility of the prone position is still debated (King-Robson et al., 2022) and no recovery, long follow-up, or specific kinetic studies have yet been performed on these neurological PACS patients. This explains the important loss in specificity that is evaluated by experts (Table 3), who nevertheless recommend still using this RAPA.

4.3. Speech RAPAs are still recommended

For over a decade, many authors have worked on AD - connected speech assessments (Boschi et al., 2017), as confirmed by experts' interest in this RAPA, especially since the development of computer-assisted voice analysis. These speech and voice assessments have focused on the lexico-semantic and discourse-pragmatic aspects, which account for around 80 and 77.5% of the actual research, respectively (Boschi et al., 2017). The syntactic, phonetic and phonemic, and finally morphological aspects comprise, respectively, 57.5, 55, and 35% of current studies (Boschi et al., 2017). In AD patients phonetic and phonological errors have been reported, as well as a low speech rate and increase in hesitations (Hoffmann et al., 2010; Sajjadi et al., 2012), lexico-semantic errors, word findings difficulties (Forbes-McKay et al., 2013), and a greater number of closed class (Drummond et al., 2015) and high-frequency words (Kavé and Levy, 2003). In this review, frequent [49% Davis et al., 2021] impairments of speech were reported in PACS patients with imprecise speech and language issues that could be linked more to lexico-semantic, phonetic, and phonological features. In PACS patients, general (Ahmad et al., 2021) and verbal communication difficulties or slurring words were reported (Davis et al., 2021) as did cross lexical and semantic RAPA or different types of aphasia (Deer et al., 2021). However, few studies reported speech-specific PACS in the 6 months after the onset of COVID-19. Although remote European (semi) automated speech analysis projects are being carried out, this sort of specific speech/acoustic measures are rarely investigated (Boschi et al., 2017) in AD and never recorded in PACS. Because of these short-lasting voice PACS and without acoustic persistent issues, experts recommend continuing using speech RAPA.

4.4. Eye tracking, visual abilities, and central hearing RAPAs are still recommended

Finally, these three RAPAs were not suggested as significatively relevant by experts. Eye-tracking as RAPA is based on eye saccades and fixation recording during specific tasks (reading, cognitive, or memory test) through devices embedded-cameras (laptop, tablet, phone). Eye-tracking has been validated in AD and MCI screening 10 years ago (Peltsch et al., 2014; Seligman and Giovannetti, 2015) with a cognitive impairment diagnosis sensitivity and specificity of respectively 0,75 and 0,73 in a recent systematic review and meta-analysis (Liu et al., 2021). In this review, only one case was reported (Deer et al., 2021) with a saccades-modifying condition. All other eye-tracking-related studies pointed to potential fixation difficulties (Ahmad et al., 2021; Davis et al., 2021; Deer et al., 2021; Fernández-de-Las-Peñas et al., 2021; Michelutti et al., 2022) in PACS patients but these were presumed to be curable for some items (Deer et al., 2021) [conjunctivitis (8.9%), keratoconjunctivitis (28.6%)]. However, good vision is mandatory to be able to use new spatial navigation assessments in addition to good visuospatial cognitive functions. Even if VR computer-generated environments were used to assess spatial navigation, RAPAs (Öhman et al., 2021) could destabilize AD older patients. PACS was younger, and zero to few spatial navigation abilities impairments were reported. Eye-tracking has been validated in combination with virtual reality (VR) simulation (Davis, 2021) as a RAPA, but under some conditions, there is a mismatch between the use of contemporary technologies and AD/control patients age (VR induced nausea, the inability to calibrate a device, or understand the instructions). Finally, persistent visual disturbances were reported in 3.3% ($n = 5/151$) to 8% ($n = 5/62$) of a 213 PACS cohort observational study, 3 months after the onset of COVID-19 (Michelutti et al., 2022).

The last RAPA is central hearing, which is less relevant for experts. Central hearing RAPA includes auditory temporal processing, dichotic tests, monaural low-redundancy speech tests, and auditory discrimination and memory tests (Tarawneh et al., 2022). These all depend on possessing efficient sensorineural hearing, which was reported as impaired in 4 short follow-up studies (Deer et al., 2021; Parker et al., 2021; Silva Andrade et al., 2021; Pinzon et al., 2022) and in up to 15% of PACS patients. Moreover, central hearing assessments depend on cognitive, memory, and attention abilities which could be widely impaired in respectively 70–90%, 70%, and 50–90% of a 3762 PACS patients' observational cohort. Approximately 7 months after the onset of COVID-19, (Davis et al., 2021), cognitive impairments are one of the three most frequently reported symptoms. One year after COVID-19 onset, in a non-included review, memory loss and attention abilities were still impaired in 19% and 18% of an 8591 patient PACS cohort (Han et al., 2022). Tinnitus and hyperacusis were reported in less than 30% of PACS patients, which could add a negative effect on hearing. Despite persistent hearing disorders reported in this review, no study reported central auditory tests on PACS patients justifying experts' recommendation to carry on using this RAPA.

This study has several limits. PACS has been gradually defined since the pandemic started until 6 October 2021 when a World Health Organization DELPHI consensus provided a clinical definition of PACS for adults and 16 February 2023 for children and adolescents. This evolving definition explains the extreme variability of assessment times in every review reported in this work, running from 2 to 52 weeks, and mainly in the first 30 weeks after the onset of COVID-19 (Table 1). This variability in definition could have contributed to overestimating PACS sustainability and as such, the recommendations that were made at the time. Moreover, many reviews can be classified as low or critically low quality because most of them did not provide a meta-analysis of their data, which can result in heterogeneity and a risk of biased assessments. Four of the six cohort observational studies received more than 75% quality score, a full score indicating a perfect level of quality. For the main concerns, bias was methodological. Observational studies (level 2 HAS scientific evidence) only allowed for a presumption of scientific quality compared to level 1 studies which were, mostly here, of low quality. Finally, COVID-19 papers and as such PACS ones, have been part of a larger phenomenon which consists in an increase of COVID-19-related publication numbers, a decrease in review time, and finally, a decline in methodological quality (Jung et al., 2021).

5. Conclusion

This work highlights the value of using RAPAs to screen preclinical AD, including PACS patient population. However, the stratification of RAPAs is essential in the post-COVID-19 period. Graphical, SPEECH, eye-tracking, central hearing, and spatial navigation abilities are still usable without any concern, but olfactory function may be altered by PACS and should be avoided in a preclinical AD screening assessment. This consensus statement will require an update after a few years to guarantee that treatments and recommendations continue to be supported by the latest evidence. More longitudinal studies are required to provide more evidence for the future of RAPA target modifications in PACS patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

AG led the supervision of this project. CV and AP organized the database and the first draft of the manuscript. VM and AG performed the entire consensus recommendations in which all authors took part. KS performed the extensive English editing. All authors contributed to the conception and design of the study, research study, manuscript revision, read, and approved the submitted version.

Funding

This research was funded in whole or in part by the Project ERANET JPcofuND 2-WG and French National Research Agency (ANR) under the Project ANR-22-JPW2-0002-01. With the aim

Acknowledgments

We would like to thank the ERANET JPcofuND 2 and French National Research Agency for funding and the NeuroMod Institute and Académie 5 of University Cote d'Azur for their support.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1206123/full#supplementary-material

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frontiers | Frontiers in Aging Neuroscience

TYPE Review
PUBLISHED 27 July 2023
DOI 10.3389/fnagi.2023.1221653

OPEN ACCESS

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RECEIVED 12 May 2023
ACCEPTED 07 July 2023
PUBLISHED 27 July 2023

CITATION
Han X, Ashraf M, Tipparaju SM and Xuan W (2023) Muscle–Brain crosstalk in cognitive impairment.
Front. Aging Neurosci. 15:1221653.
doi: 10.3389/fnagi.2023.1221653

Muscle–Brain crosstalk in cognitive impairment

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Sarcopenia is an age-related, involuntary loss of skeletal muscle mass and strength. Alzheimer's disease (AD) is the most common cause of dementia in elderly adults. To date, no effective cures for sarcopenia and AD are available. Physical and cognitive impairments are two major causes of disability in the elderly population, which severely decrease their quality of life and increase their economic burden. Clinically, sarcopenia is strongly associated with AD. However, the underlying factors for this association remain unknown. Mechanistic studies on muscle–brain crosstalk during cognitive impairment might shed light on new insights and novel therapeutic approaches for combating cognitive decline and AD. In this review, we summarize the latest studies emphasizing the association between sarcopenia and cognitive impairment. The underlying mechanisms involved in muscle–brain crosstalk and the potential implications of such crosstalk are discussed. Finally, future directions for drug development to improve age-related cognitive impairment and AD-related cognitive dysfunction are also explored.

KEYWORDS

skeletal muscle, sarcopenia, cognitive impairment, Alzheimer's disease, aging

1. Introduction

Aging is often considered an inevitable progressive process along with deteriorating functional decline. With increased longevity and decreased mortality, population aging has been sweeping the world rapidly in recent years (Beard et al., 2016). In the United States, there were more than 56 million individuals aged over 65 years in 2020, which accounts for 16.9% of the national population, and is estimated to be roughly 22% by 2050.[1]

Aging is often associated with decreased function in multiple key organs, including the brain, skeletal muscle, and the heart (North and Sinclair, 2012; Hambright et al., 2019; Hou et al., 2019). The strategy connecting this triple functional system could be a key to Alzheimer's disease (AD) prevention and rehabilitation. Physical and cognitive impairments are two major causes of disability in the elderly. Sarcopenia, an age-related involuntary loss of skeletal muscle mass and strength, is strongly associated with AD, a neurodegenerative disease with a prevalence of over 47 million globally (DeTure and Dickson, 2019; Beeri et al., 2021). Evidence from both clinical (Salinas-Rodriguez et al., 2021; Hu et al., 2022; Ramoo et al., 2022) and animal studies (Nagase and Tohda, 2021; Lee and Lim, 2022) demonstrates that skeletal muscle dysfunction may be a key factor that can contribute to cognitive impairment. So far, there is no effective cure for sarcopenia or AD. Drugs approved

1 https://www.americashealthrankings.org/explore/senior/measure/pct_65plus/state/ALL

for Alzheimer's disease are classified into acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists (Lin et al., 2021). However, AD patients cannot benefit much from these treatments due to the biological restriction of the blood-brain barrier (BBB), the low bioavailability, poor pharmacokinetics and pharmacodynamics of these drugs (Nunes et al., 2022). Current therapies or drugs available for AD focus on managing symptoms and mostly target the acetylcholinesterase system, which so far has turned out to generate mild effects with low clinical outcomes (Marucci et al., 2021). In addition, currently, there are no drugs approved by the Food and Drug Administration for the treatment of sarcopenia (Cho et al., 2022).

Drug treatments provided for both Alzheimer's Disease and sarcopenia remain ineffective; however, exercise has been proven to be highly effective in maintaining muscle mass and cognitive health (Beckwee et al., 2019; Huang et al., 2022). A recent study showed that exercise enhanced muscle-derived circulating factors release, which increased synaptic plasticity and hippocampal neurogenesis and thus improved cognitive function via muscle–brain crosstalk (Rendeiro and Rhodes, 2018). Therefore, early diagnosis and intervention for sarcopenia may benefit AD.

Based on earlier studies, in the present review, we summarize the latest findings on the association between sarcopenia and cognitive impairment. We also discuss the underlying mechanisms responsible for muscle–brain crosstalk. Finally, we will explore the potential strategies for targeting such crosstalk and future directions for drug development to improve cognitive function during aging and AD.

2. Association between sarcopenia and cognitive impairment

Skeletal muscle is the largest organ in the human body by weight and is responsible for maintaining body posture and performing voluntary movements (Tieland et al., 2018). Normal physiological functioning of skeletal muscle allows both physical activity and metabolic regulation. Thus, changes in skeletal muscle function and mass may significantly affect metabolism due to its sensitivity to insulin (Stump et al., 2006). Interestingly, the brain is also an insulin-sensitive metabolic organ that consumes 25% of the glucose in the body (Rossi et al., 2001). Therefore, there is potential endocrine crosstalk between skeletal muscle and the brain. Both animal studies and clinical trials have shown a strong association between sarcopenia and cognitive impairment. It has been demonstrated that skeletal muscle atrophy may have detrimental effects on cognitive function in multiple animal models. For instance, in 5XFAD transgenic mice (an Alzheimer's disease mouse model), muscle atrophy accelerated the onset of cognitive impairment, and the underlying mechanism may be mediated by hemopexin secreted from the atrophy muscle (Nagase and Tohda, 2021). Myokines released by atrophying muscles caused aberrant energy metabolism and thus impaired cognition in a type 2 diabetes mellitus mouse model (Lee and Lim, 2022). Consistent with these animal studies, clinical studies and meta-analyses revealed that sarcopenia is implicated in increased risk for cognitive impairment (Wu et al., 2021; Hu et al., 2022; Li et al., 2022). A meta-analysis including 18,788 participants based on 26 cohort, cross-sectional, and case-control studies found that participants with sarcopenia showed a higher risk of developing cognitive impairment [OR = 1.75; 95% CI = 1.57, 1.95; $P < 0.00001$]. Additionally, the MMSE score was lower in the sarcopenia group than that in the non-sarcopenia group [OR = −2.23; 95% CI = −2.48, −1.99; $P < 0.00001$] (Chen et al., 2022). Similarly, other meta-analyses demonstrated that sarcopenia is an independent risk factor for cognitive impairment (Chang et al., 2016; Cipolli et al., 2019; Peng et al., 2020). Two recent clinical studies further demonstrated the higher prevalence of cognitive impairment in older adults with sarcopenia. Longitudinal associations between sarcopenia and mild cognitive impairment (OR = 1.74; 95% CI 1.02, 2.96; $P = 0.04$), decreased cognitive function (β = −0.57; 95% CI−0.93, −0.21; $P < 0.01$), immediate verbal recall (β = −0.14; 95% CI−0.28, −0.01; $P = 0.04$), delayed verbal recall (β = −0.12; 95% CI−0.23, −0.01; $P = 0.03$), and semantic verbal fluency (β = −0.17; 95% CI−0.28, −0.05; $P = 0.01$) have been found in a study including 496 older Mexican adults. Sarcopenic elderly adults showed a 0.7% higher annual rate of mild cognitive impairment (Salinas-Rodriguez et al., 2021). Another cohort study including 1,946 respondents in rural Malaysia showed similar results. Sarcopenic elderly adults have an 80% higher risk of cognitive impairment compared with those without sarcopenia (RR 1.80; 95% CI 1.18–2.75) (Ramoo et al., 2022). Taken together, these studies support a strong link between muscle atrophy and cognitive impairment. Early diagnosis and intervention for sarcopenia may impede the progression of cognitive impairment.

3. Potential mechanisms of skeletal muscle–brain crosstalk in cognitive function regulation

Clinical studies support a potential association between skeletal muscle and cognitive function, but the underlying mechanisms remain unknown. In this review, we have focused on the association between sarcopenia and cognitive function during aging and AD. It is very likely that the aging brain could have an impact on skeletal muscle function, and it is a challenge to identify all the connecting dots. People with cognitive dysfunction or AD may have less physical activity, causing a decline in muscle function. Skeletal muscle could release different cytokines and other muscle fiber-derived peptides or myokines under distinct conditions (So et al., 2014). However, here, we emphasize the myokines signal within the muscle, which potentially leads to crosstalk between skeletal muscle and the brain, involving age as a common denominator between cognitive dysfunction and AD-related cognitive impairment. Thus, skeletal muscle could act as an active endocrine organ and regulate the function of distant organs or tissues. These cytokines and myokines serve as messengers for communication between skeletal muscle and the brain (Kim et al., 2019). In the present review, we summarize potential beneficial factors and detrimental factors in muscle–brain crosstalk during aging.

3.1. Beneficial factors governing muscle and cognitive function

3.1.1. IGF-1

Insulin-like growth factor-1 (IGF-1) is a 70-amino acid polypeptide and is synthesized by hepatocytes and other organs, including skeletal muscle (Yakar et al., 2018; Li et al., 2019). IGF-1 is essential to skeletal myogenesis, which plays a critical role in maintaining muscle mass and function (Vitale et al., 2019). Decreased IGF-1 was observed in muscle atrophy (Grounds, 2002) and was also noted to be essential for brain function. Previous studies demonstrated that IGF-1 deficiency induced cognitive impairment during aging both in human and rodent models (Deak and Sonntag, 2012; Toth et al., 2022). The level of IGF-1 is significantly decreased in sarcopenia patients, which might be due to physical inactivity (Widajanti et al., 2022). Skeletal muscle release of IGF-1 was also decreased in aged mice. However, no specific effects on muscle recovery were observed when IGF-1 alone was replenished; the combination of IGF-1 and exercise was demonstrated to reduce skeletal muscle wasting to some extent (McMahon et al., 2014). This study indicates the specific role of skeletal muscle-secreted IGF-1 in improving muscle loss and cognitive function. So far, no direct evidence shows that exogenous IGF-1 could improve cognitive function during aging. But exogenous supplementation of IGF-1 showed improvement in cognitive function. The beneficial effect is likely due to inhibition of inflammation and oxidative stress (Wang et al., 2020).

3.1.2. Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF), which is classified into the neurotrophin family, was initially found to be essential for brain development and the nervous system (Chao et al., 2006). BDNF is extensively expressed in the nervous system, but recent studies show that skeletal muscle can also release BDNF, which supports the myokine role of BDNF (Lebrun et al., 2006; Raschke et al., 2013). BDNF also promotes myoblast differentiation, maintains the survival of motor neurons (Sakuma et al., 2015), and functions as a contractile-inducible protein (Moreira-Pais et al., 2022). Therefore, deterioration of skeletal muscle mass in sarcopenia, along with limited physical activity or a sedentary lifestyle in the elderly, may contribute to decreased levels of BDNF. Low BDNF levels were closely related to cognitive impairment, which may increase the incidence of AD (Bathina and Das, 2015; Siuda et al., 2017). Taken together, these findings support the idea that dysregulated BDNF could be the potential link between sarcopenia and AD.

3.1.3. Irisin

In recent years, Irisin has emerged as a key factor secreted mostly from the skeletal muscle that provides beneficial effects to both the skeletal muscle and the brain. At the molecular level, Irisin is a pro-myogenic factor that is a cleaved form of fibronectin type III domain-containing protein 5 (FNDC5) (Moreno-Navarrete et al., 2013). Irisin has been proven to enhance insulin sensitivity and boost glucose and lipid metabolism in skeletal muscle (Shen et al., 2022). Irisin has been demonstrated to ameliorate muscle wasting by accelerating myoblast fusion and protein synthesis (Huh et al., 2014). A recent study found that the level of irisin decreased during aging, and chronic administration of irisin can improve metabolic dysfunction and ameliorate skeletal muscle atrophy in aged mice (Guo et al., 2023). Regarding brain function, the genetic deletion of irisin impaired cognitive function (Islam et al., 2021). As a mediator of muscle-brain crosstalk, irisin improved cognitive function with an increase in BDNF expression (Peng and Wu, 2022). Loss of irisin is involved in cognitive impairment during aging, and exogenous administration of irisin improved cognitive function in the AD preclinical model (Madhu et al., 2022). Hence, irisin may be a promising cure for aging-related sarcopenia and cognitive impairment (Gao et al., 2013).

3.1.4. Secreted protein acidic and rich in cysteine

Secreted protein acidic and rich in cysteine (SPARC) is a novel secretory matricellular glycoprotein, defined as a myokine, which is released by skeletal muscle contraction during exercise (Aoi et al., 2013). SPARC is involved in skeletal muscle biology, which is upregulated during muscle regeneration (Petersson et al., 2013). It could counteract the abnormal deposition and accumulation of adipose tissue in aged skeletal muscle (Ko et al., 2016). In addition, during aging, the level of SPARC is decreased and SPARC knockout mice showed the sarcopenia phenotype (Ghanemi et al., 2022). Overall, there are potential beneficial roles for SPARC in skeletal muscle, and studies demonstrate that SPARC can be a potential new therapeutic target via muscle–brain crosstalk.

3.2. Mediators with dual roles

3.2.1. IL-15

Interleukin-15 (IL-15) is a pleiotropic myokine released by skeletal muscle during exercise. IL-15 is widely involved in skeletal muscle metabolism (Quinn et al., 1995) and protects proteins from degradation while improving insulin sensitivity and promoting myogenesis (O'Leary et al., 2017; Nadeau and Aguer, 2019). During aging, the level of IL-15 in skeletal muscle decreases (Quinn et al., 2010) as shown in a cross-sectional study with 160 outpatient elderly people which demonstrated the inverse correlation between plasma IL-15 levels and sarcopenia (Yalcin et al., 2018). The human data correlate well with the animal data, in which it was noted that IL-15 was decreased in gastrocnemius muscle in aged rats (Marzetti et al., 2009). Another study identified that IL-15 could also serve as a detrimental pro-inflammatory factor in the brain and showed increased serum IL-15 levels, which can be utilized as a biomarker for Alzheimer's disease since IL-15 has been extensively studied in AD pathophysiology (Rentzos et al., 2006; Bishnoi et al., 2015). The contradictory roles of IL-15 in the skeletal muscle and in the brain may be due to an aging-related inflammation environment and different sources of IL-15. Low-grade inflammation during aging increases the release of the pro-inflammatory IL-15 from reticular stromal cells and other myeloid cell types, while it decreases the release of IL-15 from skeletal muscle (Naismith and Pangrazzi, 2019). The level of IL-15 could be a potential contributor to exercise

benefits in sarcopenia and cognitive function improvement (Tsai et al., 2019; Pahlavani, 2022).

3.2.2. LIF

Leukemia inhibitory factor (LIF) is an important member of the IL-6 type cytokine family with 180 amino acid residues (Nicola and Babon, 2015). Skeletal muscle produces and releases LIF (Broholm and Pedersen, 2010), which is associated with the skeletal muscle homeostasis. Previous reports showed that LIF increased muscle glucose uptake via the PI3K-Akt signaling pathway (Brandt et al., 2015). Additionally, LIF stimulates the proliferation of satellite cells and muscle regeneration, which is a promising therapy for muscle atrophy (Kurek et al., 1998; Broholm et al., 2011). The level of LIF has been found to decline in sarcopenic obesity (Pahlavani, 2022). Importantly, LIF could cross the blood-spinal cord barrier and behave as a neuropoietic cytokine in the central nervous system. LIF is essential for the recovery of the nervous system from injury. Furthermore, LIF mediates inflammatory reactions in AD (Lemke et al., 1996). In AD patients, a higher expression of LIF was observed in degenerating human brains compared with normal brains (Soilu-Hanninen et al., 2010). However, the specific mechanism by which LIF could influence the AD brain remains unknown.

3.2.3. IL-6

Interleukin-6 (IL-6), a member of the cytokine family, has both inflammatory and anti-inflammatory effects. The proinflammatory function of IL-6 is involved in aging-related diseases. Studies in the elderly have found that an increased level of IL-6 is associated with the occurrence of sarcopenia (Bian et al., 2017; Rong et al., 2018). However, enhanced release of IL-6 during muscle contraction also induced myogenic differentiation (Steyn et al., 2019). A combination of recombinant IL-6 and treadmill training in old mice could enhance their endurance training adaptation together with functional capacity improvement (Leuchtmann et al., 2022). However, due to the sedentary lifestyle of sarcopenia patients, the beneficial role of IL-6 may decrease, and the inflammatory effects may overwhelm the anti-inflammatory roles. As an inflammatory factor, IL-6 can cross the BBB and impair brain function (Banks et al., 1994). Inflammatory IL-6 is involved in cognitive impairment during AD. An increase in IL-6 levels in AD brains was observed, and its neutralization or inhibition of the IL-6 signaling pathway alleviated cognition decline (Silva et al., 2021). Based on the above evidence, it is likely that during aging, the release of muscle-derived anti-inflammatory IL-6 decreases, accelerating the progression of AD.

3.2.4. Lactate

Lactate is a metabolic substrate, secreted from skeletal muscle during mechanical muscle contractile stimulation. A previous study showed that lactate promoted myoblast differentiation *in vitro* via myogenic determination protein-dependent signaling pathway, and moreover, lactate could cross the BBB, facilitating the expression of BDNF in the brain (El Hayek et al., 2019). The role of lactate in cognitive function is not clear, and additional studies are necessary for understanding its role in the brain. A cross-sectional study including 2,523 participants showed that a higher plasma lactate level was associated with systemic inflammation and an increased probability of mild cognitive impairment (Pan et al., 2019). However, another study evaluating the cerebrospinal fluid (CSF) lactate in 267 outpatients reported the opposite results, and the level of lactate in CSF was decreased in patients with AD (Bonomi et al., 2021). Therefore, additional studies are needed to explain these contradictory observations.

3.3. Detrimental factors governing muscle and cognitive function

3.3.1. Cathepsin B

Cathepsin B is a typical member of the cysteine lysosomal protease family. It is recognized as a myokine released from skeletal muscle following exercise (Kim et al., 2019). An *in vitro* study showed that cathepsin B participated in myotube formation (Jane et al., 2002). During aging, cathepsin B levels were upregulated in microglia, which contributed to the generation of mitochondrial-derived reactive oxygen species (ROS), causing increased inflammation and thereby impaired memory (Ni et al., 2019). Similarly, enhanced translocation of cathepsin B reduced sirtuins and promoted proinflammatory reactions in senescent microglia, resulting in cognitive impairment (Meng et al., 2020). On the other hand, cathepsin B could cross the BBB and promote BDNF expression in the hippocampal area and improve memory function (Moon et al., 2016). It is obvious from the above reports that additional studies are needed to determine the function of cathepsin B in muscle–brain crosstalk in elderly adults.

3.3.2. Myostatin

Myostatin, which is known as growth and differentiation factor 8, is secreted by skeletal muscle. It is a negative mediator in skeletal muscle growth (Gao et al., 2013), which decreases muscle size and mass. Myostatin deficiency is beneficial to skeletal muscle metabolism (Cleasby et al., 2016). Myostatin inhibits the expression of myogenic differentiation-related genes, such as Myod and Myf5, in a smad3-dependent manner (Langley et al., 2002). Myostatin could accelerate proteolysis in the soleus and impede protein turnover *in vivo* and in C2C12 cells. The potential mechanism may be mediated by the phosphorylation of Smad3 (Manfredi et al., 2017). Interestingly, the level of myostatin in 12-month-old double transgenic amyloid precursor protein and presenilin 1 (APP/PS1) mice was elevated, which may trigger skeletal muscle atrophy and cognitive deficits. Knockdown of myostatin with shRNA in these mice attenuated skeletal muscle degradation and memory loss (Lin et al., 2019). Importantly, increased release of myostatin by skeletal muscle in sarcopenia patients promoted cognition decline in the elderly population, thus increasing the risk of AD (Siriett et al., 2006; Bergen et al., 2015).

3.3.3. Growth differentiation factor-15

Growth differentiation factor-15 (GDF-15) belongs to the transforming growth factor β (TGF-β) superfamily. Stress enhances its release. GDF-15 has been reported as a biomarker for sarcopenia. An elevated level of GDF-15 during aging was found, which was related to the decline of skeletal muscle mass and function (Kim et al., 2020). Cross-sectional and 2 year prospective analyses involving 788 participants supported the finding that an increased level of GDF-15 was associated with the prevalent sarcopenia (Kim et al., 2022). GDF-15 has also been recognized as a biomarker for aging-related cognitive decline (Jiang et al., 2016). A cohort study with 1,603 participants demonstrated an association between elevated plasma GDF-15 and an increased risk of dementia (McGrath et al., 2020). Another longitudinal Sydney Memory and Aging Study, consisting of 1,037 participants, also reached similar conclusions (Fuchs et al., 2013). Hence, GDF-15 is a detrimental mediator for muscle–brain crosstalk and a potential target for the treatment of sarcopenia and cognitive dysfunction.

3.3.4. IL-8

Interleukin 8 (IL-8) is a CXC member of the chemokine family, which is a myokine released by skeletal muscle during exercise (Akerstrom et al., 2005). IL-8 acts as a pro-inflammatory factor in sarcopenia (da Costa Teixeira et al., 2023). A UK cohort study including 336 community-dwelling elderly men and women demonstrated that an elevated IL-8 level was associated with an increased risk of sarcopenia (Oflazoglu et al., 2020). Consistent with this, several clinical studies have shown that sarcopenia in the elderly had higher levels of IL-8 compared with the non-sarcopenia group (Fan et al., 2022; Teixeira et al., 2022). Interestingly, IL-8 is also identified as a biomarker during AD progression (Swardfager et al., 2010; Alsadany et al., 2013). In addition, a higher level of IL-8 in the elderly was associated with poorer cognitive performance (Baune et al., 2008). The potential mechanism may be related to its role in microglia migration toward Aβ deposits associated with senile plaques and activation of microglial cells (Li et al., 2009). However, besides skeletal muscle cells, other cell types, including macrophages and endothelial cells, also release IL-8 (Nielsen and Pedersen, 2007; Luo et al., 2022). Therefore, the cellular sources of IL-8 and its biological role in sarcopenia and AD need further study.

4. Targeting the skeletal muscle to combat cognitive decline

4.1. Exercise

Different studies support the fact that exercises benefit the skeletal muscle system and improve memory function. Here, we summarize aerobic exercise and resistance exercise, which are two major types of exercise, along with their effects on skeletal muscle and cognitive function during aging.

4.1.1. Aerobic exercise

Multiple animal studies demonstrate the beneficial effects of AE on sarcopenia. These studies show that AE improved skeletal muscle atrophy in sarcopenia mice and reversed chronic inflammation and dysfunctional mitochondria via sestrin2 in an AMPK alpha-2-dependent manner (Liu et al., 2021). Lifelong aerobic exercise activates autophagy and inhibits protein degradation via AMPK/PGC-1α signaling, thereby improving aging-related muscle atrophy (Liang et al., 2021). Similar findings showed the therapeutic effects of habitual aerobic exercise on sarcopenia in a senescence-accelerated mice prone8 model via enhanced mitochondrial maintenance and muscle protein synthesis (Aoki et al., 2020). Despite promising results in animal experiments, so far limited clinical studies regarding AE and its beneficial effects in humans are inconclusive. A cross-sectional study including older women treated with aerobic training, secondary lifestyle, and resistance training showed that AE could not decrease the prevalence of sarcopenia, but resistance training was effective (Supriya et al., 2022). AE showed beneficial effects on cognitive impairment as well. A meta-analysis involving 1,364 mild cognitive impairment participants demonstrated that AE could improve the cognitive function of older adults with mild cognitive impairment (Yong et al., 2021). The underlying mechanism of such beneficial effects might be due to activation of the NF-κB/miR-503/BDNF pathway (Niu et al., 2018), increased myokines (BDNF and IGF-1), and reduction of inflammatory cytokines (Tsai et al., 2018, 2019).

4.1.2. Resistance exercise

Resistance exercise (RE) is a form of exercise intended to increase muscular strength and endurance. Consistent evidence from clinical trials supports the benefits of RE in sarcopenia. RE improves muscle strength, muscle quality, and muscle performance in elderly adults with sarcopenia (Chen et al., 2021; Mende et al., 2022; Zhao et al., 2022). Potential mechanisms include the rejuvenation of satellite cells (Hsu et al., 2022) and the improvement of mitochondrial and autophagic function in skeletal muscle (White et al., 2016). Furthermore, a number of multilevel meta-analyses were used to demonstrate that RE enhances cognitive function regardless of cognitive status and age (Northey et al., 2018; Wilke et al., 2019; Landrigan et al., 2020; Zhang et al., 2020). It is believed that myokines are the key factors in RE that contribute to cognitive function improvement. However, it was demonstrated that RE could either increase or demonstrate no effect on the IGF-1 level (Titus et al., 2021). Furthermore, compared with traditional resistance exercise, the combination of RE and cognitive tasks improved brain function and BDNF level (Castano et al., 2022). The effect of RE on myokine release was also sex-dependent, and previous studies showed that mixed low-resistance training only increased plasma levels of BDNF in male participants, but no changes in female participants were noted. RE could be beneficial to counteract sarcopenia and memory loss in elderly adults. However, RE might be suitable only for early intervention. Patients suffering from dementia, AD, or sarcopenia are significantly associated with a low level of physical activity, higher disability, and poor quality of life. Thus, physical exercise is not a good option for these patients. In either case, a better understanding of the

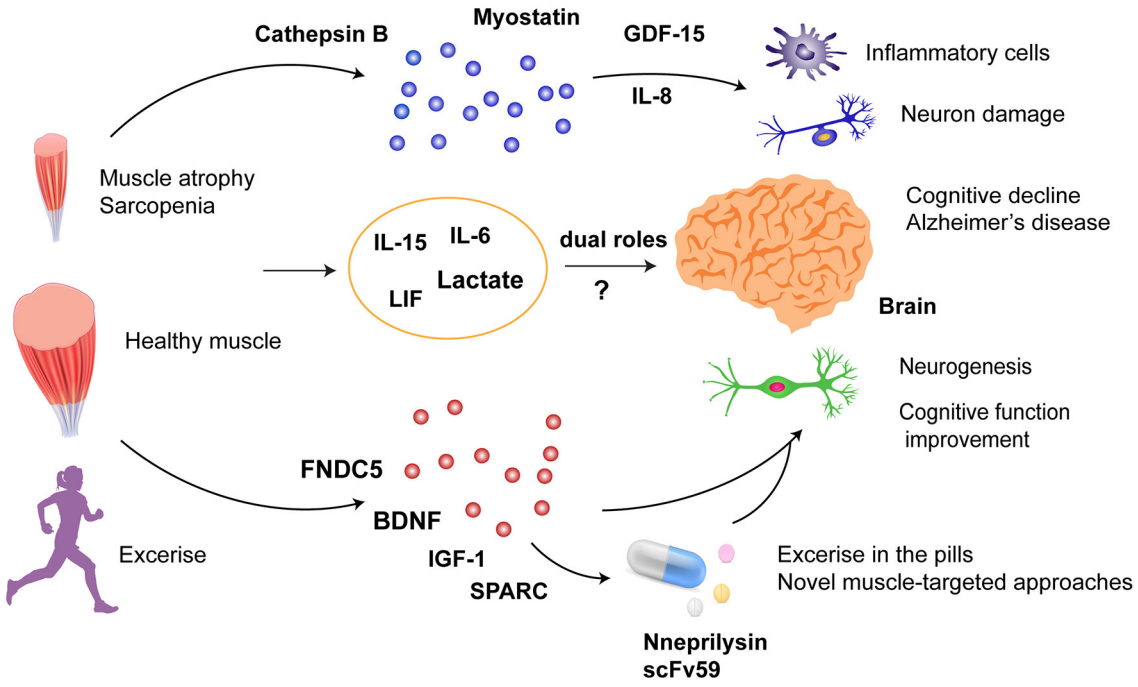

FIGURE 1
Muscle–brain crosstalk in cognitive dysfunction. Myokines or cytokines released from skeletal muscle affect neurons and inflammation in the brain: (1) detrimental factors: cathepsin B, myostatin, and GDF-15; (2) dual roles: IL-15, IL-6, LIF, and lactate; (3) beneficial factors: FNDC5, BDNF, IGF-1, and SPARC. Exercise-enhancing release of beneficial factors and specific overexpression of neprilysin and scFv59 in the skeletal muscle could be promising strategies against cognitive dysfunction. GDF15, Growth differentiation factor-15; IL-8, interleukin 8; IL-15, interleukin-15; IL-6, interleukin-6; LIF, leukemia inhibitory factor; FNDC5, fibronectin type III domain containing protein 5; BDNF, brain-derived neurotrophic factor; IGF-1, insulin-like growth factor-1; SPARC, secreted protein acidic and rich in cysteine.

molecular and cellular mechanisms that mediate the benefits of physical activity will help in the development of potential therapeutic approaches.

4.1.3. Muscle-targeted strategies for cognitive function improvement

Compared with the brain, muscles have more accessibility for intervention, especially using invasive strategies. Preclinical studies have shown that several muscle-targeted treatments enhance cognitive function. Muscle-specific overexpression of neprilysin and scFv59 or knockdown of myostatin using genetic approaches showed favorable effects on the brain. Overexpression of neprilysin in the muscle reduces Aβ amyloid deposits in the brain (Li et al., 2020), while increased scFv59 expression in the muscle reduces Aβ amyloid levels in the cerebrospinal fluid (Yang et al., 2013). Cell-based therapy is another promising strategy. For example, intramuscular injection of stem cells releasing regenerative factors enhanced neurogenesis and astrogliogenesis in the aged mouse hippocampus (Huntsman et al., 2018). These muscle-targeted strategies have translational potential in cognitive impairment therapy.

5. Limitations and perspectives

Sarcopenia and dementia are common geriatric diseases. AD is the most common cause of dementia and the fifth leading cause of death in elderly adults. Importantly, the estimated total healthcare costs for the treatment of AD in 2020 were estimated at US $305 billion, which is expected to increase to more than US $1 trillion as the population ages (Wong, 2020). To date, no effective cures for AD have been reported. Therefore, drug development for cognitive dysfunction and AD is important. Clinical observations and pre-clinical studies revealed muscle–brain crosstalk on cognitive function (Figure 1). In pre-clinical studies, it seems that myokines are the key mediators in muscle–brain crosstalk during cognitive dysfunction, but currently, no clinical trials on the effects of these myokines have been conducted. Exercise seems to be a promising intervention for sarcopenia and cognitive impairment. Due to physical inactivity in patients with sarcopenia or AD, exercise might not be the first-line intervention for patients in the late stages of the disease. However, exercise could be used as a platform to discover potential beneficial factors contributing to a favorable outcome. In addition, muscle-specific conditional knockout animals and AD preclinical models are useful for studying the underlying mechanisms. A few muscle-targeted approaches via the regulation

of muscle gene expression, extrinsic supplementation, and stem cell transplantation showed promising results to improve cognitive function or promote neurogenesis. However, for future clinical applications, dose-dependent efficacy, pharmacokinetics, and delivery routes need to be taken into consideration.

6. Conclusion

Evidence from pre-clinical studies and clinical observations supports the idea that muscle–brain crosstalk plays a critical role in cognitive function. Muscle-targeted intervention is promising for improving aging or AD-related cognitive decline. In the present review, we outlined three principal areas for skeletal muscle and brain crosstalk, namely, (a) beneficial strategies, (b) mediators that play dual roles (i.e., protective and damaging roles), and (c) strategies that may cause increased risk and advance the disease condition during aging.

Author contributions

XH drafted the manuscript. ST, MA, and WX reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Funding

This study was supported by NIH AG070145 and USF startup funds (to WX), NIH DK119066 and William Saunders Endowment (to ST), and NIH AR070029 (to MA).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Aging Neuroscience

TYPE Review
PUBLISHED 03 August 2023
DOI 10.3389/fnagi.2023.1209863

OPEN ACCESS

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RECEIVED 21 April 2023
ACCEPTED 10 July 2023
PUBLISHED 03 August 2023

CITATION
Chen D, Chen Q, Qin X, Tong P, Peng L, Zhang T and Xia C (2023) Development and evolution of human glutaminyl cyclase inhibitors (QCIs): an alternative promising approach for disease-modifying treatment of Alzheimer's disease.
Front. Aging Neurosci. 15:1209863.
doi: 10.3389/fnagi.2023.1209863

Development and evolution of human glutaminyl cyclase inhibitors (QCIs): an alternative promising approach for disease-modifying treatment of Alzheimer's disease

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Human glutaminyl cyclase (hQC) is drawing considerable attention and emerging as a potential druggable target for Alzheimer's disease (AD) due to its close involvement in the pathology of AD via the post-translational pyroglutamate modification of amyloid-β. A recent phase 2a study has shown promising early evidence of efficacy for AD with a competitive benzimidazole-based QC inhibitor, PQ912, which also demonstrated favorable safety profiles. This finding has sparked new hope for the treatment of AD. In this review, we briefly summarize the discovery and evolution of hQC inhibitors, with a particular interest in classic Zinc binding group (ZBG)-containing chemicals reported in recent years. Additionally, we highlight several high-potency inhibitors and discuss new trends and challenges in the development of QC inhibitors as an alternative and promising disease-modifying therapy for AD.

KEYWORDS

Alzheimer's disease, human glutaminyl cyclase, amyloid-β, pyroglutamate modification, QC inhibitor, PQ912, PBD150

1. Introduction

Alzheimer's disease (AD) is a complex neurodegenerative disease that is clinically characterized by progressive and irreversible dysfunction of language, memory, and cognition (Association, 2023). AD is the leading cause of dementia in the elderly, representing 60–80% of dementia cases globally (Association, 2023). Projections indicate that the number of people living with dementia around the world will sharply increase from 55 million to 139 million by 2050 (Association, 2023). However, for more than a century, only five drugs have been approved for the symptomatic treatment of AD, and these drugs are incapable of retarding or reversing disease progression. China and the United States have recently approved the mannan oligosaccharide GV-971 (Syed, 2020) and the anti-Aβ antibody aducanumab (Aduhelm) (Dhillon, 2021) as novel disease-modifying treatments for AD, respectively. Nevertheless, both treatments have been questioned for their limited clinical efficacy in clinical trials. Therefore, it is still urgently needed to develop new disease-modifying therapies for the early intervention of AD.

The deposition of senile plaques, dominantly consisting of β-amyloid proteins (Aβs), is one of the pathological hallmarks of AD brains. Full-length $Aβ_{1-40/42}$ is generated through the amyloidogenic processing of the amyloid precursor protein (APP) mediated by the β-site APP cleaving enzyme (BACE) and γ-secretase complex (Chen et al., 2017). Compelling evidence showed that the highly hydrophobic and aggregation-prone $Aβ_{1-40/42}$ plays an upstream role in the pathological progression of AD via inducing tau hyperphosphorylation, synaptic dysfunction, and neuroinflammation (Selkoe and Hardy, 2016; Lee et al., 2017). Hundreds of Aβ targeting or Aβ-related therapeutic strategies have thus been proposed in the past three decades (van Bokhoven et al., 2021), while unfortunately most of the interventions failed in clinical trials due to limited effects on cognition recovery or unfavorable safety profiles in AD patients.

Aβs in the senile plaques are highly diverse and heterogeneous due to various post-translational modifications (PTMs) such as truncations, oxidation, and pyroglutamation (Roher et al., 2017). The continuous failures have prompted researchers to reevaluate the role of PTMs of Aβ in the pathogenesis of AD (Grochowska et al., 2017; Roher et al., 2017). Among the PTMs, the pyroglutamation product pE_3-Aβ has recently been shown to be closely involved in AD (Figure 1) and is gradually presumed to be a highly desirable biomarker and intervention target (Jawhar et al., 2011a; Bayer, 2022). pE_3-Aβ is formed through the dehydration and cyclization of the Glu3 residue of the truncated $Aβ_{3-40/42}$ under the catalytic action of human glutaminyl cyclase (hQC) (Figure 1) (Schilling et al., 2004; Cynis et al., 2008). It is noteworthy that the release of truncated $Aβ_{3-40/42}$ is independent of BACE and may primarily relate to Meprins, members of the "astacin family" of metalloproteinases, which are able to cleave APP after the Ala2 at the N-terminus of the Aβ sequence (Stephan Schilling and Demuth, 2010).

pE_3-Aβ constitutes a prominent fraction of the total Aβ species in AD brains (Harigaya et al., 2000; Wu et al., 2014) and the critical initiating role of pE_3-Aβ in AD was supported by several lines of evidence (Figure 1) (Gunn et al., 2010; Nussbaum et al., 2012). First, pE_3-Aβ has hundreds-fold higher aggregation ability (Schilling et al., 2006) and is much easier to maintain the neurotoxic oligomeric states compared with full-length Aβ (Lee et al., 2014; Gunn et al., 2016; Wulff et al., 2016). It can also act as seeds to accelerate Aβ assembly (Dammers et al., 2017b) and subsequently form denser, more stable, and cytotoxic Aβ/pE-Aβ copolymers than those of $Aβ_{1-40/42}$ aggregates (Schilling et al., 2006; Nussbaum et al., 2012). Second, pE_3-Aβ is perhaps more resistant to aminopeptidase due to the lactam ring in the N-terminus of pE_3-Aβ (Gontsarova et al., 2008), which contributes to prolonged neurotoxicity *in vivo*. In addition, observations revealed that pE_3-Aβ acts upstream of the neurotoxic Aβ cascade (Dammers et al., 2017a; Bayer, 2022). It progressively accumulates in the brain at the early stage of AD, even before full-length Aβ aggregation, and subsequently triggers neurodegeneration and ultimately exacerbates the severity of AD pathology and cognition. In a most recent study, donanemab, a pE_3-Aβ-specific antibody developed by Eli Lilly, significantly cleared amyloid plaques and slowed down cognitive deterioration in patients with mild AD in a phase II trial (Mintun et al., 2021) and met all the primary and secondary endpoints in a phase III trial (TRAILBLAZER-ALZ 4), reducing brain amyloid plaque levels by 65.2% at 6 months compared to baseline (data were shared on 30 November 2022 at the Clinical Trials on Alzheimer's Disease conference). All this evidence strongly supports pE_3-Aβ as an effective therapeutic target (Perez-Garmendia and Gevorkian, 2013).

QC is intimately associated with the pathology and severity of AD by paralleling the generation of pE-Aβ in the brain (Figure 1) (Morawski et al., 2014), and the deposition of pE-Aβ was found to be restricted to APP/QC co-expression areas (Hartlage-Rübsamen et al., 2018). Furthermore, the expression and enzymatic activity of QC are significantly elevated and are positively correlated with both the accumulation of pE-Aβ and cognition decline in the brains of AD subjects compared with those of age-matched controls (Valenti et al., 2013; Gunn et al., 2021). Besides, both QC knockout and treatment with QC inhibitors (QCIs) significantly rescue the behavioral phenotype and alleviate disease-like pathology in the AD mouse model (Schilling et al., 2008; Jawhar et al., 2011b). Hence, small molecule-based QCIs provide an alternative, promising, and cost-effective therapeutic approach apart from immunotherapy for early-stage AD treatment (Coimbra et al., 2019; Coimbra and Salvador, 2021; Xu et al., 2021). Recently, PQ912 (varoglutamstat), a QC competitive inhibitor developed by Probiodrug AG, passed the clinical phase IIa trial (Scheltens et al., 2018) and is regarded as the proof-of-concept validation of QC.

Over the past two decades, a number of QCIs, including both synthetic and natural compounds, have been discovered. Several reviews focusing on the function of QC and the development of QCIs have been published (Coimbra et al., 2019; Vijayan and Zhang, 2019; Coimbra and Salvador, 2021; Xu et al., 2021; Zhang et al., 2022), while new design and screening strategies have been applied in discovering new QCIs with unique structural characteristics in recent years. Hence, we reexamine the discovery and evolution of QC inhibitors, with a particular interest in classic Zinc binding group (ZBG)-containing chemicals. In addition, we highlight several representative high potent inhibitors as well as the challenges of QCIs as potential disease-modifying therapies for AD.

2. Brief functions and structural features of hQC

N-terminal pyroglutamation of proteins is ubiquitously found in a variety of organisms, including bacteria, plants, and animals, and two types of QCs with distinctive structures and catalytic sites have been identified and classified in these organisms so far. Type I QCs are mainly found in plants and bacteria, as exemplified by *Papaya* QC and *Myxococcus xanthus* QC, while type II QCs are primarily present in animals (Taudte et al., 2021), such as *Drosophila melanogaster* QC and human QC (hQC), which share substantial sequence identity and structural similarity (Koch et al., 2012b). Type I QC exhibits a five-bladed β-propeller structure composed of β-sheets and antiparallel β-strands, together with a Ca^{2+}-binding motif in the active core (Carrillo et al., 2010), which significantly differs from the α/β topology and Zn^{2+}-binding motif in the catalytic center of Type II hQCs (Taudte et al., 2021).

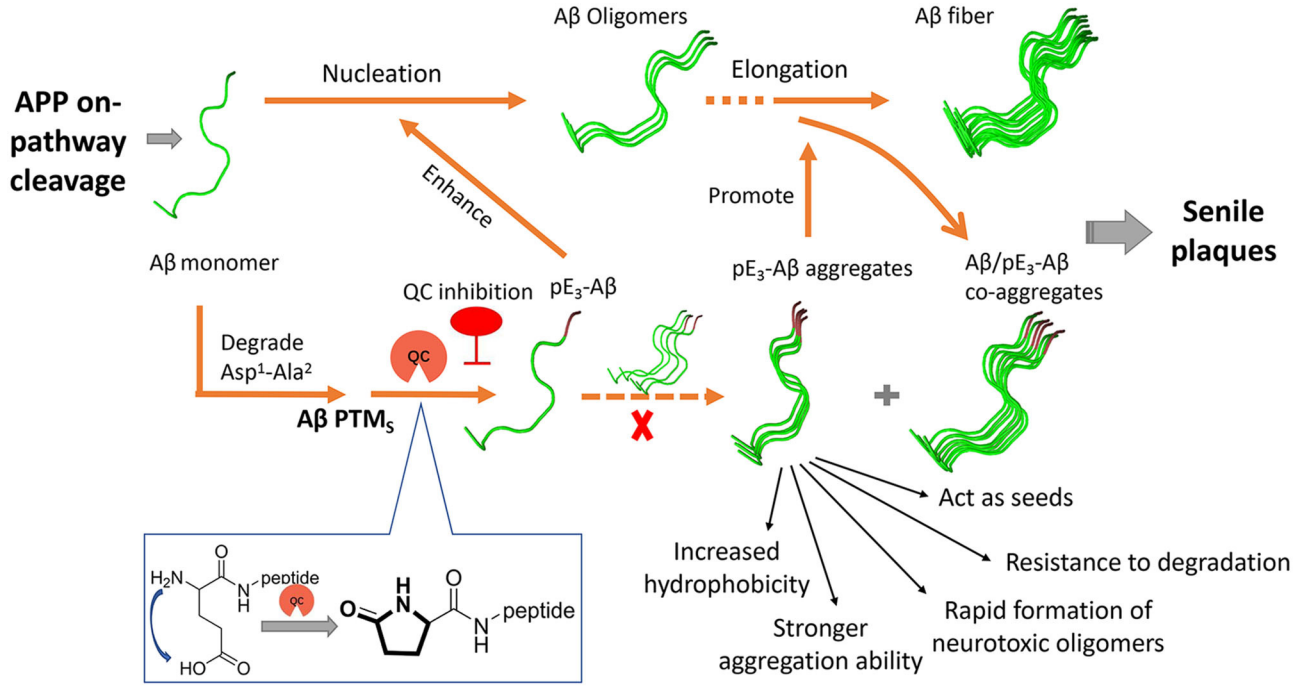


FIGURE 1
Generation and roles of pE_3-Aβ in AD and schematic drawing of the QC inhibition approach.

hQC, known as human glutaminyl-peptide acyltransferase (QPCT, EC2.3.2.5), belongs to the acyltransferase family and is abundant in the human brain and neuronal tissues. hQC is broadly expressed in various neurons, including urocortin-1 and cholinergic Edinger-Westphal neurons, as well as locus coeruleus and nucleus basalis Meynert neurons (Morawski et al., 2010). Normally, hQC promotes the maturation of neuropeptides or cytokines such as gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), and chemokine CCL-2 via catalyzing the cyclization of glutamine residue at the N-terminus of proteins (Cynis et al., 2011; Becker et al., 2016; Vijayan and Zhang, 2019). It was later revealed that QC only shows modest specificity for cyclization of their primary glutaminyl substrates (Seifert et al., 2009), it can also catalyze N-terminal glutamate cyclization (Schilling S. H. et al., 2003; Schilling et al., 2004), which thus provides a close link between QC and AD pathophysiology via the formation of pE-Aβ. Nevertheless, the enzymatic conversion has strikingly different condition preferences, with glutaminyl conversion occurring with an optimum pH of 8.0, whereas glutamyl conversion is favored at a pH of 6.0 (Schilling et al., 2004).

There are two isoforms of QC in humans, namely, the secretory QC (sQC, 361aa, encoded by the QPCT gene located at 2p22.2) and golgi-resident QC (gQC or isoQC, 382aa, encoded by the QPCTL gene located at 19p13.32). sQC is a secreted protein that contains a N-terminal secretion signal, while gQC contains a N-terminal anchor responsible for the retention within the Golgi complex. sQC and gQC share a sequence identity of >45%, have similar catalytic domain sizes, and catalyze the same enzymatic reaction (Stephan et al., 2009), making it uneasy to design iso-specific inhibitors. The discrepancy distribution of sQC and gQC results in the conversion of different substrates and even distinct physiological roles, which was suggested to be beneficial to the complementary function regulation of QC in a non-catalytic specificity manner (Coimbra and Salvador, 2021). As pE-Aβ in humans is mainly catalyzed by sQC rather than gQC *in vivo*, we will focus on the sQC inhibitors for the treatment of AD in this review.

The catalytic domain of sQC contains Zn^{2+} and approximately 330 amino acid residues, exhibiting a globular α/β-fold open-sandwich topology that comprises a central six-stranded β-sheet (among which two were antiparallel) surrounded by two and six α-helices on the opposite sides and flanked by two α-helices at one edge of the β-sheet (Huang et al., 2005; Xu et al., 2021). The catalytic domain has a hydrophobic entrance and a relatively narrow binding pocket. The essential Zn^{2+} is located at the bottom of the active pocket, coordinating with three conservative residues (Asp159, Glu202, and His330) and a water molecule to form a tetrahedral structure, which is necessary for catalysis (Huang et al., 2005). The loop domains near the active center of sQC have certain conformational variabilities that might be affected by N-linked glycosylation (Ruiz-Carrillo et al., 2011); meanwhile, the glycosylation has a limited impact on the overall structure and catalytic activity of sQC but may influence its solubility (Schilling et al., 2002; Ruiz-Carrillo et al., 2011). The crystal structure of hQC also revealed a unique hydrogen-bond network in the active site, formed by five highly conserved residues (Ser160, Glu201, Asp248, Asp305, and His319), within which Glu201 and Asp248 participate in binding to the substrate. When natural substrates or inhibitors enter the catalytic center, the carbonyl of glutamine, glutamate, or other metal binding groups can replace water molecules to coordinate with Zn^{2+} (Huang et al., 2008; Coimbra and Salvador,

2021), thereby catalyzing or inhibiting the cyclization of glutamine and glutamate of the substrates. The structural features, especially the mono-Zn^{2+} binding model, offer the most valuable guidance for the design and discovery of QCIs.

3. Development and evolution of QCIs

3.1. Rational design and experiment-based QCIs

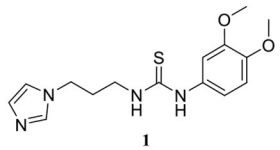
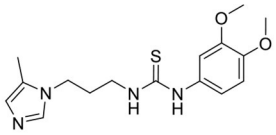
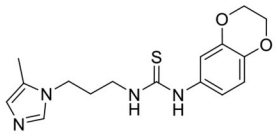
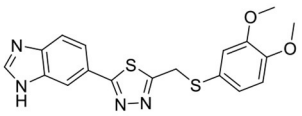
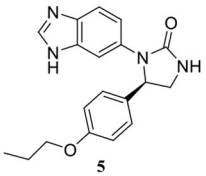
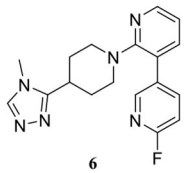
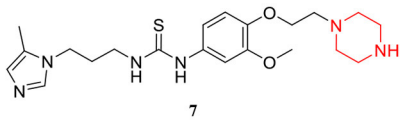
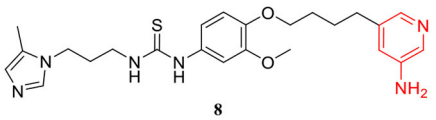
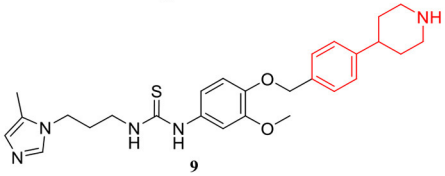
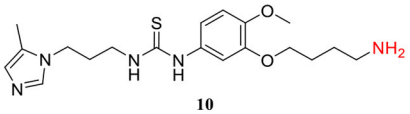
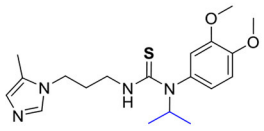
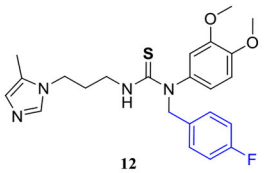
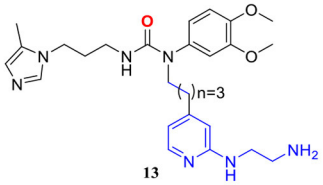
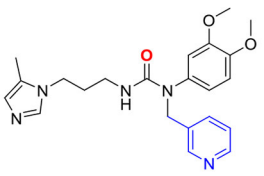
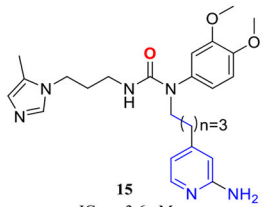
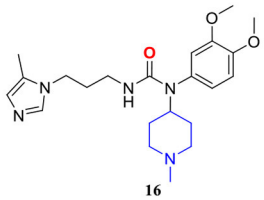
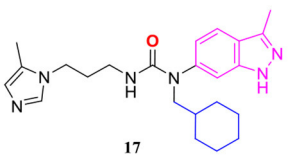
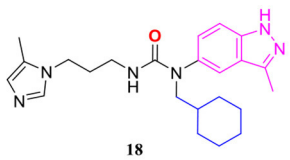
A metal-chelating group has been initially considered an essential functional component for the construction of QCIs since the identification of hQC as a Zn^{2+}-dependent metalloenzyme and the discovery that chelators such as imidazole and its analogs have weak QC inhibitory activity (Schilling S. et al., 2003; Schilling S. H. et al., 2003; Demuth et al., 2004a,b). Probiodrug AG (currently Vivoryon Therapeutics N.V.) was a pioneer in developing high-activity QCIs (Demuth et al., 2004a,b; Buchholz et al., 2008), and as early as 2006, the company contributed the foundational literature for the design and discovery of the first high potent imidazole-containing QC inhibitor via mimicking a tripeptide (Gln-Phe-Ala-NH_2) substrate (Buchholz et al., 2006). The strategy has been proven to be highly efficient in generating a library of QCIs with K_i ranging from nanomolar to micromolar. In particular, the strongest inhibitor **1** (Table 1A), known as PBD150 or PQ50, had an excellent K_i of 60 nM (Buchholz et al., 2006). It was unexpected that PBD150 was approximately 19-fold more effective toward sQC than gQC, whereas the co-crystallization of PBD150-sQC complex revealed an almost identical binding mode as observed in PBD150-gQC complex, except for the slightly stronger hydrophobic interaction with Ile303 compared with that of Val324 in gQC (Huang et al., 2011). The binding properties of PBD150 to sQC in solution provide additional evidence that the conformation of PBD150 is susceptible to disruption through protein-protein interactions (Koch et al., 2012a). Surprisedly, replacing imidazole in PBD150 with 5-methyl imidazole leads to a stronger inhibitor **2** (Table 1A), with almost a 10-fold increase in the activity compared with PBD150 (Buchholz et al., 2009). However, the inhibitory activity of **3** (Table 1A) decreased to basal level when connecting with the two methoxy groups on the benzene ring (Tran et al., 2013). Subsequent studies regularly employed comparable substrate-mimicking approaches utilizing an alternative $A\beta_{3-5}$ (Glu-Phe-Arg) or used PBD150 and **2** as lead compounds, leading to the identification of inhibitors with shared pharmacophores and an increasingly elucidated structure-activity relationship (SAR).

The classic framework of these inhibitors consists of three crucial motifs A, B, and C (Figure 2). The motif A contains a zinc-binding group (ZBG) or general metal-binding group (MBG), with imidazole, benzimidazole, and triazole as the most common structure entities. The imidazole-based ZBG, particularly the 5-methyl imidazole, is commonly the first choice (Kumar et al., 2013), leading to the fact that the imidazole-based inhibitors constitute the vast majority of the total QCIs. Recently, hydrazides were identified as the most potent ZBG compared with other classic Zn-binders (Kupski et al., 2020), which offer another option for designing novel inhibitors. The motif B contains at least a hydrogen bond donor (HBD) or a hydrogen bond acceptor (HBA); it is usually peptide amide analogs such as urea, thiourea, and their derivatives. Both urea and thiourea contributed not only more than one HBD and HBA but also flexible bonding (Tran et al., 2019). The motif C is normally an aromatic ring opposite or close to the ZBG, mimicking the Phe2 residue of $A\beta_{3-5}$, which participates in the π-π interaction with the benzyl side chain of the essential Phe325 of QC. Among these classic inhibitors, PBD150 (Buchholz et al., 2006), **5** (PQ912) (Lues et al., 2015), and **6** (SEN177) (Jimenez-Sanchez et al., 2015) were the most outstanding representatives of imidazole, benzimidazole, and triazole-based QCIs, respectively (Table 1A). These inhibitors exhibit favorable pharmacodynamic profiles and are widely used as positive controls in numerous studies. However, only PQ912 is undergoing clinical trials until now.

The Phe2 and Arg3 residues of $A\beta_{3-5}$ both are deeply involved in the interaction with QC. Nevertheless, the significant role of the guanidine side chain of Arg3 was underestimated earlier. To further mimic the feature of the guanidine group and to improve the QC inhibitory activity, Jeewoo Lee et al. added a nitrogen-containing heterocyclic group as an extended motif D based on the scaffold of **2** (Hoang et al., 2017). The newly developed inhibitors displayed 5- to 40-fold activity increase compared with **2** (IC_{50} =29.2 nM in this assay). Though **7** (IC_{50} =0.7 nM for hQC, Table 1B) was the most potent candidate even among previously reported inhibitors, it was found to be inactive in an acute ICR mice model to study the *in vivo* pE_3-$A\beta_{40}$ lowering efficacy. Whereas compound **8** (IC_{50} = 4.5 nM for hQC, Table 1B) exhibited a prominent efficacy of lowing pE_3-$A\beta_{40}$ by 54.7%, significantly reducing the brain pE_3-$A\beta_{42}$ level of APP/PS1 mice, and restoring the cognitive function of 5×FAD mice. Based on these encouraging results, the authors then systematically studied the SAR of **7** and **8** by modifying the Arg-mimetic motif, leading to the discovery of **9** (IC_{50} = 6.2 nM, Table 1B) (Ngo et al., 2018a) and **10** (IC_{50} = 8.8 nM, Table 1B) (Ngo et al., 2018b). Molecular modeling studies demonstrated that all these inhibitors formed extra strong salt bridge interactions with the carboxylate residue of Glu327, supporting the necessity of the extended motif D in high potent QC inhibitor design.

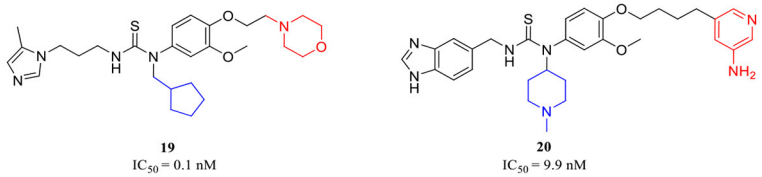
The X-ray structure showed that the PBD150 resided in the active site of hQC with a bent Z-E conformation (Huang et al., 2011; Hoang et al., 2019), while the 2-aminopyridine of extended D in **8** can freely rotate in the active site as revealed by molecular modeling (Hoang et al., 2017), suggesting the possibility of improving binding potency and inhibitory activity by a conformational restriction. Jeewoo Lee et al. creatively incorporated a conformational blocker into the urea or thiourea nitrogen of motif B to induce the formation of bent Z-E conformers (Hoang et al., 2019). The strategy was proven to be effective as well. 24 inhibitors with various rigid blocks showed a significant activity enhancement with *in vitro* IC_{50} below 10 nM compared with PBD150 (evaluated IC_{50} = 29.2 nM in this assay). The **11**, **12**, and **13** have a remarkably low IC_{50} value of 2.8 nM, 1.3 nM, and 1.6 nM, respectively, while the *in vivo* QC inhibition efficacy of these compounds was much weaker than that of **14** (IC_{50} = 8.7 nM), **15** (IC_{50} =3.6 nM), and **16** (IC_{50} = 6.1 nM) (Table 1C), which suppressed the generation of pE_3-$A\beta_{40}$ by more than 20% in an acute mouse model compared with a negative control. Among the selected inhibitors,

TABLE 1 Representative design and experiment-based QCIs.

(A) QCIs with classic motifs A, B, and C	
 **1** **PBD150** K_i = 60 nM  **2** K_i = 6.3 nM  **3** K_i = 58 nM  **4** K_i = 23 nM  **5** **PQ912** K_i = 24.6 nM  **6** **SEN177** K_i = 20 nM	**1** (Buchholz et al., 2006); **2** (Buchholz et al., 2009); **3** (Tran et al., 2013); **4** (Ramsbeck et al., 2013); **5** (Lues et al., 2015); **6** (Pozzi et al., 2018)
(B) QCIs with extended motif D	
 **7** IC_{50} = 0.7 nM  **8** IC_{50} = 4.5 nM  **9** IC_{50} = 6.2 nM  **10** IC_{50} = 8.8 nM	**7**, **8** (Hoang et al., 2017); **9** (Ngo et al., 2018a); **10** (Ngo et al., 2018b)
(C) QCIs with restricted conformation	
 **11** IC_{50} = 2.8 nM  **12** IC_{50} = 1.3 nM  **13** IC_{50} = 1.6 nM  **14** IC_{50} = 8.7 nM  **15** IC_{50} = 3.6 nM  **16** IC_{50} = 6.1 nM	**11–16** (Hoang et al., 2019)
 **17** IC_{50} = 3.2 nM  **18** IC_{50} = 2.3 nM	**17**, **18** (Van Manh et al., 2022)

(Continued)

TABLE 1 (Continued)

(D) QCIs with conformational blockers and extended motif D	
 **19** IC_{50} = 0.1 nM **20** IC_{50} = 9.9 nM	**19**, **20** (Van Manh et al., 2021)

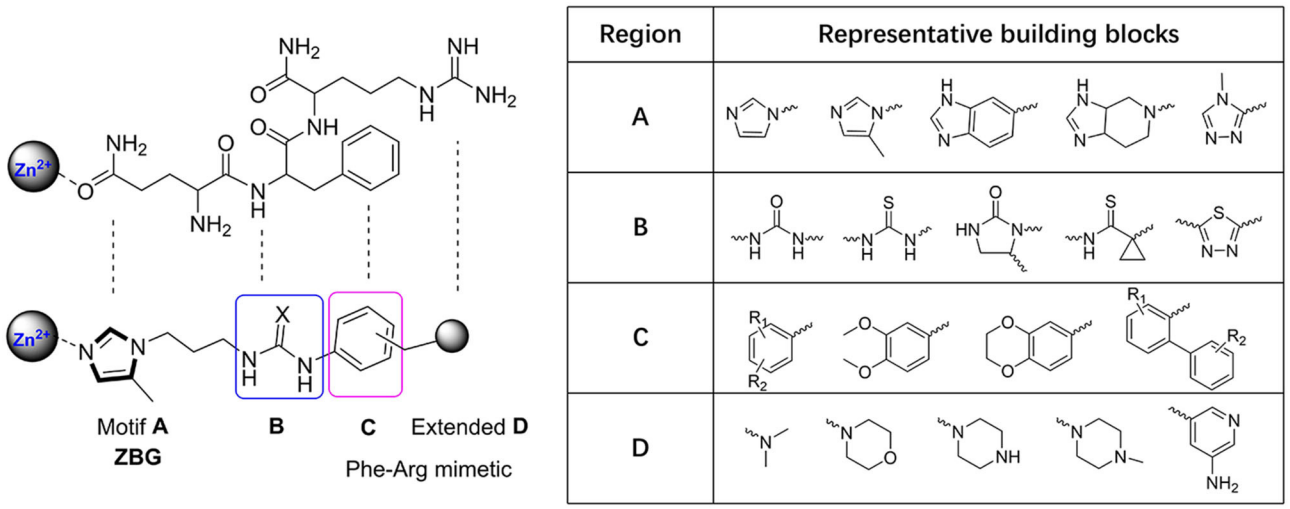


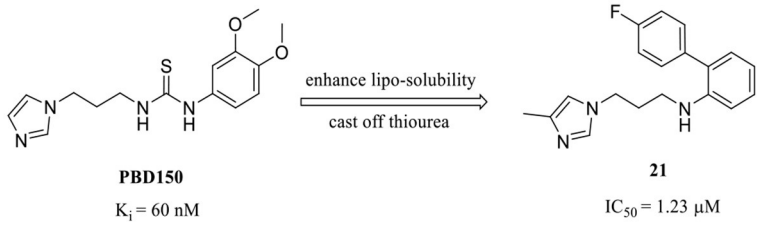
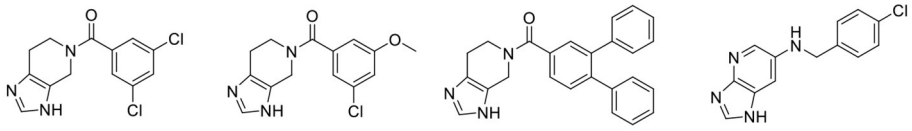
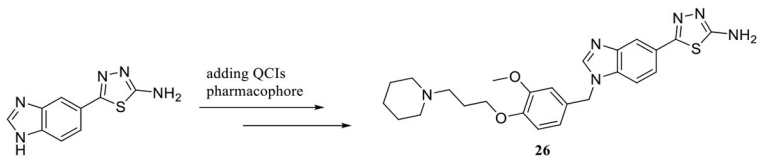
FIGURE 2
Essential pharmacophores of the classic QC inhibitor and its representative building blocks.

16 exhibited the most promising *in vivo* efficacy and druggable profiles, such as liver microsomal stability and up to 50-fold inhibitory selectivity against gQC. The molecular docking further demonstrated that **16** displayed a Z-E conformation at the active site of QC, as anticipated. The N-substituted piperidinyl blocker of **16** not only restricted the conformation but also formed additional hydrophobic interactions with Tyr299, Val302, and Ile303, which may be highly correlated with the high inhibitory activity and QC selectivity. Remarkably, the SAR indicates that the effect of conformational restriction was more marked in the urea series than that of thiourea. In their recent study, the 3,4-dimethoxyphenyl group of the urea series scaffold was replaced by indazole bio-isosteres, which were regarded as more metabolically stable. The representative **17** and **18** (Table 1D), both containing an N-cyclohexylurea blocker, displayed remarkable inhibitory IC_{50} values of 3.2 and 2.3 nM, respectively (Van Manh et al., 2022).

Inspired by the encouraging results of both mimetic-Arg motif D and conformational restriction strategies on the classic QC scaffold. A combination of the two approaches was rationally performed, leading to the discovery of **19** (Table 1D), the most potent QC inhibitor reported even to date, with a sub-nanomolar IC_{50} value of 0.1 nM and up to 290-fold inhibitory enhancement compared with PQ912. While similar to the denouement of **12**, another weaker benzimidazole inhibitor **20** (IC_{50} = 9.9 nM, Table 1D) showed the most promising *in vivo* efficacy and selective profile with respect to its 21.5-fold sQC selectivity index toward gQC. Besides, **20** also has low toxicity and favorable pharmacokinetic properties, and it significantly improved the alternation behavior of mice in Y-maze tests as well.

Among these QCIs with high scaffold similarity, the common large polar groups such as urea and thiourea reduce the blood-brain barrier (BBB) permeability of the compounds, which may be the most likely reasons for the moderate or even inactive *in vivo* efficacy of the high potent inhibitors PBD150 (Brooks et al., 2015), **7**, **11**, **12**, **19**, etc. To ameliorate BBB permeability, Wu et al. tried to introduce a more hydrophobic biphenyl group in motif C to enhance molecular lipo-solubility as well as π-π stacking interaction and abandon the urea group in motif B (Li et al., 2017). The obtained **21** (Table 2A) exhibited potent inhibitory activity and significantly improved BBB permeability. Further assessments corroborated that **21** dramatically reduced the pE-Aβs level in cultured cells and *in vivo* and improved the behavior of B6C3-Tg AD mice. Interestingly, contrary to the commonly reported relationship, the SAR of DPCIs showed that 4-methyl substitution was better than that of 5-methyl substitution in imidazole. Although the activity of **21** was significantly decreased compared with the lead compound PBD150 due to the loss of the classic urea motif, the acquisition of SAR and the simple synthesis route of DPCIs still made it an ideal lead scaffold for further structural optimization.

TABLE 2 Other representative QCIs.

(A) QCIs designed for improving BBB permeability	
 **PBD150** K_i = 60 nM **21** IC_{50} = 1.23 μM	**21** (Li et al., 2017)
(B) QCIs designed for non-hsQC with potent hsQC inhibitory activity	
 **22** PgQC K_i = 0.100 μM hQC K_i = 0.387 μM **23** PgQC K_i = 0.087 μM hQC K_i = 0.385 μM **24** PgQC K_i = 0.126 μM hQC K_i = 0.132 μM **25** PgQC K_i = 53 nM hQC K_i = 0.655 μM	**22–24** (Ramsbeck et al., 2021); **25** (Taudte et al., 2021)
 novel ZBG fragment hit **26** Human gQC IC_{50} = 73 nM Human sQC IC_{50} = 12 nM Modification CD47/SIRPa axis	**26** (Park et al., 2022)

3.2. Representative QCIs designed for non-hsQC with potent hsQC inhibitory activity

Although the structural differences in both the overall conformations and active cores are essential and convenient for the design of type I/II QC-specific inhibitors, some bacterial QCs, such as *porphyromonas gingivalis* QC (PgQC), show similar structures and enzymatic features to hQC and were thus characterized as Mammalian-like type II QCs (Lamers et al., 2021). Therefore, inhibitors designed for bacterial QCs may also bind to and suppress hQC activity. For example, PgQC inhibitors **22–24** (Table 2B) designed for the treatment of periodontitis are almost equally potent in suppressing hQC activity *in vitro* (Lamers et al., 2021; Ramsbeck et al., 2021). Meanwhile, another inhibitor **25** with imidazo[4,5-b]pyridin scaffold exhibited a significantly improved selectivity (>12) over PgQC (Taudte et al., 2021).

Human gQC was recently recognized as an important modulator of the CD47-SIRPα pathway via promoting pGlu formation on the N-terminus of CD47 (Logtenberg et al., 2019). The gQC blockade contributes to reducing the "do not eat me" immune signals of CD47 on tumor cells. Therefore, developing gQC inhibitors is regarded as a novel and promising strategy for cancer immunotherapy. In a most recent study, a novel ZBG (1*H*-benzimidazol-5-yl)-1,3,4-thiadiazol-2-amine was hit by a fragment identified through library screening, and an aromatic ring and alkylamine were further added as additional QC pharmacophores. The most potent gQC inhibitor **26** (Table 2B) showed an outstanding IC_{50} of 73 nM, while unluckily it has 6-fold stronger activity against sQC with an IC_{50} of 12 nM (Park et al., 2022), which further indicates that more attentions should be paid to the selectivity of inhibitors when developing QCIs for the treatment of AD.

3.3. Virtual screening-based QCIs

In addition to the various rational design and experimental-based QCI discoveries, virtual screening offers another efficient tool to advance the understanding of activity profiles, and the development of new QCIs (Kumar et al., 2013; Lin et al., 2019). Those screening strategies include fragment-based screening (Szaszko et al., 2017), QSAR modeling (Al-Attraqchi and Venugopala, 2020; Kumar et al., 2021), and pharmacophore-assisted high-throughput virtual screening (Lin et al., 2019). Katharigatta N. Venugopala et al. developed linear and non-linear 2D QSAR models and a partial least squares-based 3D model to help predict the activity of not yet synthesized compounds.

Combined with ADME filtering and 2D-similarity search, potential QCIs **27**–**29** (Table 3) were identified from the ZINC database (Al-Attraqchi and Venugopala, 2020). Similarly, Ashwani Kumar et al. identified the structural features that are both positively and negatively responsible for the QC inhibitory activity based on a dataset of 125 QCIs for QSAR analysis via Monte Carlo modeling studies. The QSAR further supports the importance of 5-methy substituted imidazole and alkyl-substituted benzene in activity enhancement, as previous SAR revealed, and novel compounds **30**–**32** (Table 3) were then computationally designed and showed improved *pKi* and QC binding affinities (Kumar et al., 2021). The hits of the two studies actually inherited typical features of classic QCIs with imidazole or methyl-imidazole as ZBG and an aromatic group located in the opposite position, while the QC inhibitory activities were not experimentally evaluated and validated *in vitro*.

Combining activity evaluation with virtual screening will provide more convincing evidence. Kam Y. J. Zhang et al. reported a QC inhibitor **33** (Table 3) with a novel MBG moiety, peperidine-4-carboxamide, through a pharmacophore-assisted high-throughput virtual screening (Dileep et al., 2021). **33** showed moderate activity against QC with $IC_{50} = 33.4 \pm 5.1\,\mu M$, and docking, MD simulation, and crystallographic studies suggested that **33** anchors to the active site via a coordinate bond with Zn^{2+} located deeply in the active site cleft of the QC, while it lacks stacking interactions with Tyr299, Phe325, and Trp329, which are assumed to be critical for QC activity.

Wu et al. performed a less efficient but simple and direct approach for new scaffold QCIs discovery by repurposing FDA-approved drugs (Xu et al., 2020). Such a repurposing strategy is more likely to succeed since the drugs have been fully evaluated in both pre-clinical and clinical trials. The QC inhibitory evaluation of 1,621 drugs was performed at a concentration of 10 μM *in vitro*, and the top five compounds were highlighted with reasonable activity. Although the inhibitory activity was relatively weak with IC_{50} values at the millimolar level, only two drugs contained the imidazole group; the other three drugs **34**–**36** (Belinostat, Amlexanox, and Acipimox; Table 3) have completely different structures from the classic QCIs model, which may still offer insights for the design and discovery of novel QCIs with new structural features.

3.4. Natural product-based QCIs

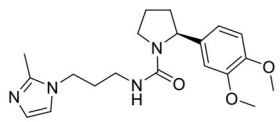
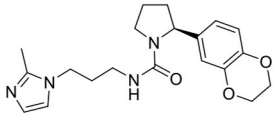
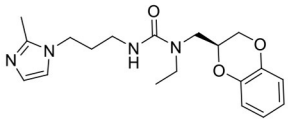
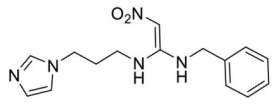
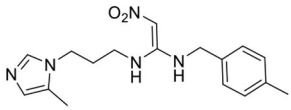
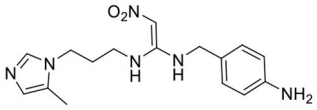
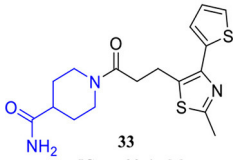
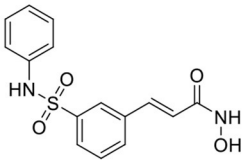
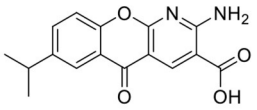
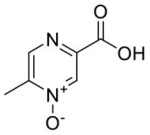
Imidazole- and benzimidazole-based ZBGs have so far been the first choice for the design of QC inhibitors. Nevertheless, these ZBG groups are less selective and are likely to interact with various metalloproteins *in vivo* and thus increase the risk of side effects (Park et al., 2022). Natural products are an important resource for the discovery of new activity scaffolds, which may offer opportunities to overcome the potential drawbacks of classic QCIs with new pharmacophores (Table 4). The oleuropein aglycone (OLE, **37**, Table 4), a natural phenol (secoiridoid) abundant in extra virgin olive oil, was found to be protective both in memory and behavioral performance of young and middle-aged TgCRND8 mice (Grossi et al., 2013). In an extended study of aged TgCRND8 mice showing increased pE_3-$A\beta_{42}$ deposits in the brain, OLE could also retard the growth of pE_3-$A\beta_{42}$ aggregates even in advanced and late stages of Aβ deposition (Luccarini et al., 2015). Several reviews summarized OLE as a QC inhibitor, while OLE certainly showed weak inhibitory activity at a concentration of 10 μM. Immunofluorescence staining and immunoblot analysis demonstrated that QC levels were significantly reduced in the brains of the OLE-fed Tg mice, suggesting that OLE is active against pE-Aβ generation by reducing QC expression rather than direct inhibition (Luccarini et al., 2015).

Some algal extracts were preliminary reported to have positive effects on QC inhibition, while the bioactive chemical entities were not isolated and clearly identified by traditional methods, Wessjohann et al. identified three sulfolipid QC inhibitors (**38**–**40**, Table 4) from microalgae using a new "Reverse Metabolomics" technique including an activity-correlation analysis. The sulfolipids showed a noteworthy QC inhibition of 76% at a low concentration of 0.025 mg/ml, and the authors proposed that sulfolipids provide similar pharmacophore characteristics to PBD150, in which the negative sulfonate group and the polyhydroxy elements probably act as a ZBG and the glucose as the core scaffold. Interestingly, SODG (structure not shown), a lipid product used as a standard reference in the assay, was first shown to exhibit quite similar QC inhibition activity compared with sulfolipids (Hielscher-Michael et al., 2016). Unlike traditional natural product screening approaches, Wu et al. explored apigenin-based QCI discovery via chemical modification. A total of 40 apigenin derivatives belonging to the phenol-4′(R1), C5-OH(R2), and C7-OH(R3) modified series were synthesized and evaluated. The compound **41** (Table 4) has remarkable inhibitory potency with an IC_{50} value of 16.1±2 μM, and the SAR study indicated that the C7-OH was required for binding with Zn^{2+} and that the C5-OH was favored, whereas phenol-4′ was tolerant for the inhibitory activity. The essential role of C7-OH was further supported by the binding interaction with conservative Zn^{2+} via molecular docking. Although the activity of apigenin derivates was relatively weak compared with nanomolar level classic QCIs, the non-imidazole ZBG, acquisition of SAR, and simple synthesis route made it a potential lead scaffold for further optimization (Li et al., 2016).

4. QC inhibitor undergoing clinical trials

Hundreds of QC inhibitors have been revealed in the literature, and reports of novel, high-potency QC inhibitors have dramatically increased in recent years with the structure-activity relationships becoming clear, while only PQ912 is currently undergoing clinical trials in human subjects for AD treatment. PQ912 has a scaffold slightly different from the common classic QCIs (Table 1A). It is a heterocyclic competitive inhibitor with benzimidazole as the ZBG at position 1 of the imidazolidine-2-one. PQ912 has strong human, rat, and mouse QC inhibitory activity with K_i values ranging between 20 and 65 nM (Hoffmann et al., 2017). Preclinical studies revealed that PQ912 has an attractive drug-like profile and

TABLE 3 Representative screening-based QCIs.

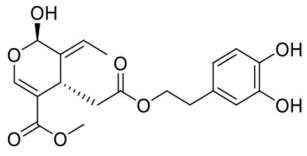
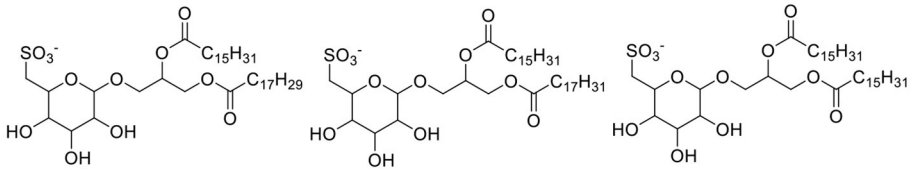
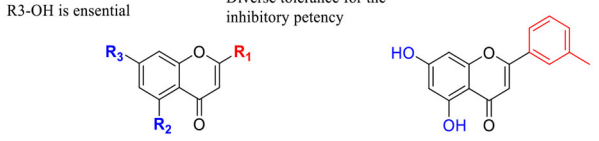
 **27**  **28**  **29**	**27–29** (Al-Attraqchi and Venugopala, 2020)
 **30**  **31**  **32**	**30–32** (Kumar et al., 2021)
 **33** IC_{50} = 33.4 μM	**33** (Dileep et al., 2021)
 **34** Belinostat IC_{50} = 2.98 mM  **35** Amlexanox IC_{50} = 3.80 mM  **36** Acipimox IC_{50} = 6.23 mM	**34–36** (Xu et al., 2020)

robust pharmacological therapeutic effects, both *in vitro* and *in vivo* (Hoffmann et al., 2017). PQ912 was considered safe and well tolerated with dose-proportional pharmacokinetics up to doses of 200 mg in the first-in-man phase 1 study (Lues et al., 2015). In the subsequent randomized, double-blind, placebo-controlled phase IIa trial (NCT 02389413), the safety, tolerability, and efficacy of higher doses of PQ912 (800 mg twice daily for 12 weeks) were carefully evaluated in biomarkers confirmed early AD patients (n = 120). PQ912 showed an acceptable safety and tolerability profile in a treatment regime of lower doses and slower titration (Scheltens et al., 2018). The treatment of PQ912 resulted in an average QC target occupancy of >90% in cerebrospinal fluid (CSF), an improvement of working memory, and a reduction of synaptotoxicity and neurogranin levels, as well as improvements in some other experimental endpoints (Scheltens et al., 2018). However, no PQ912 treatment effects were found on the composite scores of episodic memory, executive function, attention, or overall cognition (Scheltens et al., 2018). The results of the phase IIa study might indicate early beneficial effects of PQ912 on cognition by preventing the synaptotoxicity of pE-Aβ in the central nervous system and thus rescuing impaired synaptic functions. While episodic memory is the most impaired area of function in AD pathology, a relatively short intervention (12-week time period) by PQ912 was actually not expected to have an obvious clinical influence on episodic and long-term memory. To further test the efficacy (particularly on cognition and brain activity) of PQ912 as a disease modifier, a phase IIb program in participants with MCI and mild AD-VIVIAD was recently launched, and results are expected early in 2023 (Vijverberg et al., 2021).

5. New trends toward QCIs

Theoretically, QC inhibition can significantly decrease the formation of pE-Aβ while having little influence on the clearance of full-length Aβ and the existing pE-Aβ, which may still induce Aβ cascades and lead to the deposition of senile plaques. Hence, QC inhibition-based combination therapy and multi-target-directed ligands (MTDL) have drawn considerable attentions in recent years. The combination effects of PQ912 and a pE-Aβ specific antibody m6 on the formation and clearance of pE-Aβ in an AD mouse model were evaluated. The study showed that combination treatments resulted in significant reductions of total Aβ by 45–65% in the brain of AD mouse overexpressing both human amyloid precursor protein containing the Swedish and London mutations and human QC (hAPPsl × hQC), while single treatments at subtherapeutic levels only showed a moderate (16–41%) but statistically insignificant reduction in Aβ level. The additive effects of the combination of PQ912 and m6 on brain Aβ pathology were evaluated using a bliss independence model, and a combination index of ≈1 was determined (Hoffmann et al., 2021). The combination strategy may achieve a better therapeutic effect than a single treatment, even at a reduced dose for the individual drug.

TABLE 4 Natural compounds with potential QC inhibitory activity.

 **37** (oleuropein aglycone, OLE)	**37** (Luccarini et al., 2015) and CAS: 31773-95-2
 **38** **39** **40** 76% inhibition of QC at 0.025 mg/mL	**38–40** (Hielscher-Michael et al., 2016)
R3-OH is ensential Diverse tolerance for the inhibitory petency  R2-OH is favored **Scaffold of apigenin** **41** 93.0% inhibition of QC at 100 μM QC IC_{50} = 16.1μM	**41** (Li et al., 2016)

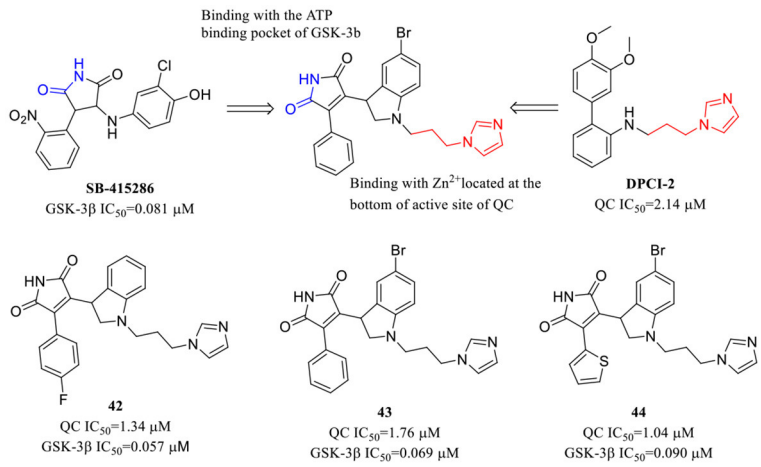
Instead of drug combination treatment, Wu et al. in their recent study developed a new class of maleimide-DPCI hybrid QC/GSK-3β dual inhibitors by rationally combining the essential pharmacophores of QC and GSK-3β inhibitors. GSK-3β, namely, glycogen synthase kinase-3, is regarded as a critical pivotal kinase and a high-potential anti-AD target that links both Aβ and tau pathologies of AD. The most potent compounds **42**–**44** (Table 5) exhibited slightly enhanced QC inhibitory activity and similar GSK-3β inhibitory activity compared with individual control compounds DPCI-2 and SB-415286, respectively. The selected dual-target inhibitor **42** can dramatically reduce pE-Aβ accumulation and Tau hyperphosphorylation in the brains of 3 × Tg-AD mice. In addition, **42** also effectively attenuates cognitive deficits and decreases anxiety-like behavior in 3 × Tg mouse (Xie et al., 2023).

6. Perspective and conclusion

pE_3-Aβ represents a highly desirable and abundant target due to its distinctive aggregation properties and neurotoxicity. As QC plays a key role in the conversion and formation of pE_3-Aβ, QC inhibition is emerging as an alternative promising strategy apart from expensive active immune clearance to decrease the pathological toxicity of pE_3-Aβ for the treatment of AD. Over the past two decades, a number of different scaffold QCIs have been designed and discovered, and the efficacy of several high potent inhibitors has been evaluated both *in vitro* and *in vivo* using different AD mice models. Moreover, PQ912 is regarded as the proof-of-concept validation of the QC target. However, there are still issues to be considered before QC inhibitors can effectively translate from bench to bedside.

First, the specificity of QC inhibitors, which includes the selective inhibition of hQC among various metalloproteins *in vivo* and selectivity toward the QC-Aβ pathway rather than other QC normal PTMs processes. Because QC is abundant in mammalian neuroendocrine tissues and is responsible for the maturation of numerous hormones and cytokines, non-selective QC inhibition may lead to wide and unpredictable side effects. In the phase IIa trial of PQ912, one-third (20/60) of subjects discontinued PQ912 treatment due to adverse events related to gastrointestinal disorders, skin disorders, etc. A broader battery of CSF biomarkers, including growth-associated protein 43 and pE-CCL2, have thus been set as exploratory endpoints to better monitor the potential adverse effects of the treatment in AD patients. Second, the pathological reversing effects of QC enzyme inhibitors remain questionable. Given that pE-Aβ acts as seeds to induce the formation of stable toxic heterogeneity polymers, QC inhibition can suppress but not completely prevent the pE-Aβ formation. The existing pE-Aβ may still trigger Aβ cascades. Fortunately, the QC-based combination strategy and MTDL strategy are drawing attention lately, which might be an ideal solution to enhance the additive effects. Last but not least, the pE-Aβ cascade is essentially an optimization of the original Aβ cascade hypothesis,

TABLE 5 Dual-target QCIs.

	**42–44** (Xie et al., 2023)

in which the pE-Aβ replaces full-length Aβ serving as the core initiator in the progression of AD. In the context of endless clinical failures of Aβ-directed or related interventions and the controversy regarding the exact role of Aβ cascade in the pathogenesis of AD, how far will QC inhibition go remains blurred in clinical trials. Nevertheless, the encouraging effect of the pE-Aβ-targeting donanemab in clinical trials envisions the promising role of the pE-Aβ-related key protein QC as an alternative potential target for the novel disease-modifying treatment of AD.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

This study was financially supported by the National Natural Science Foundation of China (No. 22007107), the Science and Technology Foundation of Guizhou Province (Qian Ke He J ZK [2022]585), the Science and Technology Fund Project of Guizhou Provincial Health Commission (gzwjkj2020-1-207), the Zhuhai Basic and Applied Basic Research Foundation (ZH22017003210074PWC), the Talent Project of Guizhou Science and Technology Cooperation Platform [2017]5733-041, and the Future Science and Technology Elite Project of Zunyi Medical University (ZYSE-2021-02).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Aging Neuroscience

TYPE Review
PUBLISHED 17 August 2023
DOI 10.3389/fnagi.2023.1213968

OPEN ACCESS

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RECEIVED 28 April 2023
ACCEPTED 24 July 2023
PUBLISHED 17 August 2023

CITATION
Devi G (2023) A how-to guide for a precision medicine approach to the diagnosis and treatment of Alzheimer's disease.
Front. Aging Neurosci. 15:1213968.
doi: 10.3389/fnagi.2023.1213968

A how-to guide for a precision medicine approach to the diagnosis and treatment of Alzheimer's disease

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Article purpose: The clinical approach to Alzheimer's disease (AD) is challenging, particularly in high-functioning individuals. Accurate diagnosis is crucial, especially given the significant side effects, including brain hemorrhage, of newer monoclonal antibodies approved for treating earlier stages of Alzheimer's. Although early treatment is more effective, early diagnosis is also more difficult. Several clinical mimickers of AD exist either separately, or in conjunction with AD pathology, adding to the diagnostic complexity. To illustrate the clinical decision-making process, this study includes de-identified cases and reviews of the underlying etiology and pathology of Alzheimer's and available therapies to exemplify diagnostic and treatment subtleties.

Problem: The clinical presentation of Alzheimer's is complex and varied. Multiple other primary brain pathologies present with clinical phenotypes that can be difficult to distinguish from AD. Furthermore, Alzheimer's rarely exists in isolation, as almost all patients also show evidence of other primary brain pathologies, including Lewy body disease and argyrophilic grain disease. The phenotype and progression of AD can vary based on the brain regions affected by pathology, the coexistence and severity of other brain pathologies, the presence and severity of systemic comorbidities such as cardiac disease, the common co-occurrence with psychiatric diagnoses, and genetic risk factors. Additionally, symptoms and progression are influenced by an individual's brain reserve and cognitive reserve, as well as the timing of the diagnosis, which depends on the demographics of both the patient and the diagnosing physician, as well as the availability of biomarkers.

Methods: The optimal clinical and biomarker strategy for accurately diagnosing AD, common neuropathologic co-morbidities and mimickers, and available medication and non-medication-based treatments are discussed. Real-life examples of cognitive loss illustrate the diagnostic and treatment decision-making process as well as illustrative treatment responses.

Implications: AD is best considered a syndromic disorder, influenced by a multitude of patient and environmental characteristics. Additionally, AD existing alone is a unicorn, as there are nearly always coexisting other brain pathologies. Accurate diagnosis with biomarkers is essential. Treatment response is affected by the variables involved, and the effective treatment of Alzheimer's disease, as well as its prevention, requires an individualized, precision medicine strategy.

KEYWORDS

Alzheimer's disease, treatment and diagnosis, precision medicine, differential diagnosis, biomarkers, lecanemab, aducanumab, prognosis

Introduction

Alzheimer's disease (AD) is a complex and heterogenous disorder characterized by synaptic dysfunction in crucial brain networks, accompanied by the presence of intracellular neurofibrillary tangles and extracellular amyloid plaques, as well as glial inflammatory changes (Deture and Dickson, 2019). While the precise mechanisms by which these pathological events cause the clinical symptoms of AD are not entirely understood, the normal brain's continuous synaptic pruning by microglia goes awry (Knopman et al., 2021).

AD is best conceptualized not as a single monolithic disease but as a syndromic disorder, with varying neurocognitive profiles and prognoses based on the brain regions affected (Devi, 2018a). While memory impairment, with associated hippocampal involvement, is the most frequent complaint, impairment of other cognitive domains, including language, maybe the presenting complaint. Based on the subtype of Alzheimer's, progression can vary from a decline of 1 point per year on the mini-mental state examination to 5 points annually (Murray et al., 2011).

The prodromal stage of AD, with minimal-to-mild cognitive impairment without significant functional dysfunction, may last for years (Figure 1) (Long and Holtzman, 2019). The progressive loss of synapses and subsequent failure of eloquent cortical networks occur over decades, providing a long window of opportunity for the prevention of clinical disease and intervention with disease-modifying therapies. The age of onset, genetic risk, co-existing primary brain pathologies (such as cerebrovascular disease, argyrophilic grain disease, or Lewy body disease), systemic comorbidities (including cardiovascular disease), psychiatric co-pathology, an individual's brain reserve and cognitive reserve, as well as educational and socioeconomic factors, all influence the symptoms, progression, and treatment response in AD.

Diagnosing AD based solely on clinical symptoms lacks sensitivity and specificity due to the overlap of symptoms with normal aging and the routine occurrence of concomitant primary brain pathology with similar clinical presentations, as AD occurring in isolation is a rarity. Multiple other primary brain conditions routinely co-exist with AD (Hampel et al., 2018). Biomarkers play a crucial role in accurately diagnosing AD and guiding appropriate care. Even in specialized memory disorder centers, before the advent of biomarkers, the positive predictive value on autopsy, of a clinical diagnosis of AD, ranged from 46% to 83% and one-third of patients in clinical trials did not have AD pathology (Beach et al., 2012). The reverse is also true, with patients being misdiagnosed with other conditions when, in fact, they have AD. As many as a quarter of patients with a clinical diagnosis of frontotemporal dementia, for instance, turn out to have AD instead on biomarker analysis, with important therapeutic and prognostic implications (Padovani et al., 2013).

Currently available treatments, when used in a biologically complementary manner tailored to the individual patient, may be more effective in helping slow disease progression. This may be especially the case in older-age AD, which is typically multifactorial in etiology and comprises 95% of cases (Devi and Scheltens, 2018). Treatment success may be pragmatically defined as maintaining functional independence until death, even if the primary pathology remains unchanged.

An n-of-1, precision medicine approach to the prevention and treatment of AD, taking into consideration the unique characteristics of each patient, can optimize outcomes and improve the potential for maintaining independent functioning (Arafah et al., 2023). To illustrate this approach to treating AD in a clinical setting, actual patients are presented, highlighting both diagnostic and treatment dilemmas, as well as illustrative therapeutic responses.

Prevalence and risk factors

Estimating the true prevalence of AD is problematic due to numerous factors, including the evolving definition of the disease, different methods used for diagnosis (clinical vs. biomarker-based), presence of confounding variables such as co-pathologies, patient characteristics such as education and socioeconomic status, and diagnosing physician characteristics such as specialty. However, a widely accepted estimate places prevalence at ∼1 in 9 people at and above the age of 65 years, with the proportion increasing with age.

Age is the greatest risk factor for sporadic, older-age Alzheimer's disease. Gender is another risk factor, as more women than men have AD. Men succumb earlier to cardiovascular disease, which may be one explanation for the higher prevalence of AD in women (Podcasy and Epperson, 2016). The lack of estrogen in post-menopausal women may also increase the risk for AD which may be ameliorated by estrogen use (Henderson, 2006; Saleh et al., 2023).

Genetics plays a role, with the ε4 isoform of the apolipoprotein E (APOE) gene being an established risk factor. A single copy of the ε4 allele increases the risk for older-age AD by three- to four-fold when compared with ε3 carriers, while two copies increased the risk 12–15-fold (Knopman et al., 2021). APOE genotyping has become clinically more relevant with the advent of newer therapies, as patients with an ε4 allele are at higher risk of serious side effects (Salloway et al., 2022; Devi, 2023). Rare protein-damaging variants in other genes, such as *SORL1*, *ABCA7*, and *TREM2,* have also been associated with an increased risk for AD (Scheltens et al., 2021). Mutations in the presenilin (PSEN) 1 gene on chromosome 14 and the PSEN2 gene on chromosome 1 are the most common *cause*, not a *risk*, for younger-age AD. The terms younger- and older-age AD arbitrarily divided at age 60 or 65 years, are used here in lieu of early-onset and late-onset AD, as patients and families often conflate the latter terms with earlier and later disease stages.

Modifiable risk factors, which can be addressed through lifestyle changes, may further increase the risk for older-age AD (Knopman et al., 2021). Cardiovascular disease, cerebrovascular disease, diabetes mellitus, hypertension, obesity, and hyperlipidemia increase the risk for AD. Other modifiable risk factors include hearing and vision loss, traumatic brain injury, smoking, alcohol abuse, depression, reduced physical activity, and reduced social engagement causing isolation and loneliness. Depression and anxiety may confer additional risk for developing AD or may be part of the prodromal phase.

Because AD pathology begins in patients as early as their thirties and forties, but clinical manifestations are delayed until a

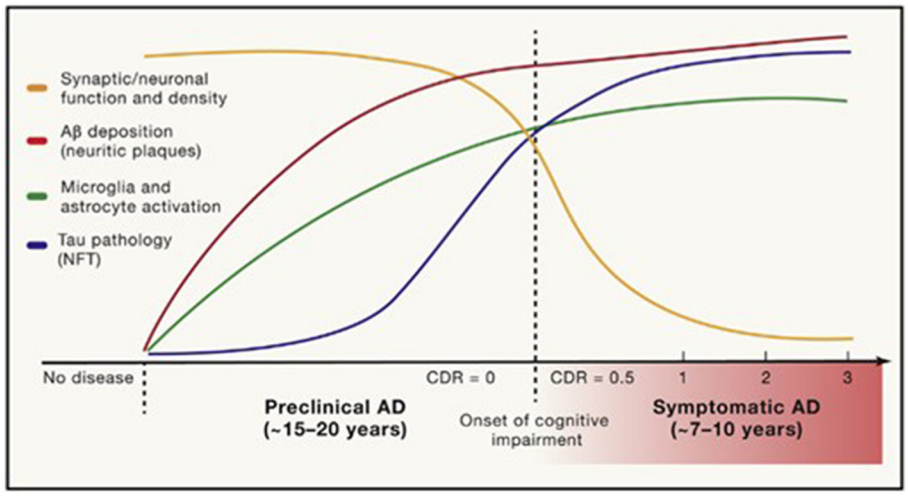


FIGURE 1
Timing of pathological and clinical events in AD. Long and Holtzman (2019) in Cell 179, used with author-permitted text adaptation and publisher permission.

much older age, intervention in young adulthood would be the preferred strategy to reduce the risk for AD.

Definition of Alzheimer's disease

The evolving definition of Alzheimer's disease has led to improvements in antemortem diagnostic accuracy, particularly with the availability of neuroimaging and laboratory biomarkers. Historically, criteria for diagnosing Alzheimer's disease focused on excluding other causes of dementia, such as stroke (McKhann et al., 1984). The European International Working Group (IWG) proposed incorporating biomarkers into the diagnostic framework (Dubois et al., 2010). Further refinements led to the two current definitions for AD—the American radiologist-led purely biomarker-based amyloid, tau, and neurodegeneration (ATN) on neuroimaging definition proposed in 2018 and the 2021 European neurologist-led IWG definition that requires functional impairment in addition to biomarkers (Jack et al., 2018; Dubois et al., 2021).

There is debate about the sole use of biomarkers to diagnose AD. While the ATN premise is that individuals with positive biomarkers will surely develop clinical symptoms given enough time and may benefit from early enrollment in clinical trials, the IWG perspective is that the presence of biomarkers does not necessarily equate to Alzheimer's, as biomarker-positive persons may remain asymptomatic. To avoid giving a potentially devasting diagnosis to an asymptomatic person, the IWG proposes classifying asymptomatic individuals with positive biomarkers as "asymptomatic, with features associated with future development of AD," rather than diagnosing them with Alzheimer's disease (Dubois et al., 2021).

Amyloid plaques, one of the biomarkers used to diagnose AD, are present in 20% of cognitively normal persons in their 60 s, one-third of those 70 years and over, and half of those 95 years and older (Jansen et al., 2022). Additionally, <5% of 76-year-olds with cognitive complaints and amyloid plaques progress to AD after 2.5 years (Dubois et al., 2018). Such data support a combined clinical-biomarker approach, as proposed by the IWG, avoiding over diagnosis, and yet identifying candidates for intervention.

Neuropathology in Alzheimer's disease (tau, aβ protein, and neuroinflammation)

The neuropathological hallmarks of Alzheimer's disease are extracellular plaques composed of Aβ protein and intracellular tangles composed of abnormally phosphorylated tau (Knopman et al., 2021). First described by the German psychiatrist Alois Alzheimer in 1906, his department chairman Emil Kraepelin named the condition after him (Devi and Quitschke, 1999). Inflammatory glial changes are now further considered part of AD pathology.

Both tau and Aβ proteins are highly disordered and unstructured, and therefore prone to instability and pathologic misfolding, which processes are exacerbated by aging (Hipp et al., 2019). These pathologic protein confirmations behave like seeds, instigating further pathologic misfolding of normal tau and Aβ proteins, with the changes propagating across cells and spreading pathology, as seen in prion diseases (Plotkin and Cashman, 2020). Tau normally maintains cell structure, axonal transport, and synaptic function. Abnormal hyperphosphorylation of tau disrupts these functions by forming insoluble, intracellular tangles, leading to neurotoxicity (Figure 2). Similarly, Aβ protein of varying lengths is derived from the larger amyloid precursor protein (APP) and is involved in neuroprotection and synaptic function. However, cleavage of APP by γ and β secretase enzymes produces longer, primarily Aβ-42 amino acid chains which assemble into oligomers,

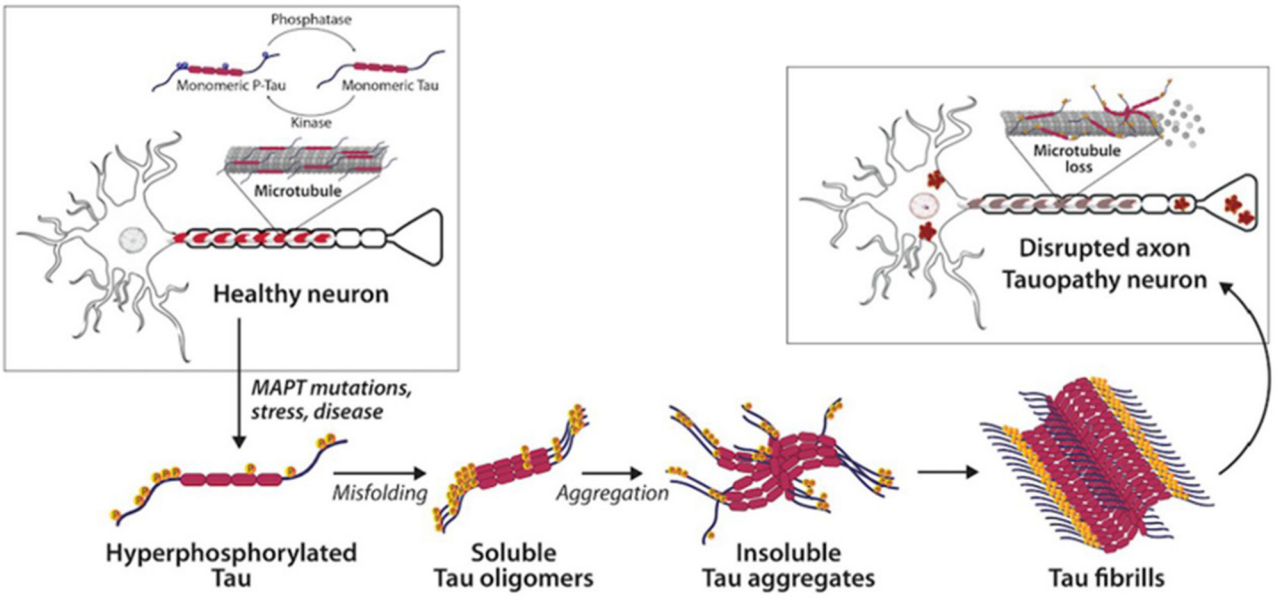


FIGURE 2
Tau and neurofibrillary tangles in health and disease (Catarina Silva and Haggarty, 2020).

then protofibrils and amyloid fibrils, which ultimately assemble into amyloid plaques (Figure 3).

Although amyloid plaque density correlates with AD severity, it is generally accepted that the plaques are likely neuroprotective, sequestering and neutralizing the component, longer-chain, rogue Aβ oligomers which are neurotoxic (Tamagno et al., 2018). That Aβ oligomers, rather than plaques, drive AD pathology is supported by the "Osaka" mutation, where patients have a rapid onset of AD with characteristic Aβ and tau levels in CSF without the presence of plaques (Tomiyama and Shimada, 2020). Intriguingly, tau aggregation into neurofibrillary tangles may also be protective with soluble, oligomeric tau being neurotoxic (Morsch et al., 1999; Takeda et al., 2016).

A critical role of Aβ in the pathogenesis of AD is clear from the fact that mutations in genes related to Aβ production and clearance are involved in *all* genetic causes of AD such as trisomy 21, presenilin (PSEN)1, and PSEN2 mutations. Additionally, the ε4 isoform of the APOE gene, associated with a greater risk for older-age AD, is less efficient at clearing Aβ than the ε2 and ε3 isoforms (Deture and Dickson, 2019). Interestingly, although abnormal tau is clearly implicated in AD pathogenesis, mutations in the gene instructing tau production, the MAPT gene, are not associated with Alzheimer's disease.

Tau and amyloid pathology are present in a benign fashion in various brain areas and are deposited in a chronologically asynchronous fashion. However, when a certain amyloid threshold burden is reached, which varies among persons, tau begins to spread pathologically, also in varying patterns, ultimately leading to each person's n-of-1 specific Alzheimer's disease state (Karran and De Strooper, 2022).

As tau accumulates closer to the time of symptom onset and continues to accumulate as the disease progresses, while amyloid plaques begin accumulating decades before symptoms, plaque deposition may be viewed as more disease-specific, and tau deposition as more stage-specific (Knopman et al., 2021) (Figure 3). There may also be pathologic interaction between the two, causing further aggregation.

Additionally, neuro-inflammation plays a critical role in AD pathogenesis, contributing to neurodegeneration and disease progression. Alterations in microglia and astroglia lead to neuro-inflammation, alterations in vasculature, and dysfunction of the glymphatic system, acting in tandem with or before Aβ accumulation, as a driver and component of AD neuropathology (Deture and Dickson, 2019).

Differential diagnosis; other primary brain pathologies coexisting with Alzheimer's disease

Several other primary brain pathologies commonly coexist with AD, making diagnosis, prognosis, and response to treatment more complex. This is important from a diagnostic, therapeutic, and prognostic perspective, as patients with AD or another primary brain disease such as cerebrovascular disease or normal pressure hydrocephalus nearly always have a concomitant diagnosis that needs monitoring and assessment for treatment.

It is easy to see why, with increasing age, there is a higher co-prevalence of common aging-related brain diseases such as vascular dementia. However, younger-age AD also has a high association with other primary brain disease. This suggests that the neurodegenerative pathology that drives AD may be a catalyst for other primary brain pathologies, regardless of age.

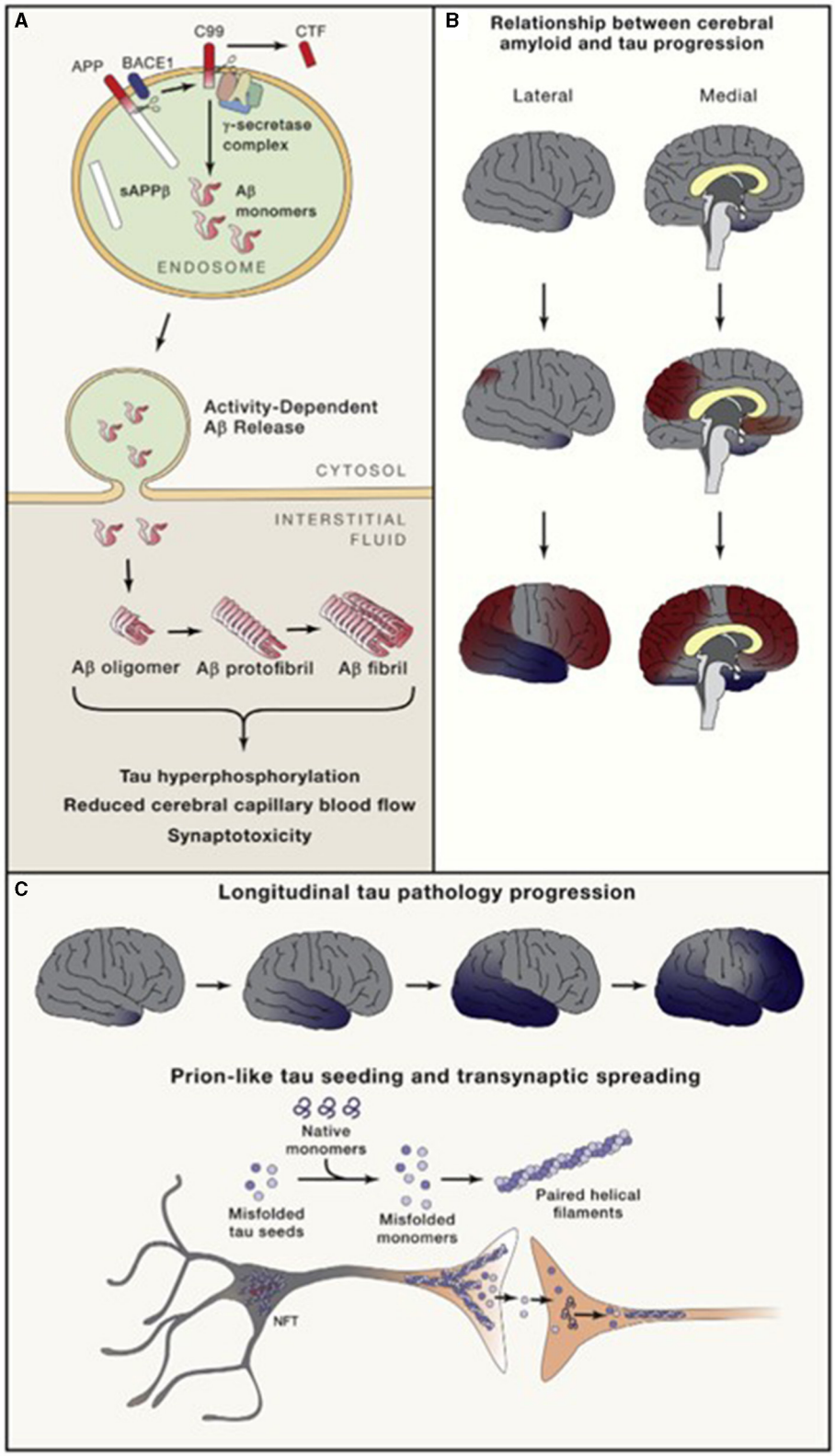


FIGURE 3
Amyloid **(A)** and neurofibrillary tangle production and direction of cortical spread of pathology **(B, C)**. Long and Holtzman (2019) in Cell 179 used with author-permitted text adaptation and publisher permission. APP, Amyloid precursor protein; BACE, Beta amyloid cleaving enzyme; CTF, C-terminal fragment; NFT, Neurofibrillary tangles; sAPP, soluble APP.

One study found that 98% of younger-age AD and 100% of older-age AD had additional primary brain pathologies, including argyrophilic grain disease and vascular disease (Spina et al., 2021). As compared to younger-age AD, older-age AD patients were more likely to have common co-pathologies, including limbic-predominant, age-associated transactive response DNA-binding protein of 43 kDa (TDP-43) encephalopathy (8% vs. 35%), hippocampal sclerosis (3% vs. 15%), argyrophilic grain disease (41% vs. 58%), and vascular brain injury (39% vs. 65%) (Spina et al., 2021).

In an autopsy series of neuropathological AD, only one-third had AD-only pathology (and even within this group, between 30% and 50% had at least one infarct), 50% had additional TDP-43 pathology, 22% had additional α-synuclein pathology, and 18% had additional combined α-synuclein and TDP-43 pathology (Karanth et al., 2020).

While Alzheimer's, cerebrovascular disease, Parkinson's, and normal pressure hydrocephalus have biomarker-based laboratory or neuroimaging antemortem diagnosis available, other neurodegenerative primary brain pathologies do not as yet.

Cerebrovascular disease

There is nearly always some level of cerebrovascular disease (CVD) in patients with older-age AD, as both conditions become increasingly more common with age. Up to 84% of persons who die in their 80s have some level of CVD, most often cerebral amyloid angiopathy and small vessel disease. Cerebral amyloid angiopathy results from Aβ deposition in brain parenchymal arteries, arterioles, and capillaries. Vascular pathology may directly increase Aβ deposition by inducing accumulation and impeding clearance (Attems and Jellinger, 2014). Both CVD and AD share many risk factors aside from age, including hypertension, diabetes mellitus, smoking, hypercholesterolemia, and cardiovascular issues such as atrial fibrillation. Such sharing of risk factors in both conditions led to a provocative, highly cited article suggesting that Alzheimer's disease be considered a cerebrovascular disorder (De La Torre, 2002).

Normal pressure hydrocephalus

In a large autopsy series of persons with a clinical diagnosis of normal pressure hydrocephalus (NPH), 74% had evidence of other primary brain neuropathology, with AD contributing to 53% of these cases (Cabral et al., 2011). While NPH is present in 5–9% of those in their 80s and older, the classic triad of cognitive disturbance, a broad-based shuffling gait, and urinary incontinence is present in <60% of patients (Jaraj et al., 2014; Graff-Radford and Jones, 2019; Müller-Schmitz et al., 2020). Additionally, multiple factors contribute to gait disturbance in the elderly, such as lower extremity arthritis and neuropathy (Graff-Radford and Jones, 2019). Neuroimaging revealing enlarged subarachnoid space and a tight high convexity in addition to ventriculomegaly, which is common in the elderly, is supportive of NPH (Graff-Radford and Jones, 2019). Even those patients who improved initially with shunting over the first few years deteriorate with time, suggesting a shared basis for neurodegenerative NPH and AD (Müller-Schmitz et al., 2020).

TDP-43 pathology and hippocampal sclerosis

Transactive response DNA binding protein of 43 kDa (TDP-43) regulates gene expression, and truncated forms of TDP-43 are found in several neurodegenerative diseases. Limbic predominant, age-associated, TDP-43 encephalopathy (LATE) is as prevalent as AD in persons 80 years and older. LATE presents as a dementia syndrome with memory impairment that is clinically indistinguishable from AD. To make matters even more challenging, the diseases often present together, and the prevalence of TDP-43 pathology increases with the severity of AD, presenting in 20–57% during the earlier stages of AD and in 75% of those with more advanced AD (Jo et al., 2020; Meneses et al., 2021).

Case 1 (Figure 4) illustrates likely TDP-43-related LATE pathology in a woman seen at age 71 years and followed over 7 years. She had significant temporal lobe atrophy that spared her parietal cortex along with moderate white matter disease on MRI. She was strongly positive on amyloid imaging with severe memory deficits, scoring at the lowest 1st percentile on nearly all memory domains. She was initially treated as having mild cognitive impairment due to Alzheimer's pathology and vascular disease. When aducanumab became commercially available, a spinal tap was done to confirm the diagnosis of AD. The spinal fluid analysis revealed a low cerebrospinal fluid Aβ42, consistent with AD and consistent with brain amyloid deposition seen on her earlier neuroimaging. However, her low level of cerebrospinal p-tau was inconsistent with a diagnosis of AD. She has remained stable over several years without deterioration in language and visuospatial or physical skills, despite even further diminution of memory. Her mini-mental state examination score has remained stable at 25/30, with an initial score of 24/30 7 years previously.

In persons 80 years and older, 20–50% have enough TDP-43 accumulation to cause cognitive loss in a large community-based autopsy series (Jo et al., 2020). Hippocampal sclerosis pathology may be observed but is neither necessary nor sufficient for a diagnosis of LATE.

Neuronal loss and gliosis of the hippocampal formation that is out of proportion to AD-type pathology is termed hippocampal sclerosis of aging (HS-Aging) and is strongly associated with TDP-43 pathology. In one study, 90% of aged persons with HS-Aging pathology exhibited TDP-43 pathology while only 10% of controls without HS-Aging did (Nelson et al., 2019). HS-Aging is present in 5–30% of nonagenarians along with astrocytic changes that are a histopathologic feature of HS-Aging. Hippocampal sclerosis due to epilepsy or vascular insufficiency does not stain for TDP-43.

α-synuclein pathology: lewy body disease and Parkinson's disease

Lewy bodies are abnormal intracellular inclusions of α-synuclein, a protein that normally regulates neurotransmitter

Ms. Broker is a 78-year-old woman who was evaluated 7 years ago at age 71 for a change in "attention or concentration… I used to be able to read mysteries, but you have to follow them and that has been hard…" Her children wanted the evaluation although she herself did not feel it was necessary. On her MMSE, she had difficulty with serial sevens and recall, scoring 24/30. She functioned independently. She had hyperlipidemia, hypertension, underwent menopause in her 40's and stopped hormone therapy two years previously. She was on zolpidem, atorvastatin, and metoprolol. Her 99-year-old mother had mild memory loss but there was no other family history of dementia. Her exam was normal. Her **APOE genotype was ε3/4; Her MRI showed moderate white matter disease and disproportionate temporal lobe loss without atrophy of parietal lobe.** Her cognitive evaluation showed significant loss of memory. The diagnosis was amnestic mild cognitive impairment due to Alzheimer's disease with contribution from stroke. She underwent amyloid imaging.

Variable	Time 1 2016	Time 7 2022
Mini Mental State Examination Score	24/30	25/30
WAIS Verbal Scale Quotient Percentile	68%	70%
WAIS Performance Scale Quotient Percentile	73%	37%
WAIS Full Scale Quotient Percentile	70%	58%
WMS Auditory Immediate Memory Percentile	30%	0.3%
WMS Visual Immediate Memory Percentile	1%	1%
WMS Immediate Memory Percentile	4%	0.1%
WMS Auditory Delayed Memory Percentile	1%	1%
WMS Visual Delayed Memory Percentile	14%	2%
WMS Working Memory Percentile	70%	10%
Buschke Selective Recall Test: Total Recall	47/72	21/72
Delayed Recall (Free recall)	0/12	0/12
Delayed Recognition (Cued recall)	10/12	6/12
60-item Boston Naming Test	49/60	45/60
CFL Fluency Percentile	90%	56%

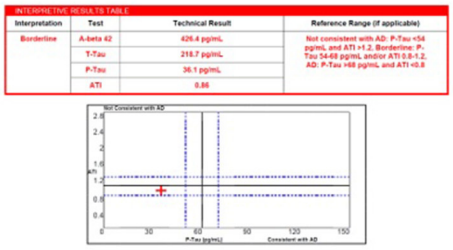
Initial Working Diagnosis: Amnestic Mild Cognitive Impairment due to Alzheimer's disease and vascular dementia.

Current Working Diagnosis: Dementia due to limbic predominant age-associated TDP-43 encephalopathy, cerebrovascular disease and possible argyrophilic grain disease.

IMPRESSION

Positive Amyvid scan, indicating moderate to frequent amyloid neuritic plaques.

CSF negative for AD 2021



Management: She was switched from zolpidem to trazodone for insomnia and treated with memantine, B12, alendronate & transcranial magnetic stimulation, she did not tolerate cholinesterase inhibitors.

Follow up (7 years): Continued slow decline in memory & overall functioning requiring home care; (MMSE 24/30 initially, currently 25/30)

FIGURE 4
Case 1—Amyloid positive, tau negative, likely limbic predominant age-associated TDP-43 encephalopathy. WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.

release. Based on the brain regions affected, Lewy bodies lead to Parkinson's disease (PD), Parkinson's disease dementia (PDD), and dementia due to Lewy bodies (DLB). The distinction between PDD and DLB is arbitrarily based on the difference in time of onset between motor and cognitive symptoms and not on distinctive neuropathology (Jellinger and Korczyn, 2018). If motor symptoms antedate cognitive symptoms by <1 year, the diagnosis is DLB, and if by more than a year before cognitive symptoms begin, the diagnosis is PDD.

As there are no neuropathological criteria that distinguish DLB from PDD and as the two conditions share genetic risk factors and prodromal features, they may be regarded as a single disease across a spectrum (Walker et al., 2015; Coughlin et al., 2020). Lewy body pathology is found in nearly half of patients with both younger- and older-age AD (Chung et al., 2015; Ferman et al., 2018; Spina et al., 2021).

Patients with DLB present with a history of restless legs, have early visual hallucinations, and depression. Interestingly, they often have insight into their hallucinations ("they seem real at the time, but I know they are not"). Patients have more prominent visuo-spatial disturbances on formal cognitive testing. Resting tremors are rare in patients with DLB and common in patients with PD. Dopamine uptake scans may help distinguish between the two conditions, as one study found that patients with PD show markedly reduced putaminal and asymmetric caudate uptake, while DLB shows nearly absent caudate and putaminal uptake (Nichols et al., 2018). All patients with α-synuclein pathology are more susceptible to the extrapyramidal side effects of dopamine antagonists such as those commonly used to treat hallucinations.

Case 2 (Figure 5) highlights the diagnostic and treatment dilemma in a high-functioning patient, initially diagnosed with Alzheimer's by a neuropsychologist, then as essentially normal or

possibly dementia due to Lewy bodies by his cognitive neurologist, now with a diagnosis of AD and PD, based on biomarkers. Such shifts in diagnoses will have obvious treatment consequences.

Argyrophilic grain disease

Argyrophilic grain disease (AGD) is a widely prevalent primary brain pathology that is often underrecognized. It affects 9% of 65-year-olds, rising to 31% in centenarians (Ferrer et al., 2008). Unless appropriate stains are used, argyrophilic grains may be missed, but with appropriate staining, AGD pathology is seen in over a quarter of all AD cases (Yokota et al., 2018). Most cases of AGD are asymptomatic, although some present with a dementia that is indistinguishable from AD. Case 1 (Figure 4) may have some components of AGD. Personality changes and psychiatric symptoms may be presenting features and AGD should be considered in the differential of late-life psychosis. AGD progresses from the anterior entorhinal cortex to the neocortex and brain stem, as is characteristic of tau propagation (Saito et al., 2004).

Aging-related tau astrogliopathy and primary age-related tauopathy

Aging-related tau astrogliopathy (ARTAG) may present clinically with focal symptoms such as aphasia when the pathology is regionally limited. A common co-pathology, ARTAG, is found in about 40% of patients with AD post-mortem (Liu et al., 2016). ARTAG is generally seen in persons 60 years and older and is rarely an isolated finding. The pathology is found in astroglia and not in neurons (Kovacs, 2020).

Primary age-related tauopathy (PART) was previously considered normal aging or neurofibrillary tangle predominant senile dementia without significant amyloid pathology (Crary et al., 2014). Cognitively normal persons may exhibit pathologically definite PART. Cognitive impairment in PART is more often seen in those over 80 years of age with a family history of cognitive disorders. Even patients with severe PART can be asymptomatic, although some exhibit mild cognitive loss and rarely, dementia. While ARTAG or PART are generally not clinically relevant in the differential diagnosis of AD, they may affect the progression of AD.

Menopause-related cognitive impairment (MeRCI)

Cognitive impairment is seen in 60% of menopausal women in their 40 and 50 s (Devi et al., 2005). Subjective memory complaints are associated with objective reductions in verbal, episodic, and list-learning memory, verbal fluency, and executive functioning, indistinguishable from Alzheimer's disease (Henderson and Sherwin, 2007). Estrogen is crucial to brain health and multiple mechanisms drive these deficits. Estrogen increases hippocampal synaptic spine density and synaptic formation, boosts cholinergic and serotonergic function, reduces free radical damage in neurons, reduces cortisol, improves mitochondrial function-important for optimizing brain energy utilization, and improves aspects of cardiovascular health (Toran-Allerand et al., 1999; Davis et al., 2015). Menopause-related cognitive impairment (MeRCI) should be considered in the differential diagnosis of cognitive loss in perimenopausal and menopausal women. A menopausal history is necessary in any memory evaluation of women to avoid misdiagnosis (Devi, 2018b; Devere, 2019).

Case 3 (Figure 6) concerns a woman diagnosed with AD at an academic memory disorders center, based on cognitive changes and FDG-PET scanning, without taking into consideration her menopausal status (Devi, 2018b). While her neurocognitive performance showed cognitive loss in a pattern that was difficult to distinguish from early AD, as is common in MeRCI, her cerebrospinal fluid biomarkers were negative for AD. Amyloid scanning was performed at her request several years after her cerebrospinal fluid evaluation was negative. At follow-up, nearly a decade later, she remained stable (Devi, 2018b).

Psychiatric co-morbidities in AD

Early during Alzheimer's disease, anxiety and depression are common psychiatric co-morbidities, with a prevalence of 10–40% (Chemerinski et al., 1998; Botto et al., 2022). Patients often worry about having their deficits discovered, withdraw socially, and stop participating in conversations for fear of being "thought stupid". Depression is driven by prevailing themes of loss of capacity, institutional placement, and being a familial burden. Conversely, nearly one-third of adults with depression have associated cognitive impairment. Neurochemical changes in cholinergic, serotoninergic, and dopaminergic activity, common to both AD and psychiatric syndromes, drive symptomatology (Botto et al., 2022).

Later in the course of AD, but earlier in the disease if there is concomitant Lewy Body or argyrophilic grain disease co-pathology, there may be paranoia and psychosis. Paranoia is often related to delusions of theft, generally felt to be perpetrated by those physically proximate to the patient, usually the primary caregiver. Concerns about losing financial control are common and understandably exacerbated when the family begins to take control of finances as the patient's capacity declines.

Accurate diagnosis of Alzheimer's disease

Cognitive dysfunction in AD can be challenging to accurately assess and quantify. Several variables impact the assessment of cognitive function in AD, including patient-specific, physician-specific, and test-specific factors. Patient-specific factors include gender, race, level of education, current level of cognitive demand, brain and cognitive reserve, other primary brain, systemic, and psychiatric co-morbidities, as well as available support systems. Physician-specific variables include specialty, comfort with biomarker usage, expertise with neurocognitive testing, and time available to spend with the patient. Test-specific variables include types of cognitive tests administered,

Dr. Physician is a 67-year-old man who was here for a second opinion, with conflicting diagnoses of Lewy body disease by his neurologist and Alzheimer's disease by his neuropsychologist, both from the same memory disorders center. Over the last year, his baseline level of absentmindedness had exacerbated. His wife stated, "For 48 years, every day was a new day for him, because he doesn't connect the dots..." He rates himself at 70-80% of his general level of functioning. His wife stated he was "more like 90%."

He has hyperlipidemia, thrombocytopenia, hearing loss, essential tremor, and surgically treated obstructive sleep apnea. He was on atorvastatin, tadalafil, and tamsulosin. He worked as a physician until retiring a few years ago and was physically very active. His mother died of dementia at 94, developing symptoms in her late 70s, his father died at 94 with dementia beginning at his mid-late 80s. His paternal grandmother developed dementia in her 70s. His maternal aunt died with dementia in her 80s (no children), developing it in her early 70s. One of his four paternal aunts and uncles had stroke and related cognitive issues, another had Parkinson's disease. His neurological examination was significant for a bilateral intention tremor, cogwheeling, and a mild stoop, consistent with essential tremor and early Parkinson's disease.

His **MRI showed no evidence of hippocampal atrophy and mild white matter disease**. His APOE genotype was **ε3/4.** His cognitive performance showed overall ability at the 98th percentile with reductions in memory. The clinical presentation without any psychiatric symptoms or fluctuation in symptoms made dementia due to Lewy bodies less likely. He underwent a lumbar puncture and a dopamine uptake scan to clarify diagnosis.

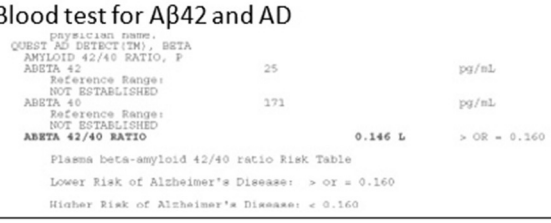
Variable	2023
Mini Mental State Examination Score	30/30
WAIS Verbal Scale Quotient Percentile	87%
WAIS Performance Scale Quotient Percentile	55%
WAIS Full Scale Quotient Percentile	77%
WMS Auditory Immediate Memory Percentile	18%
WMS Visual Immediate Memory Percentile	27%
WMS Immediate Memory Percentile	18%
WMS Auditory Delayed Memory Percentile	30%
WMS Visual Delayed Memory Percentile	27%
WMS Working Memory Percentile	21%
Buschke Selective Recall Test: Total Recall	45/12
Delayed Recall (Free recall)	2/12
Delayed Recognition (Cued recall)	8/12
60-item Boston Naming Test	44/60
CFL Fluency Percentile	22%

Initial Diagnosis: Alzheimer's Disease or Dementia due to Lewy bodies

Working Diagnosis: Alzheimer's Disease and Parkinson's Disease

Proposed Management: Selegiline, memantine, valacyclovir, donepezil, lecanemab biweekly, transcranial magnetic stimulation.

Blood test for Aβ42 and AD


physician name,
QUEST AD DETECT(TM), BETA AMYLOID 42/40 RATIO, P
ABETA 42 25 pg/mL
Reference Range: NOT ESTABLISHED
ABETA 40 171 pg/mL
Reference Range: NOT ESTABLISHED
ABETA 42/40 RATIO 0.146 L > OR = 0.160
Plasma beta-amyloid 42/40 ratio Risk Table
Lower Risk of Alzheimer's Disease: > or = 0.160
Higher Risk of Alzheimer's Disease: < 0.160

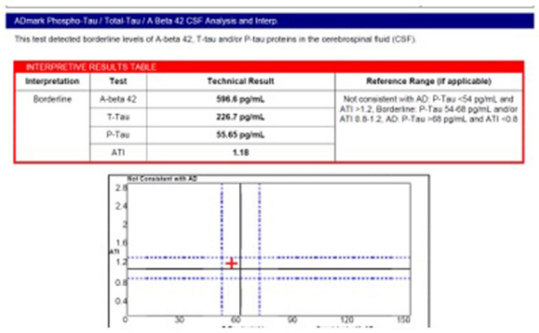
DAT SCAN positive for Parkinson's

Normal activity is present in the right caudate head with decreased activity in the right putamen. Decreased activity in the left caudate head is noted with markedly decreased activity in the left putamen.

Findings:

Normal activity is present in the right caudate head with decreased activity in the right putamen. Decreased activity in the left caudate head is noted with markedly decreased activity in the left putamen.

Cerebrospinal fluid borderline for AD


ADmark Phospho-Tau / Total-Tau / A Beta 42 CSF Analysis and Interp.
This test detected borderline levels of A-beta 42, T-tau and/or P-tau proteins in the cerebrospinal fluid (CSF).
INTERPRETIVE RESULTS TABLE

Interpretation	Test	Technical Result	Reference Range (if applicable)
Borderline	A-beta 42	596.6 pg/mL	Not consistent with AD: P-Tau <54 pg/mL and ATI >1.2; Borderline: P-Tau 54-68 pg/mL and/or ATI 0.8-1.2; AD: P-Tau >68 pg/mL and ATI <0.8
	T-Tau	226.7 pg/mL	
	P-Tau	55.65 pg/mL	
	ATI	1.18	

Follow Up: Pending

FIGURE 5
Case 2—Co-pathology in Alzheimer's disease: Lewy body disease, versus Parkinson's disease dementia.

either screening tests or extensive neurocognitive tests, and biomarkers used, whether imaging, blood-based, or cerebrospinal fluid analysis.

The level of routine cognitive demand in a person's daily life, such as being employed vs. retired, can also impact their perception of cognitive dysfunction. A retired person may notice less dysfunction than someone in a new job or someone in a high-cognitive demand position such as law. The availability of ancillary staff or support systems can further impact the ability to maintain functioning (Devi, 2018a).

Ms. Executive was a 55-year-old, right-handed woman referred by her gynecologist for a second opinion on a diagnosis of mild Alzheimer's disease made six years earlier at a memory disorders center. She needs to maintain lists for everything. On her last MMSE, she scored 25/30 and her Hamilton Depression score was 6/61, without evidence of depression. She underwent menopause at age 46 and was started on hormone therapy. She had a diagnosis of bipolar disorder 2 and was hospitalized at age 20 for suicidal ideation. She was on lamotrigine 375 mg, bupropion 437.5 mg, ziprasidone 80 mg and lorazepam 2mg daily. Her estrogen replacement had been stopped 2 months previously. A married executive with a master's degree, she was on disability with a diagnosis of AD. There was a family history of depression, but no cognitive loss. **Her brain MRI showed minimal white matter disease.** Based on cognitive testing and the menopausal history, the diagnosis was of menopause related cognitive loss. She underwent cerebrospinal fluid analysis to clarify her diagnosis.

Variable	Time 1 2010	Time 2 2013
Mini Mental State Examination Score	25/30	-
WAIS Verbal Scale Quotient Percentile	95%	98%
WAIS Performance Scale Quotient Percentile	81%	92%
WAIS Full Scale Quotient Percentile	93%	99%
WMS Auditory Immediate Memory Percentile	79%	86%
WMS Visual Immediate Memory Percentile	70%	98%
WMS Immediate Memory Percentile	84%	50%
WMS Auditory Delayed Memory Percentile	50%	25%
WMS Visual Delayed Memory Percentile	77%	77%
WMS Working Memory Percentile	63%	32%
Buschke Selective Recall Test: Total Recall	52/72	54/72
Delayed Recall (Free recall)	10/12	9/12
Delayed Recognition (Cued recall)	12/12	12/12
60-item Boston Naming Test	57/60	57/60
CFL Fluency Percentile	51%	77%

Initial Diagnosis: Alzheimer's disease
Current Diagnosis: Menopause related cognitive impairment.

Management: She was placed back on estrogen replacement.

4 year and 10-year follow up: She has been stable and lives at home, functioning independently.

PET Scan in 2010, compared to 2008, positive for AD

IMPRESSION:

1. Interval decreased metabolism in the mesial temporal lobes and temporoparietal regions, suggestive of mild progression of disease.
2. Stable cerebellar hypometabolism, possibly secondary to medication.

Amyvid Scan in 2013, negative for AD, performed at patient behest

IMPRESSION

The scan is negative, indicating sparse to no beta-amyloid neuritic plaques.

CSF analysis 2010, negative for AD

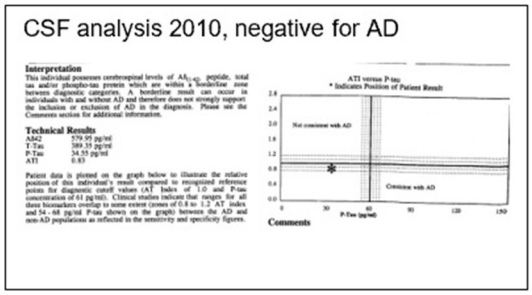


FIGURE 6
Case 3—An Underrecognized Alzheimer's Disease Mimic: Menopause Related Cognitive Impairment (MeRCI).

An approach informed by the patient, physician, and test-specific factors involved is important in obtaining as accurate and reliable an assessment of cognitive function as possible. This is particularly important for early intervention and treatment. Table 1 delineates a comprehensive method for the diagnosis of cognitive disorders.

Neurocognitive evaluation

The type of cognitive assessment administered can affect the determination of cognitive function. Highly educated persons may do well on simple screening tests such as the mini-mental state examination (MMSE) or the Montreal cognitive assessment (MoCA) despite significant cognitive impairment, although the MoCA is more sensitive than the MMSE (Gagnon et al., 2013). On the other hand, highly educated persons may complain of a change in functioning without significant pathology.

Screening tests such as the MMSE or MoCA may also not detect changes in patients with high cognitive reserves or levels of education. Case 2 (Figure 5), a professional, had a perfect MMSE score of 30/30 but could only recall 2/12 items on a more thorough list learning memory task.

A comprehensive neurocognitive assessment that evaluates multiple cognitive domains, including verbal, visual, and executive skills, auditory, visual and working memory, language and verbal fluency, provides a better baseline. However, such testing is expensive and requires skilled personnel to not only administer,

TABLE 1 Workup of patient of cognitive loss.

History: Family history of younger and older-age dementia: Unless family members have had autopsy or biomarker-confirmed Alzheimer's disease (AD), it should not be notated as AD.
Personal history: cardiovascular and cerebrovascular risk factors. History of head injury.
General medical, neurological, and psychiatric evaluation; Cognitive testing
Ideally, a comprehensive cognitive battery in persons who score well on screening tests such as the mini-mental state examination or the Montreal cognitive assessment.
Laboratory workup:
APOE genotype Younger-age AD mutation screen (for patients with symptoms beginning before age 65 years) Cerebrospinal fluid evaluation for tau and βA-42 analysis β42 amyloid in the blood
Imaging and other testing:
Fluorodeoxyglucose positron emission tomography (FDG-PET) may be used to differentiate between frontotemporal dementia and Alzheimer's disease. Positron emission tomography (PET) for amyloid uptake. Computed Tomography (CT) of the brain to evaluate for strokes. Transcranial Doppler may be used to assess blood flow for vascular cognitive impairment. Electroencephalogram may be used to assess change in pattern over time. Magnetic Resonance Imaging (MRI) of the brain evaluates the transependymal fluid flow, stroke, hippocampal atrophy, and general atrophy.

but also, separately, interpret the results. An alternative may be to use relatively comprehensive batteries, with ease of use, such as the Cognitive Assessment Toolkit made possible by the Alzheimer's Association (Cordell et al., 2013; Alzheimer's Association, 2018).

Neuroimaging diagnosis

Neuroimaging techniques used in diagnosing AD and to aid in the differential diagnosis include CT (computed tomography), MRI (magnetic resonance imaging), FDG-PET (fluorodeoxyglucose positron emission tomography), dopamine transporter (DaT) Scan, and amyloid PET scanning. Tau PET scanning is not yet commercially available.

MRI is preferred to CT for better delineation of brain structures, particularly the hippocampus, ability to gauge fluid flow, important for differentiating NPH, and for superior determination of cerebrovascular pathology. Significant hippocampal atrophy may help to diagnose LATE as in Case 1 (Figure 4). FDG-PET scan may reveal characteristic temporoparietal hypometabolism in AD and may also help in differentiating from FTD, although as seen in Case 3 (Figure 6), reliance on FDG-PET as the primary biomarker may lead to misdiagnosis, particularly in atypical presentations. A DaT scan may help to distinguish PD, PDD, and DBLD from AD as illustrated by Case 2 (Figure 5).

Pittsburgh compound B, used in amyloid scanning, is a radioactive tracer that binds to amyloid plaques in the brain. It is quantified in Centiloid units, with lower values indicating amyloid negativity. The presence of amyloid plaques can help make an AD diagnosis, although cerebrospinal fluid analysis or another measure of tau is re needed to clarify the diagnosis in some cases, as in Case 1 (Figure 4). In this person, the amyloid scan was positive, but the spinal fluid analysis was negative for AD. In addition, amyloid scanning helps determine treatment response and guide further management, as in Case 6 (Figure 9).

Tau PET scans, although not yet commercially available, hold promise for stage-specific disease quantification in AD.

Cerebrospinal fluid and blood-based biomarkers

Biomarkers in the cerebrospinal fluid (CSF), including reduced levels of Aβ, increased total tau, and increased abnormally phosphorylated tau (p-tau) levels may be used in lieu of tau and amyloid PET imaging to make a biomarker-based diagnosis. Low CSF levels of Aβ in conjunction with high p-tau levels are consistent with a diagnosis of AD. Even in cognitively normal persons, 80% of those with abnormal CSF biomarkers progress to mild cognitive impairment in 6 years, while 90% of those with cognitive impairment develop dementia within a decade (Buchhave, 2012).

Increased CSF levels of neurogranin and neural filament light chain (NFL) protein are seen in several types of neurodegeneration. The CSF biomarker profile in AD differs from that of FTD, and allows for a different treatment approach, as up to 20% of patients with a clinical diagnosis of FTD are found to have AD by biomarkers (Padovani et al., 2013; Schöll et al., 2019; Mattsson-Carlgren et al., 2022). Using polypropylene tubes which do not bind and falsely lower Aβ levels is important in CSF analysis. Glass tubes may be used if polypropylene tubes are not available.

Standardization of cutoff values for CSF varies depending on the assays used. The commercial laboratory values for diagnosing AD in the United States are conservative, with AD diagnosed when values for Aβ42 are <700 ng/L, total tau >400 ng/L, and p-tau >54 ng/L, with a Aβ42/p-tau181 ratio of >0.8 (Blennow et al., 2015). In a Spanish study, the best cutoff values for diagnosing AD were Aβ42 of 750 ng/L, a total tau of 522 ng/L, and a p-tau181 of 70 ng/L (Puig-Pijoan et al., 2022). In a cohort of European memory disorder centers, high-cutoff values for diagnosing AD found Aβ42 ranging from 613 to 978 ng/L, t-tau ranging from 228 to 421 ng/L, and p-tau-181 ranging from 20 to 75 ng/L (Dumurgier et al., 2022).

While CSF access is widely available, methods of analyzing protein, and standardization of abnormal values are variable. Disadvantages of CSF biomarkers include the invasiveness of a lumbar puncture, and while quantification of the plaque and tangle load is achieved, brain areas affected by pathology are better

visualized with neuroimaging. Neuroimaging, on the other hand, is extremely expensive because of the cost of the radioisotopes used and the need for two separate procedures, one for imaging amyloid and another for imaging tangles.

Blood-based biomarkers, including measurement of Aβ42 and tau, maybe the future of biomarker-based diagnosis of AD, given the ease of testing and lower costs involved (Leuzy et al., 2022). In Case 2 (Figure 5), blood-based Aβ42 results were used in conjunction with cerebrospinal fluid analysis to make a diagnosis. Blood levels of neurofilament light chain (NFL), glial fibrillary acid protein (GFAP), a marker of astroglial injury, and neurogranin, are increased in blood in neurodegeneration, although these are not specific to AD (Hampel et al., 2018; Hawksworth et al., 2022; Leuzy et al., 2022).

Genetic testing

Commercial genetic testing panels for younger-age AD screen for mutations in the transmembrane PSEN 1 gene, PSEN 2 gene, and the APP gene. As sporadic cases with *de novo* mutations can occur, it is important to screen all younger-age AD cases for known mutations (Lanoiselée et al., 2017). There are currently over 300 mutations of the transmembrane PSEN1 gene and 38 mutations of the PSEN2 gene leading to AD, both with autosomal dominant inheritance, although mutations of PSEN2 exhibit variable penetrance (Plotkin and Cashman, 2020). The number of known mutations continues to grow, making genetic screens for younger-age AD useful when positive, but not when negative, as an as-yet unidentified mutation may be responsible.

APOE genotyping is helpful in both younger- and older-age AD. The presence of one copy of the ε4 allele increases the risk for older-age AD 3–4-fold when compared with ε3 carriers, with two copies increasing the risk 12–15-fold. This is clinically relevant for two reasons. For a cognitively asymptomatic person, one or two copies of the ε4allele would warrant closer, more biomarker-based monitoring over time for the development of the disease. For a symptomatic person who is a candidate for anti-amyloid monoclonal antibody therapy, APOE genotyping is essential, as patients with an ε4 allele are more likely to have more brain bleeding and edema necessitating modifications in dosage and titration (Salloway et al., 2022; Devi, 2023).

Other tests

An electroencephalogram (EEG) may help aid in diagnosis, particularly when biomarkers are unavailable, and in following progression (Briel et al., 1999; Houmani et al., 2018). Early in the course of AD, there is an increase in theta and delta slow wave activity. As the illness progresses, there is an anterior drift of alpha activity from the occipital region as well as a reduction in amplitude and increasing slower rhythms (Briel et al., 1999; Houmani et al., 2018). In Case 1 (Figure 4), the EEG helped clarify diagnosis even in the absence of biomarkers, with no discernible EEG changes over time, which would be unusual for a patient with Alzheimer's disease, where there is generally progressively slower activity. Transcranial dopplers (TCD) may be of benefit in assessing vascular compromise in patients with dementia (Roher et al., 2011; Vinciguerra et al., 2019).

Neuropathologic and neurocognitive subtypes of AD

Based on the pattern of tau pathology and regional areas of MRI atrophy, four subtypes of AD exist, including typical, limbic predominant, hippocampal sparing, and minimal atrophy AD (Murray et al., 2011; Ferreira et al., 2020). Typical AD, with tau pathology in both hippocampal and association cortices, is the most common with 55% of cases, while the other three each comprise approximately one-third of the remainder. There is a difference in age of onset, disease duration, and prognosis between the subtypes. The hippocampal-sparing subtype of AD is most often associated with younger age, earlier motor symptoms, and a more aggressive course, and is less associated with the ε4 allele. The limbic-predominant subtype is associated with a more indolent progression and the longest period to death (Ferreira et al., 2020). The limbic predominant subtype is more affected by TDP-43 pathology. Women are more likely to be affected by the limbic predominant subtype. Hippocampal-sparing AD patients decline at the rate of 5 points on the MMSE yearly, limbic predominant AD patients by 1 point annually and typical AD patients by 3 points annually (Murray et al., 2011).

Analysis of neurocognitive profiles reveals as many as eight neurocognitive clusters of Alzheimer's based on cognitive areas affected, with distinct demographics, symptoms, and progression (Scheltens et al., 2016). Memory-impaired clusters progressed more slowly and were associated with the ε4 genotype while the memory-spared clusters with visuospatial impairment had onset at a younger age and progressed more rapidly. Given the vast heterogeneity of AD, only a precise and meticulous mapping of findings to each individual patient can guide diagnosis, prognosis, and therapy (Devi and Scheltens, 2018).

The informing visit (after workup is complete)

This is a key step in the care of a person with Alzheimer's disease or any other dementia. This visit provides information about the results of testing and how the diagnosis was arrived at. Information is provided about the relative certainty of diagnosis including the role and reliability of biomarkers. For example, in a person with evidence of cognitive impairment on standardized testing, with evidence of small vessel disease on neuroimaging, along with significant hippocampal atrophy and evidence of significant deposits of amyloid on imaging, the diagnosis of dementia would be attributable to several conditions, including cerebrovascular disease, hippocampal sclerosis, and AD, although a definitive diagnosis of AD would not be possible until tau load was assessed. This attention to tau is a departure from the current recommendation for treatment with monoclonal antibodies, which requires only a positive amyloid scan for implementation. But, as seen in Case 1 (Figure 4), a patient may present with profound and progressive cognitive impairment over

time, with amyloid deposition, but without tau abnormalities. Based on current diagnostic guidelines for AD, requiring the presence of both plaques and tangles, this patient does not have AD and would not be appropriate for treatment with an anti-amyloid monoclonal antibody.

This is also the visit where the likely subtype of AD may be discussed, which has prognostic implications for patients and their families. Genetic risk for family members may be brought up then, and it is important to factor in time for such discussions. Patients and families inquire about the level of severity, or stage, of Alzheimer's disease. Early during AD, the impairment may stabilize for years. Given the heterogeneity of AD, as well as the co-pathologies involved, including primary brain and systemic and psychiatric co-pathology, it is generally difficult to prognosticate with any degree of accuracy.

The author has found, over 30 years of clinical experience, that it may be more helpful to stage the various cognitive areas, primarily, visuospatial, language, praxis, social, verbal memory, visual memory, and motor abilities separately, rather than assign an overarching stage. Patients progress along different trajectories in different cognitive arenas, making general staging neither accurate nor helpful. Monitoring response to treatment with neurocognitive data over at least a year to 2 years allows some measure of precision in prognosis.

It is also helpful to the patient, the family, and the physician to get a sense of overall life expectancy at some point early in the course of treatment. Life expectancy calculators are available online through life insurance companies and while they do not factor in neurodegenerative diseases, they reasonably estimate length of life, based on demographics and systemic comorbidities. This allows for planning for the individual patient, including financial and caregiving resources. General disease staging is best used at the advanced and terminal stages to help plan end-of-life care, including hospice and preferences regarding hospitalization, although these discussions should be started early in the course of treatment, so that patients can also participate.

Treatment of Alzheimer's disease

Optimal treatment of AD may be conceptualized as treatment of five broad categories, primary treatment of Alzheimer's, treatment of co-morbid brain pathology, treatment of psychiatric co-morbidities, treatment of systemic co-morbidities, and socio-behavioral treatment.

Primary interventions for treating Alzheimer's

Primary interventions for the treatment of Alzheimer's are those interventions approved for symptomatic use, treatment that modifies disease trajectory, and a third category of "off-label" interventions, which are not approved for treating AD, but may be of benefit. Over time, it has become clear that interventions traditionally viewed as symptomatic may have disease-modifying effects, including significantly prolonging time to nursing home placement. This is biologically plausible when one accepts that neuroplasticity, although attenuated, is still present in patients with AD, and changing activity in circuits by symptomatic treatment likely strengthens those neural circuits.

Symptomatic medications

Cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine may help slow cognitive decline and reduce mortality for as long as 6 years in patients with AD and other dementias (Xu et al., 2021; Zuin et al., 2022). Galantamine may be superior in slowing progression to severe dementia (Xu et al., 2021). It has been the author's practice to maintain the patient on a cholinesterase inhibitor for as long as feasible. Side effects occur even after several years of treatment, although they generally occur in the first few months of titration. They include nightmares and vivid dreams, cramps of the lower extremities, nausea, loose bowels, diarrhea, and even bowel incontinence, fatigue, weight loss, and persistent rhinorrhea. Rhinorrhea, not a widely known side effect, besets a significant number of patients on cholinesterase inhibitors who may then seek specialist consultations and procedures if not made aware of this side effect.

Side effects, present in 5–10% of patients, may be ameliorated by slower titrations over 3 months. Switching to another cholinesterase inhibitor may allay refractory side effects, as may switching from an oral to a transdermal route (Darreh-Shori and Jelic, 2010). Switching evening to morning dosage may lessen nightmares and quinine water or magnesium may help with leg cramps. Dose reduction is another option.

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, slows cognitive decline in both mild and moderate AD and may have neuroprotective properties (Lipton, 2007; Wu et al., 2009). It is a non-competitive NMDA receptor antagonist, inhibiting the intracellular influx of calcium and reducing neuronal excitotoxicity. While the guidelines for memantine in the United States suggest beginning the drug once a patient has reached the moderate stage of AD, the author begins memantine, given its neuroprotective properties, as early as the mild cognitive impairment phase. Memantine may have some antidepressant and stimulant effects. It is best taken once a day, given its very long half-life. It is generally well-tolerated.

Disease-modifying medications

Disease-modifying drugs include those that specifically target Aβ42 and p-tau production and accumulation either through active or passive immunization, or other modulation of the immune system. Non-targeted immune modulation with intravenous immunoglobulin (IVIg), showed early promise, clearing Aβ plaques and reducing the inflammatory response, although a large trial did not find benefit in AD despite significant decreases in Aβ42 (Relkin et al., 2009, 2017).

Active immunization with vaccines that elicit neutralizing antibodies or passive immunization via monoclonal antibodies

targeted to specific epitopes has become the preferred strategy. In an early trial of an active vaccination against Aβ42, aborted due to increased mortality, found that 4.6 years later, more patients who had been on drugs than on placebo lived at home (Vellas et al., 2009). Even so, by 15 years, all five patients with complete plaque clearance had progressed to severe dementia (Vellas et al., 2009). Passive immunity with targeted monoclonal antibodies (MAB) to Aβ42 ultimately yielded the two currently approved agents targeting Aβ42. Anti-p-tau MABs are in development.

Reducing Aβ plaques: monoclonal antibodies to Aβ

Passive immunization with MABs to various Aβ epitopes all reduce brain amyloid deposits, many with downstream reduction in tau, and all with trends for potential clinical benefit over placebo. However, only two have shown significant clinical benefits over placebo in phase 3 trials. It is important to note that the outcome variables in all these trials have been historical and observational data, rather than objective measures, including the commonly used clinical dementia rating sum of boxes-18 (CDR-SB18) (Cummings et al., 2021; Mintun et al., 2021; van Dyck et al., 2022). The reduction in deterioration for drug vs. placebo was 0.4/18 points over 18 months with aducanumab and 0.45/18 points over 18 months with lecanemab on the CDR-SB18, for the two MABs currently approved for treating mild AD (Cummings et al., 2021) (Table 2). These differences are small, but the hope is that benefit accumulates over time.

Aducanumab targets oligomers and amyloid plaques. Lecanemab preferentially targets soluble protofibrils (large oligomers) over plaques (Gandy and Ehrlich, 2023). Both reduce downstream tau. Of note, both aducanumab and lecanemab cause amyloid-related imaging abnormalities (ARIA), with brain edema and microhemorrhages related to plaque dissolution, and both are parenterally administered. Some level of cerebral amyloid angiopathy, with amyloid deposits in parenchymal and leptomeningeal arteries and capillaries is seen in 85–95% of AD patients (Deture and Dickson, 2019). Anti-amyloid immunization strategies may affect the cerebral amyloid angiopathy-related risk of ARIA (Deture and Dickson, 2019). A slower dose titration, further modified by the presence of the ε4 allele, appears to significantly lessen aducanumab-related ARIA, possibly related to reduced speed of clearance (Devi, 2023).

Donanemab, likely to be approved shortly, targets only plaques (Mintun et al., 2021). Lecanemab is the only drug thus far evaluated in patients on anticoagulation, with a 2.4% macro hemorrhage rate (van Dyck et al., 2022). A single MAB targeting a single epitope may not be able to reduce pathology optimally, but combination therapy with multiple MABs has not yet been described.

Case 4 (Figure 7) illustrates the treatment of a patient with Alzheimer's confirmed by biomarkers, with oral medication as well as intravenous aducanumab on a slow titration schedule. He developed three asymptomatic microhemorrhages, discovered on periodic neuroimaging mandated by the drug protocol. He has been stable on this disease-modifying regimen.

Reducing tau

Tau immunotherapy using humanized anti-tau MABs has shown less promise. Semorinemab, one of several anti-tau MABs to have entered clinical trials, failed to stem tau deposition despite extremely high doses (Teng et al., 2022). The therapeutic rationale of this approach is that the MAB intercepts extracellular tau seeds, inhibiting the spread of tau pathology. However, as tau is primarily intracellular, MABs that do not reach cytosolic tau may not be effective (Sandusky-Beltran and Sigurdsson, 2020). Additionally, pathogenic tau species differ between patients, possibly requiring patient-specific anti-tau MABs for effective anti-tau antibody treatment (Dujardin et al., 2020). Nevertheless, given the extent that tau pathology tracks disease onset and progression, the development of effective anti-tau MABs for treating AD remains an important goal.

Off-label interventions with biological plausibility for use in AD

Estrogen and other off-label medications

The use of estrogen in women as an adjunct in treating Alzheimer's disease has a strong neurobiological rationale but has had variable results, with only some studies finding benefits, particularly with estradiol, a bioequivalent estrogen (Wharton et al., 2011; Song et al., 2020; Saleh et al., 2023). One factor responsible for the variability in response may be the presence of the ε4 allele (Taxier et al., 2022; Saleh et al., 2023). Apolipoprotein E is the main cholesterol transporter in the brain and women with an ε4 allele may benefit less from estrogen therapy due to a possible inefficiency in transporting estrogen into nerve cells (Taxier et al., 2022). While the consensus recommendation is not to use estrogen therapy for treating Alzheimer's disease, the author has used estrogen as adjunctive therapy in some women, using the n-of-1 approach. Earlier age at menopause and later initiation of hormone therapy was found to increase vulnerability to tau in the presence of elevated Aβ in postmenopausal women, suggesting a protective role for estrogen (Coughlan et al., 2023).

Several common medications are being investigated for potential benefits as adjunctive treatments for Alzheimer's disease. They include antiviral agents, agents reducing insulin resistance, and immunomodulators. Interesting associations have been noted between AD pathogenesis and bacterial infections such as *Porphyromonas gingivalis*, the cause of periodontal disease, viral infections such as herpes simplex virus type 1, and commensal gut bacteria (Hardy et al., 2023). The wide variety of agents being investigated as possible treatments in AD range from amlodipine to metformin to valacyclovir and sirolimus (Cummings et al., 2022).

TABLE 2 Selected anti-amyloid monoclonal antibodies.

Drug	Aducanumab; approved	Lecanemab; approved	Donanemab; pending approval
Binding	Fibrils>oligomers	Protofibrils 75–300 kDa	Fibrils, no oligomers
Inclusion	+Amyloid PET	+Amyloid PET	+Amyloid PET and +tau PET
MMSE	24–30	22–30	20–28
Number of patients	Phase 3; 3285, half to the drug, half on placebo; 3, 6, 10 mg doses	Phase 3; 1,800 pts, half to the drug, half on placebo.	Phase 2: 257 pts; 130+/group; 93/group completed trial
Length	18 months	18 months	18 months
Dosing	10 mg/kg q m, 1 mg to10 mg titrated over 8 m	10 mg/kg biweekly, no titration	700 mg q m for 3m, then 1,400 mg q m.
Plaque Reduction	44 CL↓ in 26 wks, 50% plaque-, 57 CL↓ in 18 m	70% plaque-, 59 CL↓ in 18 m	40% plaque-, 68 CL↓ in 6 m; 70% plaque-, 85 CL↓ in 18 m
Clinical outcome	0.4 vs. placebo on 18-pt CDR-SB;10 mg dose	0.45 vs. placebo on 18-pt CDR-SB	3 pts vs. placebo, iADRS; no change on18-pt CDR-SB
ARIA H	34% 10 mg dose	17%	31%
ARIA E	35% 10 mg dose	13%	27%
ARIA E/ H	41% 10 mg dose	21%	40%

ARIA, Amyloid Related Imaging Abnormalities; ARIA H; Amyloid Related Imaging Abnormalities hemorrhage; ARIA E; Amyloid Related Imaging Abnormalities edema; MMSE, Mini-mental state examination; PET, Positron Emission Tomography; CL, Centiloid units to measure plaques; CDR-SB, Clinical dementia rating scale- sum of boxes 18-point scale of cognitive ability, higher score more impairment; iADRS, integrated Alzheimer's Disease Rating Scale is a 144-point scale of cognitive ability, lower score more impairment.

Off-label neuromodulation: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS)

Neuromodulation, using transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS), may be a promising adjunctive treatment in patients with AD (Gonsalvez et al., 2017; Holczer et al., 2020). TMS induces a magnetic field to either excite or inhibit a cortical area of '1 cm^2, modulating long-term cortical excitability by inducing changes in synaptic circuits. With TDCS, a fixed 1–2-mA current modulates brain activity. While TDCS is portable, inexpensive, and may be administered at home, focusing on a specific brain region is more feasible with TMS.

Several studies have found that neuromodulation improved cognition in patients with Alzheimer's, with additional benefits from medication or cognitive training, while others have found no beneficial effect (Holczer et al., 2020; Wang et al., 2020). A multi-national European task force found only level 3 evidence for TMS in AD, and it is not currently an approved treatment for AD (Lefaucheur et al., 2020).

The outcome of neuromodulation in treating AD is influenced by various patient and stimulation-specific parameters (Gonsalvez et al., 2017). An additional major issue with interpreting data in neuromodulation trials is the problem of the sham control, as patients can nearly always identify active treatment (Burke et al., 2019). In the author's experience, neuronavigation-guided TMS therapy may be of benefit, particularly for maintaining non-memory functions such as language, as seen in cases 1, 5, and 6 (Devi et al., 2014; Tumasian and Devi, 2021).

Case 5 (Figure 8) is a patient with AD and stroke treated with oral medications and TMS. She improved over 15 months, with her MMSE going from 20/30 to 29/30. While she had a history of chronic, low-level depression, a potential target for TMS, the depression did not appear to have affected her neurocognitive performance.

Treatment of co-morbid brain pathology

Comorbid brain pathologies in AD that can currently be addressed include cerebrovascular pathology, Parkinson's disease, and normal pressure hydrocephalus. Aggressive management of risk factors for cerebrovascular disease including treating hypertension, and hyperlipidemia reduces the possibility of future stroke and concomitant cognitive decline. A stroke workup is recommended in patients with significant cerebrovascular disease. Interventional treatment options for cardioembolic sources of stroke include cardiac ablation and the use of indwelling implants to close the left atrial appendage and prevent blood stasis, clot formation, and the risk of embolic stroke. Antiplatelet agents and anticoagulants are alternatives, although the increased risk of intraparenchymal hemorrhage with these drugs may preclude the concomitant use of anti-amyloid MABs.

In PD, using a monoamine oxidase inhibitor to delay symptom onset or levodopa to help with symptoms is beneficial (Fabbrini et al., 2012). In patients with NPH, the use of shunting helps with management, particularly gait imbalance, but those patients who benefit from shunting may also be more likely to have concomitant AD (Müller-Schmitz et al., 2020).

Treatment of psychiatric co-morbidities

Anxiety and depression in patients with AD should be treated aggressively as the benefits extend beyond alleviating psychiatric symptoms. Patients often report better cognition, improved social

Mr. Financier was a 78-year-old man who was seen at the behest of his wife who accompanied him. "I misplace things..." His wife stated, "he is a very, very bright man, who is very absent minded... he will leave things like water on, shower on... I have to tread lightly, is he being thoughtless or not...we go through ritual every morning, before we go to church, do you have your keys? do you have...? We have been doing this ritual for the last two years..." He stopped using his checkbook one year ago because it "was too much."

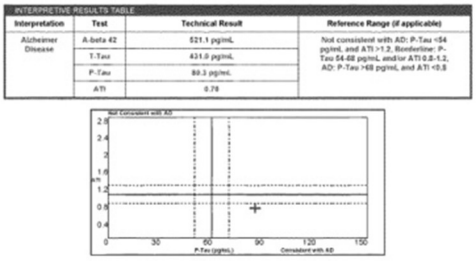
He had cardiomyopathy and 70% blockage of his left anterior descending artery although his ejection fraction was in the 50s. He had hyperlipidemia and wore hearing aids. He drank two martinis for lunch and drank in the evenings for years, never experienced withdrawal, and was abstinent for many years. He has a long history of depression. He was on atorvastatin 40 mg, venlafaxine 225 mg, trazadone 50 mg, aspirin 81 mg, carvedilol 25mg BID and over the counter memory supplements. He worked in finance, retiring decades ago, and was physically active. His mother died at 78 with dementia and cardiac issues, his father died at 68 of MI. There were no known cognitive issues in 18 paternal and maternal aunts and uncles, and in his grandparents. His neurological examination was normal. **His MRI showed no hippocampal atrophy and was normal. His APOE genotype was ε3/4**. His cognitive performance showed impairment consistent with early Alzheimer's disease. He underwent a lumbar puncture.

Variable	2021	2023
Mini Mental State Examination Score	27/30	28/30
WAIS Verbal Scale Quotient Percentile	86%	95%
WAIS Performance Scale Quotient Percentile	50%	68%
WAIS Full Scale Quotient Percentile	75%	90%
WMS Auditory Immediate Memory Percentile	63%	70%
WMS Visual Immediate Memory Percentile	50%	50%
WMS Immediate Memory Percentile	58%	63%
WMS Auditory Delayed Memory Percentile	77%	63%
WMS Visual Delayed Memory Percentile	42%	58%
WMS Working Memory Percentile	21%	32%
Buschke Selective Recall Test: Total Recall	44/72	42/72
Delayed Recall (Free recall)	2/12	2/12
Delayed Recognition (Cued recall)	8/12	11/12
60-item Boston Naming Test	59/60	57/60
CFL Fluency Percentile	86%	95%

Working Diagnosis: Alzheimer's disease.

Management: He was placed on memantine 20 mg, rivastigmine 13.4 mg patch, homotaurine 100 mg BID and aducanumab, slowly being titrated, currently 7mg/kg.

Cerebrospinal analysis, 2021 positive for AD



2-year follow up: He has remained stable; he has had three microbleeds on aducanumab, without clinical symptoms or signs.

FIGURE 7
Case 4—Alzheimer's treatment: oral medication and intravenous aducanumab.

interaction, and increased compliance with activities of daily living, which can alleviate caregiver burden. Selective serotonin reuptake inhibitors such as escitalopram are well-tolerated and effective in treating these symptoms (Knopman et al., 2021).

When aphasia and ideomotor apraxia become prominent, the patient may become anxious and agitated, perhaps not understanding what a "shower" means, and fighting when directed into it. While "agitation" is a commonly used term in these instances, it is non-specific, and it is more helpful to describe the circumstances surrounding such a response. Does the patient "get agitated" when made to change clothing or to made exercise? This may allow the physician to better understand the underlying cause and more effectively address it.

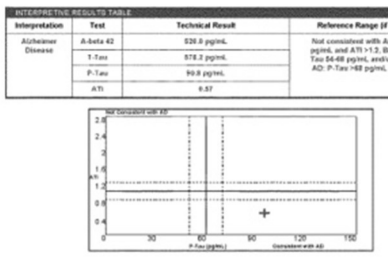
Agitation in AD is nearly always the behavioral expression of underlying anxiety and may resolve with antidepressant treatment. Psychosis, including paranoid ideations often involving caregivers, needs to be aggressively addressed. Disinhibition may also be an issue. Atypical antipsychotic agents such as olanzapine and quetiapine may be helpful, but it is essential to discuss the relevant "black box" warnings with the patient and family. Valproic acid, found by the author to be beneficial in some patients refractory to other medications, was found ineffective in a recent review (Baillon et al., 2018). Pimavanserin, an atypical antipsychotic agent approved for treating Parkinson's psychosis, is a choice in patients prone to developing extrapyramidal symptoms, such as those with Lewy body dementia. Very expensive, it may not be a viable option for many patients (Meltzer et al., 2010).

Sleep disturbances in AD patients may be addressed by low doses of antidepressants such as trazodone, mirtazapine, or doxepin, or melatonin-enhancing drugs such as ramelteon.

Ms. Fundraiser was a 69-year-old woman, self-referred and accompanied by her husband. "I have a fear that has gotten worse when I am in unfamiliar places... If we take a different route to church, my mind gets scrambled... There is no logic for my fears... I am missing words when I am typing... twice while driving I got disoriented in the car and that scared me... when I am reading, it is more of an effort to remember the story..." Her husband noted some memory loss over the last few years, but nothing "dramatic." She drank from age 16 to age 60, "towards the end, a bottle of white wine a day." She never had withdrawal symptoms and was abstinent for nearly a decade. She had hyperlipidemia and a left hip replacement. She was on venlafaxine 20 years ago for a few years which she restarted several months ago for anxiety. **Medications:** Atorvastatin 10 mg, venlafaxine 37.5 mg. She had a high school equivalency diploma. She was physically very active. There was no family history of dementia, including in two grandparents who died in their 90s. Her neurologic examination was normal. **Her brain MRI showed brain stem and subcortical infarcts due to white matter disease. Her APOE genotype was ε3/4. Her stroke work up was negative.** Her neurocognitive evaluation showed significant memory deficits, consistent with Alzheimer's disease and stroke. She underwent a lumbar puncture.

Variable	Time 1 (2021)	Time 2 (2023)
Mini Mental State Examination Score	**20/30**	**29/30**
WAIS Verbal Scale Quotient Percentile	37%	55%
WAIS Performance Scale Quotient Percentile	45%	63%
WAIS Full Scale Quotient Percentile	42%	58%
WMS Auditory Immediate Memory Percentile	1%	30%
WMS Visual Immediate Memory Percentile	27%	50%
WMS Immediate Memory Percentile	4%	37%
WMS Auditory Delayed Memory Percentile	9%	42%
WMS Visual Delayed Memory Percentile	5%	27%
WMS Working Memory Percentile	21%	39%
Buschke Selective Recall Test: Total Recall	34/72	28/72
Delayed Recall (Free recall)	5/12	5/12
Delayed Recognition (Cued recall)	10/12	11/12
60-item Boston Naming Test	52/60	47/60
CFL Fluency Percentile	37%	55%

Cerebrospinal analysis in 2021 positive for AD



Working Diagnosis: Alzheimer's disease and cerebrovascular disease

Management: Memantine 20mg in AM, donepezil 10 mg at HS, homotaurine 100 mg BID, valocyclovir 500 mg BID, clopidogrel 37.5 mg QD, TMS weekly. She did not want to go on aducanumab.

1.5-year followup:- patient has been stable, possibly even improved.

FIGURE 8
Case 5—Alzheimer's treatment: oral medication and transcranial magnetic stimulation.

Suvorexant binds orexin, a neuropeptide that promotes wakefulness and may be of benefit for insomnia in patients with Alzheimer's (Herring et al., 2020). Interestingly, suvorexant also reduces the level of p-tau and Aβ (Lucey et al., 2023). Purely anticholinergic medications such as diphenhydramine and all benzodiazepines should be avoided for treating agitation and insomnia. They may lead to tolerance, paradoxical effects, and detrimental effects on cognition. Sleep apnea, if a cause of insomnia, should be addressed. If weight contributes to sleep apnea, this should be preferentially addressed as the consistent use of a mask apparatus is challenging in patients with AD.

Overall, the treatment of psychiatric symptoms in AD patients is crucial not only for improving quality of life, but also for reducing caregiver burden. A personalized approach should be taken, considering the individual's medical history, medication use, and potential side effects. It is also important to regularly monitor and reassess treatment effectiveness to make any necessary adjustments to medications and dosages.

Treatment of systemic comorbidities

Various other strategies addressing systemic comorbidities help treat patients with AD. Intensive blood pressure control, with a target systolic blood pressure <120 mm Hg, is effective in reducing the risk of cognitive impairment compared to standard blood pressure control (Williamson et al., 2019).

A long-term, randomized Finnish trial found that a multidomain lifestyle-based intervention, including a program of healthy balanced nutrition, physical exercise, cognitive training, social activities, and vascular and metabolic risk management, was

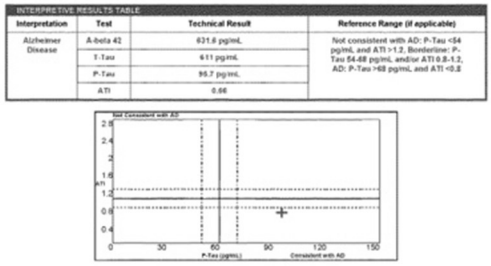
Ms. Homemaker was a 71-year-old woman who was seen unaccompanied. She stated, "It (Alzheimer's) runs on my mother's side of the family, my mother had Alzheimer's, one of her sister's had it, and both her parents… that is why I am concerned, and I am forgetting some things… something someone told me or making my schedule…I will forget a word… I really would like to have baseline testing…" Her family has not noticed any issues. She has relied on lists for years, "Someone once said to me, your lists have lists." Her past medical history was significant for bouts of pneumonia being prevented with subcutaneous immunoglobulin biweekly. She underwent menopause at age 54 and was on transdermal hormone therapy until stopping two years ago. A college graduate, she is a married homemaker. Her family history was significant for her mother developing presumed AD at age 75 and dying in her 80s. Of her five maternal aunts, four died in their 80s with only one developing dementia. Both maternal grandparents died with dementia in their 80s. **Her brain MRI showed some mild microvascular change without hippocampal atrophy. Her transcranial dopplers showed normal flow. She was APOE ε3/4.** On neurocognitive performance, her impairment was concerning for Alzheimer's disease. She therefore underwent a lumbar puncture.

Variable	Time 1 2021	Time 2 2022
Mini Mental State Examination Score	**29/30**	**27/30**
WAIS Verbal Scale Quotient Percentile	77%	93%
WAIS Performance Scale Quotient Percentile	25%	73%
WAIS Full Scale Quotient Percentile	55%	87%
WMS Auditory Immediate Memory Percentile	77%	42%
WMS Visual Immediate Memory Percentile	84%	73%
WMS Immediate Memory Percentile	86%	58%
WMS Auditory Delayed Memory Percentile	70%	70%
WMS Visual Delayed Memory Percentile	98%	42%
WMS Working Memory Percentile	27%	70%
Buschke Selective Recall Test: Total Recall	48/72	48/72
Delayed Recall (Free recall)	4/12	4/12
Delayed Recognition (Cued recall)	12/12	11/12
60-item Boston Naming Test	53/60	54/60
CFL Fluency Percentile	22%	63%

Working Diagnosis:
Alzheimer's disease

Management: Estradiol patch restarted 0.0375 mg twice weekly, memantine 10 mg BID, donepezil 10 mg, valacyclovir 1000 mg BID, TMS weekly, vitamins B12 1 g SL, aducanumab titrated up to 7mg/kg at month 21.

Cerebrospinal analysis, 2021



Follow Up: Patient has been stable, her amyloid scan was negative, and her aducanumab was therefore stopped. She continues her other treatments, and the plan is to rotate through one dose of a different monoclonal antibody every 6 month to target different epitopes.

Amyloid scan, 2023

Findings:

There is no increased Amyvid uptake in the cortical cerebral gray matter. The brain shows normal gray-white contrast throughout. The cerebellum demonstrates no evidence of abnormal Amyvid uptake.

FIGURE 9
Case 6—Alzheimer's treatment: oral medication, aducanumab, and transcranial magnetic stimulation.

effective in reducing the risk of cognitive impairment. This was true in individuals with genetic risk factors for AD (Kivipelto et al., 2018). Such an approach is also beneficial in slowing decline in patients with AD.

Cholesterol-lowering agents such as statins reduce the risk of AD, possibly through a direct effect on APP processing, in addition to reducing the risk of cerebrovascular disease (Langness et al., 2021). Hearing and visual loss should be addressed and treated aggressively as it increases social isolation in patients. However, the proper use of hearing aids may be difficult for some patients. Given the increased risk for delirium and other morbidity, hospitalizations are best avoided or shortened in patients with AD with as much as possible. The workup and care are better rendered in an outpatient setting. Urinary tract infections, rampant in women with AD, may be prevented with ongoing low-dose antibiotics and/or vaginal estrogen. Baseline bone density evaluations are recommended in both men and women, and aggressive treatment of osteopenia and osteoporosis prevents the risk of fall-related fractures.

Socio-behavioral treatment

A diagnosis of Alzheimer's disease does not necessarily mean that an individual must stop working, even in cognitively demanding positions as physicians or judges (Devi, 2018a). Recommendations regarding the ongoing ability to work should be based on the specifics of the individual circumstance, including the particulars of the neurocognitive performance, rather than on the diagnosis. Patients with other varied diagnoses such as Parkinson's disease, multiple sclerosis, depression, or stroke may be cognitively far more compromised than patients in the earlier

stages of Alzheimer's disease. The ability to continue working helps patients maintain cognitive resilience and confidence, and contribute to society.

Multimodal interventions involving diet and cognitive and physical engagement help improve cognition (Isaacson et al., 2019). Anti-inflammatory, pro-cardiac health diets with low levels of carbohydrates and fats may be helpful in both AD prevention as well as reducing ongoing inflammation, a known driver of pathology in AD (Charisis et al., 2021). Physical therapy or working with a trainer can be helpful for patients, but it may not work for everyone, particularly those with abulia and lack of initiative. Regular aerobic exercise has been consistently shown to help cognition and may slow disease progression (Devanand et al., 2023). Exercise releases myokines, increasing the expression of brain-derived neurotrophic factor, which promotes hippocampal neurogenesis and increases synaptic plasticity (Benarroch, 2022).

Cognitive exercises are beneficial in maintaining functioning and strengthening cognitive reserve (Belleville et al., 2023). Some patients find these exercises to be anxiety-provoking and depressing. Similarly, support groups such as those provided by the Alzheimer's Association may be helpful for some patients, but for others, interacting with more impaired group members may increase unease and fear over their own future. Therefore, while theoretically beneficial for all patients, these interventions may not be practical for some.

It is essential to provide ongoing education to both patients and caregivers about what to expect in terms of prognosis and care over the ensuing years. However, a directive such as "go home and put your affairs in order" is needlessly alarming, depressing, and unhelpful. Instead, it is essential to provide information in a compassionate and supportive manner to help patients and caregivers plan and prepare for future.

A biologically complementary, multimodal approach to treating Alzheimer's disease

Case 6 (Figure 9) illustrates the complementary multimodal approach to the treatment of AD. The patient, a 71-year-old woman, had no cognitive complaints but wanted a baseline evaluation given a strong maternal family history of older-age dementia, presumed to be AD (no biomarker or autopsy confirmation). Her genotype was APOE3/4 and she had significant impairment on her neurocognitive evaluation, with a brain MRI showing mild vascular changes and normal transcranial dopplers and electroencephalogram.

However, her cognitive evaluation showed significant deficits in memory and language, despite scoring 29/30 on the MMSE. She scored 4/12 on a delayed recall list-learning task and verbal fluency at the 22nd percentile, despite excellent verbal skills. This was concerning for early Alzheimer's disease. She underwent a lumbar puncture which was consistent with a diagnosis of Alzheimer's disease with a low Aβ42 of 632 ng/L, consistent with Aβ42 deposition in the brain, and a high p-tau level of 96 ng/L.

She was informed of her diagnosis of early Alzheimer's disease, and an aggressive treatment regimen to prevent progression was recommended. She embarked on a course of approved oral medications for treating AD, off-label oral medication for treatment of her AD (including estrogen replacement and valacyclovir), off-label weekly neuronavigation guided transcranial magnetic stimulation of her left dorsolateral prefrontal cortex, Broca's, Wernicke's, and biparietal cortices, and a slowly titrated monthly infusion of aducanumab. Repeat cognitive testing at 14 months showed overall stability with improvement in language and visuospatial functions. She continued to function independently at home. Her weight was optimal with good dietary habits. She was physically and socially active. While she would have benefited from cognitive exercises, these were discontinued as she became very anxious during the sessions.

Amyloid scanning was performed 22 months into treatment with aducanumab, primarily for consideration of a switch to the recently approved lecanemab. She has become plaque negative. Aducanumab was therefore stopped and she continues her other treatments. The plan will be infusions every 4 to 6 months of available monoclonal antibody therapies on a rotating basis, with ongoing objective monitoring of her cognitive status. While the therapeutic value of rotating monoclonal antibodies to target different Aβ oligomer epitopes is speculative, the goal is to ultimately allay oligomer-driven neurotoxicity.

Conclusion and future directions

Precision medicine is particularly relevant for treating Alzheimer's disease, given not only the tremendous variability in clinicopathology but also the inherent inter-individual variability of the human brain. Given the vast heterogeneity of AD, its coexistence with other primary brain co-pathologies, psychiatric and systemic co-morbidities, it is unlikely that an effective therapeutic approach for one type of Alzheimer's disease, or one subtype, may be beneficial for another. It is essential to tailor treatment and approach prognosis on a detailed, case-by-case basis.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Aging Neuroscience

TYPE Review
PUBLISHED 24 August 2023
DOI 10.3389/fnagi.2023.1224723

OPEN ACCESS

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RECEIVED 18 May 2023
ACCEPTED 04 August 2023
PUBLISHED 24 August 2023

CITATION
Qi X, Zhou Q, Dong J and Bao W (2023) Noninvasive automatic detection of Alzheimer's disease from spontaneous speech: a review. *Front. Aging Neurosci.* 15:1224723. doi: 10.3389/fnagi.2023.1224723

Noninvasive automatic detection of Alzheimer's disease from spontaneous speech: a review

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Alzheimer's disease (AD) is considered as one of the leading causes of death among people over the age of 70 that is characterized by memory degradation and language impairment. Due to language dysfunction observed in individuals with AD patients, the speech-based methods offer non-invasive, convenient, and cost-effective solutions for the automatic detection of AD. This paper systematically reviews the technologies to detect the onset of AD from spontaneous speech, including data collection, feature extraction and classification. First the paper formulates the task of automatic detection of AD and describes the process of data collection. Then, feature extractors from speech data and transcripts are reviewed, which mainly contains acoustic features from speech and linguistic features from text. Especially, general handcrafted features and deep embedding features are organized from different modalities. Additionally, this paper summarizes optimization strategies for AD detection systems. Finally, the paper addresses challenges related to data size, model explainability, reliability and multimodality fusion, and discusses potential research directions based on these challenges.

KEYWORDS

Alzheimer's disease, spontaneous speech, dataset, machine learning, deep learning, classification, optimization

1. Introduction

Alzheimer's disease (AD) is one of the most prevalent neurological disorders. It primarily affects older adults, with age being a significant risk factor for its development. Recently, AD has become one of the main causes of death among people over 70 years old (Alzheimer's Association, 2019). The World Health Organization (WHO) has reported that dementia currently affects over 50 million people worldwide, with millions of new diagnoses each year (World Health Organisation, 2020), likely increasing to above 152 million in 2050 (Nichols et al., 2022). According to Alzheimer's Society (2020), the prevalence of AD is also expected to increase, as indicated by the doubling of AD cases in individuals over the age of 60 approximately every 4-5 years. Among individuals over the age of 80, the likelihood of developing AD is estimated to be one in three (Ritchie and Lovestone, 2002). AD is characterized by a continuous deterioration of cognitive and functional abilities in individuals over time, encompassing domains such as language, memory, attention and executive function (Nestor et al., 2004; American Psychiatric Association, DSM-5 Task Force , 2013). Therapeutic interventions have shown the greatest efficacy before neuronal degeneration occurs in the brain (Nestor et al., 2004). Therefore, early identification of these deficits is crucial, as it has the potential to significantly impede the progression of cognitive impairments and enable the preservation of cognitive functions in patients (Dubois et al., 2009).

To date, there has been a lot of research focused on developing methods for detecting AD, including neuropsychological tests [e.g., self-report questionnaires, the mini-mental

state examination (MMSE) (Folstein et al., 1975)], and neuroimaging techniques [e.g., magnetic resonance imaging (MRI) (Jack et al., 2008), positron emission tomography (PET) (Samper-González et al., 2018)]. Although these methods can offer relatively accurate diagnoses of AD, they suffer from some drawbacks. Neuroimaging and cerebrospinal fluid analysis are expensive, time-consuming, invasive, and require validation by neurologists and manually clinical settings. Cognitive assessments and self-report questionnaires are tedious and may not have good test-retest reliability and validity. Therefore, there is a need for more practical and reliable methods for AD detection that are less invasive and can be used in a natural environment.

On the contrary, speech-based methods have the potential to provide non-invasive, effective, simple, and inexpensive tools for automatically detecting AD. There are several reasons why speech is so useful for this purpose. First, speech is closely related to cognitive status, and it has been widely used as the main input in various mental health assessment applications. The most significant correlation with AD is the difference in speech comprehension, reasoning, language production, and memory functions, which can result in a reduction in vocabulary and verbal fluency, as well as difficulties in performing daily tasks related to semantic information (Forbes-McKay and Venneri, 2005). Hoffmann et al. (2010) compared four temporal parameters in individuals with AD and control subjects, namely articulation rate, speech tempo, hesitation ratio and rate of grammatical errors. Significant differences were observed between the two groups, with hesitation ratio showing particularly notable disparities. These findings indicate that temporal aspects of speech play a vital role in the differentiation of AD from other neurodegenerative disorders and can even aid in the detection of early-stage AD. Additionally, the studies focusing on the speech of individuals with AD have consistently demonstrated that their acoustic and linguistic abilities are significantly impacted, even during the early stages of the disease, leading to noticeable differences when compared to individuals without AD (Ahmed et al., 2013; Szatloczki et al., 2015). These distinctive differences observed between individuals with AD and those without AD can be harnessed for the purpose of detecting AD through speech analysis. Second, spontaneous speech can be easily accessed anywhere, as it only requires a device with a recording function. Speech can also be used as a cost-effective long-term monitoring approach.

Motivated by these, research has increasingly focused on utilizing spontaneous speech to extract information for the automatic detection of AD. The studies can be broadly categorized into two main directions: extracting discriminative features from speech data to identify AD patients, and designing effective classification models to achieve high detection performance. In the feature domain, spontaneous speech of AD patients exhibits many distinguishable characteristics, such as lower speech rate, more frequent and longer hesitations, obscurer pronunciation, and longer pauses, compared to non-AD (NAD) participants (Hoffmann et al., 2010; Szatloczki et al., 2015). These distinctions can be leveraged to extract linguistic and acoustic features for the automatic detection of AD. Linguistic features encompass the linguistic content and structure of speech and can be extracted from manually annotated transcripts or generated through automatic speech recognition (ASR) systems. These features include measures of parts-of-speech (POS) tags (Bucks et al., 2000), grammatical constituents (Fraser et al., 2014), lexical diversity (Fraser et al., 2016a), global vectors (GLoVe) (Pennington et al., 2014), word2vec (Mirheidari et al., 2018), and deep embeddings using techniques such as bidirectional encoder representations from transformers (BERT) (Yuan et al., 2020) and other neural network methods (Pan et al., 2019). Acoustic features refer to the characteristics of speech that are related to its physical properties, and can be extracted using traditional handcrafted or deep embedding techniques, such as Fourier analysis, Mel-frequency cepstral coefficients (MFCCs) (Alhanai et al., 2017), term frequency-inverse document frequency (TF-IDF) (Ramos et al., 2003), and wav2vec (Baevski et al., 2020). Besides, other features can also provide useful information for AD detection, including speaker-specific attributes such as age, gender, and interactional features (e.g., turn-taking patterns).

In the model domain, the models for AD detection from speech can be divided into three types based on different modal input. Speech-based models are built with acoustic features as model input, and text-based models exploit linguistic information as model input. Multimodal-based models combine features from speech and text modalities as model input. These models are trained mainly based on statistical machine learning such as linear discriminant analysis (LDA), decision tree (DT), support vector machine (SVM) and random forests (RF), and deep learning (DL) algorithms, including fully connected neural network (FCNN), convolutional neural network (CNN), recurrent neural network (RNN), long short-term memory (LSTM) network, gated recurrent unit (GRU), and Transformer-based models.

However, automatic detection of AD is still a challenging task from spontaneous speech. One reason lies in the lack of specialist data due to the challenges associated with collecting a large amount of transcribed speech recorded from AD patients and the limited availability of clinical professionals. Then, another reason is that many NNs appear black boxes, making it challenging to understand the underlying features driving their predictions and give meaningful interpretations.

The paper presents a review of automatic detection systems for from spontaneous speech. The main contributions can be summarized as follows:

- We conduct a comprehensive review and summary of the development of each module in AD detection systems, focusing on the data collection module, feature extraction module and classification module. This provides a comprehensive understanding of the various components involved. Notably, our paper focuses on the advancements made for AD detection technologies especially in the last three years, providing an up-to-date analysis of the state-of-the-art. This distinguishes our work from previous review publications such as Petti et al. (2020) covering the period between 2013 and 2019, Pulido et al. (2020) covering 2005–2018, de la Fuente Garcia et al. (2020) covering 2000–2019, (Vigo et al., 2022) covering 1996-2020, and (Martínez-Nicolás et al., 2021) covering 2010-2020.
- Following a handbook-style approach, we provide a detailed description of the features and classifiers usually used in

AD detection models. This allows readers to easily access information on AD detection without the need to search through numerous papers.
- We compile a summary of the state-of-the-art performance on popular datasets from recent papers, providing insights into the corresponding technologies used for feature extraction, classifiers, and optimization strategies.
- We provide a discussion of the existing challenges in AD detection, with a focus on practical applications aspects such as data, modality, explainability and reliability. Additionally, we propose potential future directions to address these challenges.

The paper starts with a description of the task of automated AD detection from spontaneous speech (Section 2). Then, some recent public datasets are introduced and features extracted from speech and text are detailed shown in Section 3. In Section 4, we review popular classification algorithms used in AD detection and discuss strategies for improving performance. Section 5 presents a discussion of the challenges that still need to be addressed. Finally, Section 6 provides conclusions and outlines potential ideas for future work.

2. Task description

AD is thought to be the most prevalent neurodegenerative condition with common signs of memory and cognitive decline. AD detection and treatment is greatly helpful for delaying irreversible brain damage, and thus important in AD research. Since a key marker of early AD is decline in speech and language functionality, like the reduction of vocabulary and verbal fluency, this allows us to extract information from speech or/and the corresponding transcripts to distinguish AD and non-AD (NAD). Therefore, the automatic AD detection task is to determine a category c^* between AD and NAD with a higher probability given data $\mathbf{d}$, which is formulated as

$$c^* = \max_{c=\{AD,NAD\}} p(c|\mathbf{d}). \tag{1}$$

2.1. System architecture

To solve the problem, a typical system architecture is demonstrated in Figure 1. The process of automation detection of AD can be categorized into three stages: data collection, feature extraction and classification.

First, the data $\mathbf{d}$ are collected by recording speech from both individuals with and without AD using various methods. After data collection, it is common to partition the dataset into a training set, a validation set, and a test set. The training set is used to train the model, while the validation set is used for fine-tuning and hyperparameter tuning. Finally, the test set is kept separate and used for unbiased evaluation of the trained classifier. Given that the original audio waves and transcripts include both valuable and redundant information for AD detection, it becomes essential to extract relevant features, emphasizing the informative aspects. The process can be conceptualized as mapping the raw data $\mathbf{d}$ to meaningful representations $\mathbf{F}$ that capture the relevant characteristics for AD detection, expressed as

$$\mathbf{F} = f(\mathbf{d}). \tag{2}$$

The core is to extract discriminate features to classify AD and NAD as accurately as possible, which should be designed carefully. Three types of features are generally exploited for this purpose. One is acoustic features extracted from speech data. Many acoustic features such as MFCC, wav2vec2.0 are related to the severity of AD. Another linguistic features are obtained from transcripts which are usually from manual annotation or an ASR system, containing GLoVe, word2vec, BERT embedding and so on. Then, there are some other features including individual attributes such as age and gender, and interactional features from dialogues. More detailed description about feature extraction will be found in Section 3.2. Therefore, instead of Equation 1, the practice uses the features to detect AD, which is expressed as

$$c^* = \max_{c=\{AD,NAD\}} p(c|f(\mathbf{d})) = \max_{c=\{AD,NAD\}} p(c|\mathbf{F}). \tag{3}$$

A classification model is used to address the issue of Equation 3. The modeling methods contain two categories: traditional statistical machine learning algorithms and DL algorithms. Statistical machine learning algorithms usually have clear theories and reduction process and thus have having desirable interpretability, such as LDA, DT, SVM and RF. On the other hand, DL algorithms have been proven to achieve a better performance in many fields, such as CNN, RNN, LSTM and Tranformer-based models. Several canonical classification models will be introduced in detail in Section 4.

2.2. Evaluation metrics

The system for AD classification is typically evaluated by metrics including the accuracy (A), precision (P), recall (R) and F_1 score, which are defined as

$$A = \frac{TN + TP}{TN + TP + FN + FP}, \tag{4}$$

$$P = \frac{TP}{TP + FP}, \tag{5}$$

$$R = \frac{TP}{TP + FN}, \tag{6}$$

$$F_1 = \frac{2PR}{P + R}, \tag{7}$$

where TP represents the number of true positives, TN represents the number of true negatives, FP denotes the number of false positives and FN is false negatives.

2.3. Study selection process

To comprehensively review the aforementioned systems, we conducted a search for relevant articles published within the current year. First, our primary focus is on the automatic detection of AD based on speech data. Therefore, our inclusion criteria are

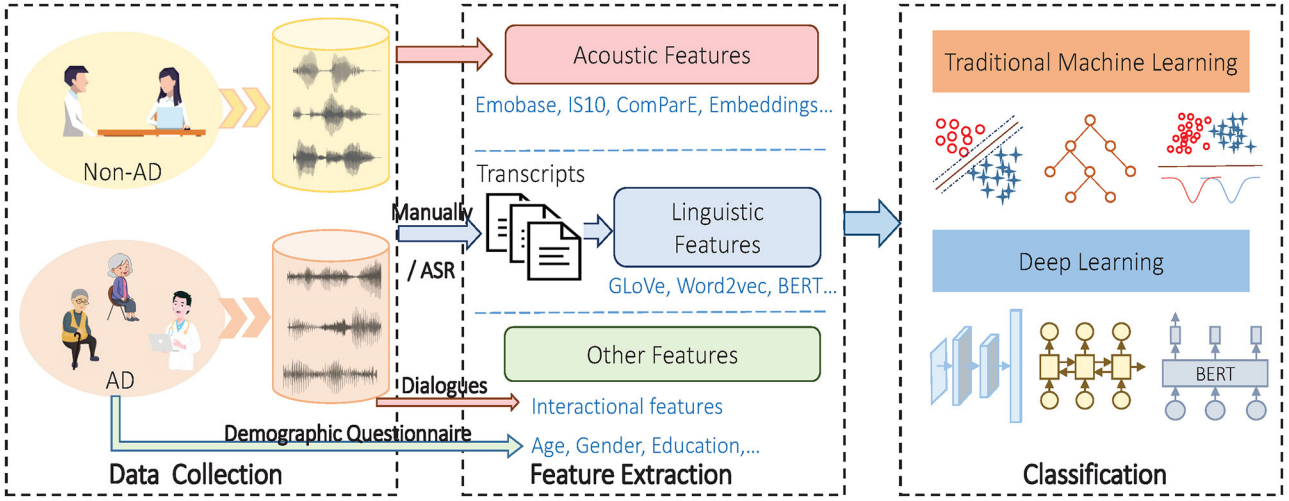

FIGURE 1
A hierarchy of automatic detection of AD from spontaneous speech.

to select articles that employ speech and/or text analysis and ML methods for the automatic detection of AD. On the other hand, we excluded studies related to other dementia conditions, such as Parkinson's disease, as well as those utilizing non-speech data like MRI. Additionally, studies solely relying on traditional statistical analysis for AD detection without incorporating ML methods were also excluded. By applying these specific criteria, we aim to narrow our focus to research that utilizes ML-driven approaches for automatic AD detection using speech data.

Then, to obtain the relevant articles, we conducted a thorough literature search using prominent academic databases like Google Scholar and conference proceedings, with a particular emphasis on conferences like Interspeech and ICASSP, renowned for their focus on speech processing and provide valuable contributions to the field of automatic AD detection through speech analysis. To refine our search and target relevant articles, we employed inclusion criteria and exclusion criteria. We applied specific inclusion and exclusion criteria to refine our search and target relevant articles. Initially, we used keywords related to "Alzheimer's disease" OR "AD" OR "dementia" AND "speech" to retrieve articles. Subsequently, we manually selected or excluded articles after careful reading to ensure their relevance to our research focus. Notably, the focus of this review is on automated AD detection from speech patterns using ML-based systems. While Mini Mental State Examination (MMSE) scores are commonly used as a quantitative measure of cognitive impairment and provide valuable insights into the disease's dynamics in monitoring the progression of AD, the vast and continuously evolving literature on AD progression and MMSE prediction goes beyond the scope of this review. Moreover, many studies employed a similar architecture for MMSE prediction (Rohanian et al., 2021; Jin et al., 2023; Tamm et al., 2023), which results in significant overlap with AD detection in terms of features and ML techniques. Due to space limitations and to maintain a clear focus on AD detection from speech data, specific aspects related to MMSE prediction were not explored in this review.

Furthermore, to ensure the most up-to-date information, we primarily searched for papers published within the last 3 years, aiming to capture the latest advancements and developments in the field of automatic AD detection.

By combining these search strategies, we gathered a robust collection of relevant studies, enriching our literature review with comprehensive insights and valuable findings related to the automatic detection of AD from speech data.

3. Materials

3.1. Datasets

A dataset used for automatic AD detection from speech is obtained by recruiting participants with and without AD and collecting recordings from them using various methods, including neuropsychological tests and natural conversations. Neuropsychological tests include but not limited to the following tests.

- The picture description test (Croisile et al., 1996; Forbes-McKay and Venneri, 2005). The picture description test involves presenting a subject with an picture and requesting them to provide a detailed description of the depicted scenario within a specified time frame.
- Verbal fluency test: animal category (Hart et al., 1988; Randolph et al., 1993). During verbal fluency assessment, participants are given a specific category, typically related to animals (e.g., dog, cat, fish), and are instructed to generate as many different words as possible within a time limit.
- Boston naming test (BNT) (Koss et al., 1996). BNT has been predominantly used to assess naming ability for the degree of language disturbances in clinical neuropsychology. A typical form consists of 60 pictures ordered from easy to difficult, and the subjects are requested to name them (Kaplan et al., 2001).

- Logical memory test (Greene et al., 1996; Rabin et al., 2009). Logical memory test is especially useful for detecting relatively mild retrieval problems, which includes word list learning, delayed recall, recognition and constructional praxis (Rosen et al., 1984). During these selected tests, spontaneous speech data will be recorded. Some of them are then manually transcribed.

Several public datasets are published for automatic detection of AD from spontaneous speech, which allows researchers to easily access the study of AD detection. Table 1 presents a compilation of public datasets, including their respective dataset names, reference papers, spoken languages, modalities, and participant information. These datasets were selected by following the criteria of public availability, and widespread usage in experiments for automatic AD detection.

DementiaBank (Boller and Becker, 2005) is the largest publicly available database, which is a multilingual data bank consisting of 15 datasets in English, German, Mandarin, Spanish and Taiwanese. DementiaBank contains 241 narrations from individuals without any cognitive impairment (referred to as healthy controls or HCs) and 310 narrations from those diagnosed with dementia. These narrations were collected annually from 1983 to 1988 from participants aged between 45 and 90 years. They were asked to perform various tasks, such as the picture description test. Audio recordings with/without textual transcriptions, annotated at the utterance level and synchronized with the audio, are available for each case in the dataset. After that, more data will be added to DementiaBank. *Pitt* corpus (Becker et al., 1994) is a widely used subset of DementiaBank. Pitt were gathered longitudinally from 104 elderly controls, 208 with probable and possible AD, and 85 unknown diagnosis participants. Responses to four language tasks were recorded, including one task of Cookie Theft picture description for all participants, and three tasks of verbal fluency, sentence construction and story recall for AD group only. *Lu* corpus from DementiaBank comprises interview recordings of 52 AD patients in Mandarin and 16 AD patients in Taiwanese, by performing tasks such as the Cookie theft picture description, category fluency, and picture naming (MacWhinney et al., 2011). Ivanova et al. (2022) collected recordings from a total of 361 Spanish native speakers aged over 60, including 74 AD patients, 197 HCs and 90 individuals with MCI. They were asked to read the first paragraph of the novel "The Ingenious Gentlemen Don Quixote of La Mancha." The **Wisconsin Longitudinal Study (WLS)** is a long-term research project that aims to understand the life course and the factors influencing individuals' lives. It includes a random sample of 10,317 Wisconsin high school graduates surveyed over nearly 60 years from 1957 to 2011 (Herd et al., 2014). While the WLS does not currently provide dementia-related diagnoses in its metadata, it offers valuable data on demographics, socioeconomic status, health behaviors, and cognitive abilities, making it a relevant resource for AD research.

The Carolinas Conversation Collection (CCC) dataset (Pope and Davis, 2011) is a collection of transcribed speech and video of conversations with people over the age of 65. It consists of over 200 consented conversations with 125 subjects who have one or more of 12 chronic conditions and over 400 conversations with 125 AD patients, recorded at least twice a year. These conversations cover topics related to the participants' daily lives and health issues and are conducted with interviewers.

The Chile dataset (Sanz et al., 2022) was created from 55 native Spanish speakers, including 21 AD patients, 18 Parkinson's disease (PD) patients, and 16 HCs. The participants were asked to perform seven language tasks covering different communicative behaviors, such as describing daily routine and primary interests, recounting a pleasant memory as well as an unpleasant memory, describing a modified picnic scene and a picture depicting a family working in an unsafe kitchen, and immediately recalling and narrating a one-minute silent animated film. Through these tasks, linguistic patterns express diverse and partly predictable. The audio was recorded using laptops in a quiet room, and the transcripts were generated using ASR and then manually revised.

The Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE) (Martin et al., 2000) was collected with the aim of studying the challenges posed by rapidly aging societies in both East and West Germany. It consists of more than 8,000 hours of recorded speech over a long period of 20 years from 1,000+ individuals diagnosed with AD, cognitive decline, mild cognitive disorder, vascular dementia, as well as HCs. Each participant was asked to complete up to four measurements and provide detailed responses to open-ended questions. So far, 380 hours of ILSE were manually transcribed (Weiner et al., 2016a).

ADReSS (The Alzheimer's Dementia Recognition through Spontaneous Speech), derived from the Cookie session of Pitt, is a "balanced and acoustically enhanced" challenge dataset hosted by Interspeech2020 conference (Luz et al., 2020). ADReSS contains the recordings of 78 AD patients and 78 HCs with a matched age and gender. The data from Pitt were enhanced with noise removal, and then segmented using voice activity detection. After volume normalization, over 5000 speech segments were generated.

ADReSSo (The Alzheimer's Dementia Recognition through Spontaneous Speech only) is a dataset used in Interspeech2021 Challenge (Luz et al., 2021). Two tasks were designed to record speech of participants: a semantic fluency task and a Cookie Theft picture description task. The resulting training set contained 166 instances with 87 AD patients and 79 HCs. There were also other 71 instances with 35 AD patients and 36 HCs in the test set. No transcripts are provided with ADreSSo.

NCMMSC's (National Conference on Man-Machine Speech Communication) AD dataset (Competition Group, 2021) is used for NCMMSC2021 AD Recognition Challenge. The recordings were collected from a total of 124 Chinese speakers, containing 26 AD patients, 44 HCs and 54 MCIs. They were required to complete tasks including picture description, fluency test and free conversation with the interviews. The resulting dataset contained 280 samples with the duration of each sample in about 30-60 seconds.

ADReSS-M (Multilingual Alzheimer's Dementia Recognition through Spontaneous Speech) is an ICASSP 2023 Signal Processing Grand Challenge that aims to explore the extraction of universal acoustic features from speech data to facilitate multilingual detection of AD (Luz et al., 2023). The ADReSS-M dataset consists of audio recordings of picture descriptions obtained from 148 AD patients and 143 HCs, in

TABLE 1 This table shows a summary of datasets for AD detection.

Dataset	References	Language	Modality	Source
DementiaBank	Boller and Becker, 2005	English, German, Mandarin, Spanish, Taiwanese	Audio, Video, or Text	310 AD patients, 241 HCs
Pitt	Becker et al., 1994	English	Audio, Text	208 AD patients, 104 HCs, 85 unknown diagnosis
Lu	MacWhinney et al., 2011	Chinese	Audio, Text	52 AD patients in Mandarin and 16 AD in Taiwanese
Ivanova	Ivanova et al., 2022	Spanish	Audio, Text	74 AD patients, 197 HCs, 90 MCI
WLS	Herd et al., 2014	English	Audio	10,317 participants
CCC	Pope and Davis, 2011	English	Audio, Text	125 AD patients, 125 non-AD controls
Chile	Sanz et al., 2022	Spanish	Audio, Text	21 AD patients, 18 Parkinson's disease patients, and 16 HCs
ILSE	Martin et al., 2000	German	Audio, Text (part)	Over 8,000 hours of recorded speech data from more than 1,000 participants over a long period of 20 years. 5.4 % AD patients, 5.4% MCI, 60.8% HCs in the third measurements
ADReSS	Luz et al., 2020	English	Audio, Text	78 AD patients, 78 HCs
ADReSSo	Luz et al., 2021	English	Audio	87 AD patients, 78 HCs
NCMMSC2021	Competition Group, 2021	Mandarin	Audio, Text	26 AD patients, 44 HCs, 54 MCI
ADReSS-M	Luz et al., 2023	English, Greek	Audio	148 AD patients, 143 HCs

Note that the datasets Pitt, Lu, Ivanova and WLS are subsets of DementiaBank. ADReSS and ADReSSo are subsets of Pitt, which have been acoustically enhanced and reorganized.

English and Greek languages. The dataset is divided into three splits: an English training split, a Greek sample split, and a Greek test split. The English training set was collected from 122 AD patients and 115 HCs. Participants were asked to describe the Cookie Theft picture in English during the recording session. On the other hand, the Greek sample split and test split consist of spontaneous speech descriptions of a different picture in the Greek language. The sample split includes recordings from 8 subjects, with 4 AD patients and 4 HCs, while the test split involves data from 46 participants, with 22 AD patients and 24 HCs. It is noteworthy that the ADReSS-M dataset's splits were meticulously balanced for both age and gender.

3.2. Feature extraction

After a dataset is prepared, it is necessary to extract features from spontaneous speech before classification. Feature extraction is expected to separate the relevant features for AD detection from redundant and irrelevant data. After that, feature selection or/and feature fusion is implemented to improve the detection performance by selecting a subset of more discriminative representative features and fusing them. As shown in Figure 1, three types of features can be extracted: acoustic features from audio, linguistic features from the transcripts and other features.

3.2.1. Acoustic features

Acoustic features may change in individuals with AD due to the physiological and cognitive changes associated with the disease. Firstly, AD can impact the coordination and control of the muscles involved in speech production, including the articulatory and vocal folds muscles. This can result in changes in articulation, such as imprecise consonant production, reduced vocal range, and alterations in speech rhythm. These changes can be reflected in features like MFCCs, which capture spectral information, and measures like jitter and shimmer, which assess perturbations in fundamental frequency and amplitude. Secondly, AD is characterized by progressive cognitive decline, including impairments in memory, attention, language, and executive functions. These changes can affect speech production, leading to alterations in acoustic features. For example, individuals with AD may exhibit difficulties in word retrieval, sentence construction, and maintaining coherent speech, which can be reflected in changes in speech rate, pauses, and speech fluency. Then, individuals with AD may experience changes in vocal quality, including hoarseness, breathiness, and reduced vocal intensity. These changes can be detected by jitter, shimmer, and harmonics-to-noise ratio, which provide measures of vocal stability, roughness, and clarity. Additionally, language impairments, such as word-finding difficulties, semantic deficits, and syntactic errors, are commonly associated with AD. These can influence the structure and content of speech, leading to changes in acoustic features related to language, such as pauses, speech rate, and the distribution of acoustic energy across different frequency bands.

Based on the recent papers, acoustic features used in AD detection can be divided into frame-level features, embedding features and paralinguistic features including prosody, disfluency and emotional features.

3.2.1.1. Frame-level features

Frame-level acoustic features are directly derived from audio files. The time and frequency characteristics and statistical functionals are captured, such as MFCCs, F_0 and energy

distribution. Frame-level features can be easily obtained by public audio processing toolkits, such as OpenSMILE (Eyben et al., 2010) and Kaldi (Povey et al., 2011). From these toolkits, different acoustic feature sets can be extracted from the raw audio files as follows.

- Emobase (Schuller et al., 2010). It includes a range of audio features including MFCC, F_0, F_0 envelope, line spectral pairs (LSP) and intensity features, along with their first and second-order derivatives.
- IS10 (Eyben et al., 2013). The set includes MFCC, loudness, F_0 envelope, LSP, voicing probability, jitter local, jitter derived perturbation parameter, and shimmer local features.
- AVEC (Valstar et al., 2013). The AVEC feature set comprises various energy, spectral, and voicing-related features, along with their statistical properties, regression features, and functionals related to local minima and maxima.
- ComParE (Schuller et al., 2013). The ComParE feature set includes a comprehensive collection of acoustic features that capture various aspects of speech and non-speech signals. Some specific features within the ComParE set include "logarithmic harmonic-to-noise ratio, voice quality features, Viterbi smoothing for F_0, spectral harmonicity and psychoacoustic spectral sharpness" (Schuller et al., 2013). Finally, statistical functionals are calculated to summarize the distributional properties of these features.
- eGeMAPS (Eyben et al., 2015). The feature set attempts to reduce the number of other sets to 88 features with theoretical significance, and thus detect physiological changes in voice production. These features encompass MFCC, loudness, spectral flux, jitter, shimmer, F_0, F_1, F_2, F_3, alpha ratio, Hammarberg index, slope V_0, and their statistical functionals.
- Bag-of-Audio-Words (BoAW) (Schmitt and Schuller, 2017). BoAW contains the quantization of acoustic low-level descriptors (LLDs), including MFCC, log-Mel, and the ComParE features.
- Multi-resolution Cochleagram features (MRCGs) (Chen et al., 2014). MRCGs are generated by mimicing the human auditory filters. Firstly, the audio signal is passed through a gammatone filter and then decomposed in the frequency domain using multiple levels of resolution. The low-resolution level encodes spectrotemporal information, while the high-resolution level focuses on capturing local information. By combining these different levels of resolution, a time-frequency representation is obtained to effectively capture the multi-resolution power distribution of the audio signal.

3.2.1.2. Acoustic embeddings features

Embedding features are generated from the embedding layer based on deep neural network.

- VGGish (Hershey et al., 2017). VGGish is an acoustic embedding model which is pretrained using a CNN-based structure on YouTube's Audio dataset. VGGish extracts and transforms the audio into high-level feature vectors.
- Speaker Embeddings. Speaker embeddings aim to extract information related to speaker identity in a compact form. The typical speaker embeddings contains i-vectors (Dehak et al., 2010) and x-vetctors (Snyder et al., 2018). I-vector embeddings are extracted based on a Universal Background Model (UBM) and a Gaussian Mixture Model (GMM) to model the variability of the speaker and channel. X-vectors are a type of speaker representation and extracted using deep neural networks. These embeddings contain information related to gender, emotion, and articulatory, phonatory and prosodic information. Pérez-Toro et al. (2021) extracted x-vectors based on a trained Time delay neural network for AD detection.
- Neural network. Popular deep neural network architectures, such as DNN, CNN, can also generate embedding features by selecting the output of a specific layer. These embeddings capture higher-level representations of the input data learned by the neural network. Cummins et al. (2020) investigated Siamese network combined with contrastive loss functions and end-to-end convolutional neural network (CNN), and found that these systems can capture the features related to different production mechanisms and extract the characteristic of AD speech from all. Pan et al. (2020) proposed Sinc-CLA as a feature extractor for the classification of neurodegenerative disorders, mild cognitive impairment and healthy controls.
- Wav2vec2.0 (Baevski et al., 2020). Wav2vec2.0 is a self-supervised end-to-end ASR system developed by Facebook AI Research. Wav2vec2.0 contains a multi-layer convolutional feature encoder which encodes raw wave into latent representations, a quantization module for masking and a Transformer to get textualized representationsoptimized by minimizing a connectionist temporal classification (CTC) loss. Since Wav2vec2.0 can also capture the speaker and language characteristics in the audio (Fan et al., 2020), the outputs of transformer layers can be extracted as the embedding representations of the input utterances. Pan et al. (2021) used the last hidden state of Wav2vec2.0 as acoustic embedding features.

3.2.1.3. Prosody

Prosody defines patterns of intonation and stress, which is easily affected by cognitive impairments. Prosodic measures focus on temporal aspects, intensity, voice quality, interruptions, voice periods, and variation in F_0, as well as statistical functionals.

3.2.1.4. Disfluency

AD patients often experience difficulties with language and cognitive skills. As the disease progresses, they may exhibit slower speech rate, longer pauses or breaks between words or sentences, and increased difficulty in finding the right words, resulting in disfluencies in their speech. There are different types of disfluency features to show the ability of subjects in organizing language, such as percentage of broken words, repetitions, sound prolongations, self-repairs (Shriberg, 1994) and pauses. Pauses include filled pauses and unfilled pauses. Cmmon filled pauses contain "uh," "um," "oh," "well," laughter, and so on. Yuan et al. (2020) calculated word frequencies and showed that AD patients had potential to use more 'uh', laughter and meaningless words like "well," "oh," but less "um," compared to HCs. Moreover, the durations of unfilled pauses calculated from forced alignment were analyzed and the results showed that AD patients had more and longer pauses. As a result,

the durations can be extracted for distinguishing AD patients as pause features.

3.2.1.5. Emotional embeddings

AD patients often experience a reduced ability to perceive and express emotions due to their memory loss (Henry et al., 2009), and thus emotional features can be extracted to capture relevant information about the emotional state of AD patients. A continuous emotion state can be expressed by a three-dimensional vector with valence, arousal, and dominance. Pérez-Toro et al. (2021) trained three models to respectively obtain three factors by combining CNN and GRU, and extracted the output of the embedding layer as emotional features.

3.2.2. Linguistic features

Linguistic features undergo changes in individuals with AD due to the progressive nature of the condition, which affects various cognitive and language-related processes. AD is characterized by language impairments, and as the disease advances, individuals may encounter difficulties in word retrieval, comprehension of complex grammatical structures, construction of grammatically correct sentences, and maintenance of coherent discourse. These language impairments are evident in alterations in vocabulary usage, sentence structure, and overall linguistic fluency. Word-finding challenges may lead to frequent pauses and the substitution of words with similar-sounding alternatives, consequently impacting the flow and coherence of speech. Furthermore, AD can result in decreased verbal expression abilities, including reduced output, shorter and less complex sentences, and a decrease in the overall quantity of speech. As a result, the range of vocabulary becomes limited, and the utilization of syntactic structures may diminish. Additionally, AD can affect the organization and coherence of discourse, leading to unrelated responses, difficulties in maintaining topic coherence, and challenges in adhering to conversational conventions. Pragmatic impairments may also arise, encompassing difficulties in appropriate language usage within social contexts. These challenges can involve struggles with turn-taking, adherence to conversational norms, and comprehension of non-literal language, such as sarcasm or metaphors.

Linguistic features used in AD detection encompass various aspects such as syntax, semantics, word embeddings, sentence embeddings, and more. These features can also be categorized as traditional handcrafted features and deep embeddings.

3.2.2.1. Traditional features

Traditional handcrafted features derived from theories of Linguistics, which include features related to syntactic, semantic, and lexical diversity. Specifically, it includes the following features.

- Parts-of-speech (POS). The production of different POS reflects language changes, including a decrease in the number of nouns, and an increase in the number of pronouns, adjectives and verbs (Bucks et al., 2000). POS and related statistical features comprise the frequency of different POS occurrences, dependency tags in the subject's transcript, ratios of nouns to verbs, pronouns to nouns, and more.
- Syntactic complexity. The syntactic complexity of the picture descriptions can be assessed through various measures, including the mean length of utterances, T-units (Hunt, 1970), clauses, the height of the parse tree and the statistics of Yngve depth (Yngve, 1960).
- Grammatical constituents. A set of context-free grammar features derived from the parse tree analysis has shown the potential to differentiate between individuals with agrammatic aphasia and HCs during a story-telling task (Fraser et al., 2014). These features includes the frequency of different grammatical constituents, as well as the rate, proportion and average length of different phrases (e.g., noun phrases, verb phrases and prepositional phrases).
- Vocabulary richness or lexical diversity. It can be measured by unique word count, type-token ratio (TTR), moving-average type-token ratio, Brunét's index and Honoré's statistic (Fraser et al., 2016a). TTR denotes the ratio of the total number of unique words to the overall text length, which is sensitive to text length, while the other three measures provide an unbiased metric of lexical richness without being influenced by text length.
- Repetitive and diverse features. AD disorder impacts memory, resulting in AD patients potentially using a more repetitive and less diverse vocabulary compared to HCs (Nicholas et al., 1985; Syed et al., 2021). To quantify it, some features are extracted such as TTR, the number of repetitive words, and the number of sweepback caused by self-corrections. A bag-of-words measures the cosine distance between each pair of utterances, with a result of zero to indicate the two identical utterances.
- TF-IDF (Ramos et al., 2003). TF-IDF is used to determining a word's relative importance in a specific document compared to its overall frequency across the entire document corpus. Common words in a single document tend to achieve a higher score than those like articles and prepositions. Given the documents $\mathbf{D} = \{d_1, d_2, d_3, ...\}$, where d_i denote a document in the corpus, the TF-IDF of a word w in a document d_i can be calculated by Salton and Buckley (1988)

$$T_w^{d_i} = c_w^{d_i} \log \frac{|\mathbf{D}|}{c_w^{\mathbf{D}}}, \tag{8}$$

where $c_w^{d_i}$ denotes the number of times the word w appears in the document d_i. $|\mathbf{D}|$ represents the total number of documents in the corpus. $c_w^{\mathbf{D}}$ denotes the number of documents in which the word w appears.

3.2.2.2. Deep embeddings

- Word2Vec. Word2Vec represents a class of neural network models, such as skip-gram and the continuous bag-of-words (CBOW). Word2Vec can encode semantic information from unlabeled data by producing embedding vectors. These vectors can be used for the semantic similarity and many other NLP tasks. The procedure for CBOW as an example is to train a NN using neighbor words to predict a target word. Specifically, text segment is first represented using the average of normalized word embeddings such as one-hot encodings, and the results are fed to a RF classifier (Bojanowski et al.,

2017). Word vectors are obtained from the activations of a hidden layer.

- BERT-based embeddings.

  BERT is a powerful unsupervised and deep pretrained model (Kenton and Toutanova, 2019). By utilizing the encoder part of the Transformer architecture, BERT transforms words/sentences in a corpus into embedding feature vectors, which can be further used for classification. BERT has spawned various variants. One widely used variant called RoBERTa (Robustly Optimized BERT approach) (Liu et al., 2019) has been developed and gained significant attention. RoBERTa benefits from the larger training corpus and optimized training procedure to learn more robust representations and exhibit improved performance across multiple tasks. Wang et al. (2022b) used fine-tuned text embedding networks, such as BERT and Roberta, to extract linguistic information, and then used majority voting to fuse the decisions.

3.2.2.3. Readability features

Considering that AD patients show difficulties in understanding the meaning of complex words and syntax (Croisile et al., 1996), readability features are extracted for AD detection to capture the complexity of language, such as gunning fog index (GFI) (Gunning, 1969), automated readability index (ARI) (Smith and Senter, 1967), the simple measure of Gobbledygook (SMOG) grading (Mc Laughlin, 1969) and the ratio of unique words. GFI and ARI are designed to evaluate the number of years of formal education required for a person to comprehend a text on the first reading, which are calculated as Martinc and Pollak (2020)

$$GFI = \frac{0.4(N_w + 100N_{lw})}{N_s}, \tag{9}$$

$$ARI = \frac{4.71N_c}{N_w} + \frac{0.5N_w}{N_s} - 21.43, \tag{10}$$

where N_c, N_w and N_s denote the number of characters, words and sentences, respectively. N_{lw} is the number of long words longer than 7 characters. SMOG grading is used to assess the reading level and comprehension difficulty of health messages, expressed as

$$SMOG = 3.1291 + 1.0430\sqrt{30N_{syl}/N_s}, \tag{11}$$

where N_{syl} is the number of polysyllabic words in samples of 30 sentences.

3.2.2.4. Acoustic and linguistic feature fusion

Besides separate acoustic and linguistic features, there are techniques providing a way of fusing acoustic and linguistic features. For example, Haider et al. (2019) developed an active data representation (ADR) to fuse bi-modal features at a word and sentence level, which can model temporal aspects of text and speech. The ADR features include cluster counts, cross-modality word embeddings, pause, centroid embeddings, embedding velocity and centroid velocity, duration (Haider et al., 2019; Martinc et al., 2021). Martinc et al. (2021) combined ADR with TF-IDF weighted bag-of-n-grams to model semantics better.

3.2.2.5. Other features

Other features encompass various aspects relevant to AD detection, such as age and gender obtained from a demographic questionnaire or natural conversations during the recording process, and interactional features from dialogues.

3.2.2.6. Meta features

Meta-features, such as age, gender, education, genetic factors and so on, are demographic or clinical characteristics of individuals that are not directly related to the disease but can have a significant impact on its development, progression, and presentation. The relationship between AD and meta-features has been a subject of significant research interest in the field of neurodegenerative diseases. For example, aging is associated with various changes in the brain, including the accumulation of amyloid plaques and neurofibrillary tangles, which are hallmark features of AD pathology. Andersen et al. (1999) has shown that gender may play a role in AD susceptibility. Women tend to have a higher risk of developing AD compared to men. Education level has been associated with cognitive reserve, which refers to the brain's ability to adapt and function despite damage. Higher education levels have been linked to greater cognitive reserve, potentially delaying the onset of cognitive decline and AD symptoms.

3.2.2.7. Interactional features

During dialogue conversations, temporal and interactional aspects are distinctive between AD patients and the interviewers. For example, the subjects with AD are older people with longer lapse and lower speech rates compared to the interviewers within the conversation. Thus, an interactional feature set can be extracted to quantify the interactions between patients and interviewers for AD detection. Nasreen et al. (2021b) exploited 32 features to describe the interaction within the natural conversations, including speech rate (measured in syllables per minute), turn length (measured in words per turn), floor control ratio (indicating the proportion of speech time by AD patients relative to the total conversation duration), normalized total duration of short and long pauses (the total duration of pauses normalized by the total duration without pauses), and so on.

Based on the available studies, it is evident that a wide range of features have been extracted with the primary aim of obtaining more discriminative features for effective AD detection. Furthermore, there is a noticeable trend in the studies toward transitioning from handcrafted features to utilizing deep embedding representations. This transition highlights the growing interest in leveraging advanced techniques to capture higher-level representations for AD detection.

4. Methods

After learning features from bi-modal speech and text data, they are used to build a classification model for recognizing AD patients. There are two typical types of algorithms for this end: statistical machine learning methods and deep learning methods.

4.1. Statistical machine learning

4.1.1. Support vector machine (SVM)

SVM (Cortes and Vapnik, 1995) is a popular type of supervised learning algorithm used for classification and regression tasks. SVM aims to find a hyperplane that separates the data points into different classes by maximizing the margin between the classes, i.e., the distance between the closest data points from each class to the hyperplane. The data points that are closest to the hyperplane are called support vectors, and used to define the hyperplane. Moreover, SVM can map the input data points into a higher-dimensional space using a kernel function, and then different classes may be more easily recognized. Zargarbashi and Babaali (2019) extracted acoustic representations of I-vectors and D-vectors for speech and N-gram representations for transcription text, and used SVM on these features to recognize AD, achieving a classification accuracy of 83.6% using the Pitts Corpus. Wang et al. (2022b) selected classifiers from five classification models: SVM, LDA, Gaussian process (GP), multilayer perceptron (MLP), and extreme gradient boost (XGB). The experimental results showed that SVM classifier combined with BERT and Roberta features achieved best performance among all.

4.1.2. Logistic regression

Logistic regression (LaValley, 2008) is used to analyze and model binary or categorical outcomes. The model first uses the logistic function to compute the probability of the binary outcome, and then utilizes the predictors to estimate the coefficients of the logistic function, which determines the relationship between the predictors and the probability of the binary outcome. Liu et al. (2020) used a logistic regression model trained on spectrogram features extracted from speech data for recognizing AD. Shah et al. (2021) tested the performance of SVM, LR and majority vote classifiers when using acoustic features only, linguistic features only and the combined features, and showed that an ensemble of acoustic-based and language-based models yielded the best performance.

4.1.3. Linear discriminant analysis (LDA)

LDA (Balakrishnama and Ganapathiraju, 1998) aims to find a linear combination of features that maximizes the separation between different classes while minimizing the variance within each class. The core concept of LDA is to project the original high-dimensional data onto a lower-dimensional subspace that retains the most discriminatory information. This subspace is defined by the eigenvectors of the between-class scatter matrix and is referred to as the discriminant subspace. Weiner et al. (2016b) developed a LDA model for classification and achieved a classification accuracy of 85.7%.

4.1.4. k-Nearest neighbors (KNN)

KNN (Fix, 1985) identifies the k-nearest neighbors to a given data point based on a distance metric, and then uses the majority vote of these neighbors to classify the data point or estimate the value of the target variable. One of the advantages of KNN is its simplicity and interpretability, as the decision boundary is determined by the data itself. However, KNN can be computationally expensive for large datasets and may suffer from the curse of dimensionality.

4.1.5. Decision tree (DT)

A decision tree is a tree-like model that consists of a series of decisions and their possible consequences (Quinlan, 1986). Each internal node of the tree represents a decision based on the value of a feature, and each leaf node represents a class or a value of the target variable. DT is popular due to its interpretability, flexibility, and ease of implementation. Mirzaei et al. (2018) used three classification models: KNN, SVM and DT to classify AD, MCI and HCs.

4.1.6. Random forest (RF)

RF (Breiman, 2001) is an ensemble learning method that combines multiple decision trees to improve the accuracy and robustness of the model. Each tree in the forest is trained on a subset of the data, and the final prediction is made by taking the majority vote of all the trees. RF is known for its high accuracy, scalability, and resistance to overfitting. Hernández-Domínguez et al. (2018) trained SVM and RF to distinguish between HCs and MCI, and the results provide insights into the effectiveness of SVM and RF classifiers in the early diagnosis of MCI. In Edwards et al. (2020), the effectiveness of multiscale (word and phoneme level) features was explored using five different classification models: LDA, KNN, DT, RF and SVM, achieving a maximum classification accuracy of 79.2%.

4.2. Deep learning

4.2.1. Convolutional neural network (CNN)

CNN (LeCun et al., 1998) is composed of multiple convolutional layers that learn a hierarchy of features from the input data, followed by one or more fully connected layers that perform the classification task. CNN is known for its ability to automatically learn spatial and temporal features from the data, and has been widely studied and applied in various fields, such as self-driving cars, medical image analysis, and robotics. Warnita et al. (2018) utilized a gated CNN and achieved an accuracy of 73.6% for AD detection on the Pitt corpus.

4.2.2. Recurrent neural network (RNN)

RNN (Werbos, 1988) is composed of a network of recurrently connected nodes that allow to maintain a state or memory of previous inputs. RNN can handle variable-length input sequences and commonly used for sequence modeling tasks. However, RNN suffers from gradients exploding or vanishing during training. To overcome this issue, long short-term memory (LSTM) is designed to use a memory cell and several gating mechanisms to selectively retain or forget information from previous inputs, which allows the network to preserve a long-term memory of past inputs. Koo et al. (2020) used an improved convolutional RNN to identify AD.

Pan et al. (2019) exploited a bidirectional hierarchical RNN with an attention layer for AD detection. Ablimit et al. (2022) used CNN-GRU-Attention and FCNN to process features and make model fusion. Yang et al. (2022) constructed AD detection model using two LSTM layers after the convolutional layers.

4.2.3. Transformer models and variations

The Transformer (Vaswani et al., 2017) is a groundbreaking deep learning model architecture that introduced the attention mechanism and revolutionized the processing of sequential data. Unlike RNNs that rely on sequential processing, the Transformer enables parallelization and more efficient training. The Transformer model consists of two key components: the encoder which processes the input sequence and extracts its contextual information, and the decoder which generates the output sequence. The key innovation of the Transformer lies in its attention mechanism, which allows the model to focus on different parts of the input sequence while processing each word or token. It helps the model capture long-range dependencies and contextual information effectively.

BERT is based on the Transformer architecture developed by Google (Kenton and Toutanova, 2019). BERT is pretrained on large amounts of unlabeled text data to predict missing words in a sentence by considering the context of both the left and right surrounding words. This bidirectional approach enables BERT to capture deeper contextual relationships and produce more meaningful representations of words. After pretraining, BERT can be fine-tuned on specific NLP tasks by adding task-specific layers, and the entire model is fine-tuned on labeled task-specific data. Fine-tuning allows BERT to adapt its representations to the specific requirements of the target task. BERT has been used for AD detection by fine-tuning it on a dataset of speech samples from individuals with and without AD (Balagopalan et al., 2021). ERNIE (Enhanced Representation through Knowledge Integration) is a language representation model based on the Transformer architecture (Zhang et al., 2019). ERNIE is designed to capture rich semantic representations of text by incorporating techniques such as knowledge masking, sentence-level discourse representation, and knowledge graph.

4.3. Optimization and performance

Based on the above classical learning methods, more research is focusing on finding optimization techniques to improve the performance of automatic AD detection. To achieve this goal, the studies have focused on two main aspects: extracting more distinguishing features, and building more powerful classification models to detect AD.

Table 2 summarized performance comparison of AD detection on different datasets when using different optimization methods, in terms of the average accuracy $A(\%)$, precision $P(\%)$, recall $R(\%)$ and $F_1(\%)$. Only the most notable studies chosen to show in Table 2, to provide a comprehensive understanding of the current state-of-the-art in AD detection. When diving into how to achieve better results, the typical optimization methods can be categorized as follows in detail.

4.3.1. Extraction of discriminative features

Features play a crucial role in determining the performance of a classifier. Numerous studies have made efforts to extract features by analyzing the impact of Alzheimer's disease (AD) on patients, focusing on characteristics that distinguish them from individuals without AD, include longer pauses, increased disfluency, slower response during dialogues, and more. These discriminative features include pauses (Yuan et al., 2020; Rohanian et al., 2021; Zhu et al., 2021), disfluency (Sarawgi et al., 2020; Qiao et al., 2021; Rohanian et al., 2021), interactional features (Nasreen et al., 2021a), cognition features (Sarawgi et al., 2020), ADR features (Martinc et al., 2021). By identifying and incorporating such specific features into the classification process, researchers aim to enhance the accuracy and effectiveness of AD detection methods. For instance, Nasreen et al. (2021a) obtained promising results using interactional features alone with an accuracy of 87%. Yuan et al. (2020) encoded pauses into three bins: long (over 2 s), medium (0.5-2 second) and short (under 0.5 second), and reported 89.58% accuracy when combining with ERNIE. Rohanian et al. (2021) extracted features (disflency, pauses, and language model probabilities) and achieved an accuracy of 84% with a classifier of LSTM with gating. Zhu et al. (2021) introduced non-semantic information, i.e., sentence-level pauses based on wav2vec, and BERT classifier achieved an accuracy of 83.1%. Pan et al. (2021) adopted ASR for feature extraction and BERT for classification, and finally achieved 74.65% and 84.51% accuracy for the acoustic-only and best linguistic-only features, respectively. Paralinguistic features, such as duration, pauses, and others, have been shown to be effective for multilingual AD detection. Shah et al. (2023) extracted paralinguistic features, including word-level duration, pause rate, as well as meta-features and confidence scores of each word from the ASR model, for cross-lingual AD detection. Chen et al. (2023) utilized paralinguistic features for cross-lingual AD detection and achieved excellent results when compared to pre-trained features. Therefore, incorporating more discriminative features has the potential to increase the accuracy of AD detection.

4.3.2. Model fusion

Model fusion can further improve the classification performance by combining data from multiple models. Two types of fusion methods are usually used, feature fusion and decision fusion. Feature fusion refers to the process of combining features from different sources or modalities at the input stage of a model. For feature fusion, different features can be concatenated, weighted, or combined in other ways to form a more comprehensive or informative representation of features. On the other hand, decision fusion combines the outputs or decisions of multiple models at or near the output stage using various techniques such as voting, averaging, or weighted aggregation. By decision fusion, the system can benefit from the complementary strengths of different models and improve the accuracy of the final decision. Wang et al. (2022b) designed a best performing system using BERT and RoBERTa feature decision voting with a SVM

TABLE 2 This table shows a performance comparison of AD detection on different datasets in terms of the average accuracy $A(\%)$, precision $P(\%)$, recall $R(\%)$ and $F_1(\%)$ defined in Equation 4.

Dataset	References	Modality	Feature	Classifier	A	P	R	F_1	Optimization
Pitt	Wang et al., 2022a	Text (ASR)	BERT, RoBERTa	SVM	91.7	88.5	95.8	92.0	ASR improvement, Model fusion
	Sarawgi et al., 2020	Speech, Text	Disfluency, ComParE, Interventions	MLP	88.0	92.0	82.0	88.0	Prosody features, Model fusion
	Ye et al., 2021	Text (ASR)	BERT	SVM	88.0	82.0	96.0	88.0	ASR improvement
ADReSS	Wang et al., 2022b	Text (ASR)	BERT, RoBERTa	SVM	93.8	92.0	95.8	93.9	Model fusion
	Martinc et al., 2021	Speech, Text	ADR, Bag-of-n-gram	k-means clustering, RF	93.8	-	-	-	ADR features, Model fusion
	Wang et al., 2022b	Text (Manual)	BERT, RoBERTa	SVM	91.7	91.7	91.7	91.7	Model fusion
	Martinc et al., 2021	Text	Bag-of-n-gram	k-means clustering, RF	89.6	-	-	-	-
	Yuan et al., 2020	Text	Pauses	ERNIE	89.6	90.2	89.5	89.6	Task-specific features
	Syed et al., 2020	Text	BERT, RoBERTa, DistilBERT	SVM, LR	85.4	-	-	-	Model fusion
	Sarawgi et al., 2020	Speech, Text	Disfluency, ComParE, Interventions	MLP	83.0	83.0	83.0	83.0	More features, Model fusion
ADReSSo	Pan et al., 2021	Text (ASR)	ASR hypotheses, Confidence score	BERT	84.5	84.7	84.6	84.5	ASR features
	Syed et al., 2021	Text (ASR)	BERT	LR	84.5	-	-	84.5	Model fusion
	Rohanian et al., 2021	Speech, Text (ASR)	Acoustic, GloVe, Disfluency, Pause	LSTM with gating	84.0	-	-	-	Prosody features
	Zhu et al., 2021	Speech, Text (ASR)	Wav2vec, Pause	BERT	83.1	83.6	83.0	83.0	Pause features
	Qiao et al., 2021	Text (ASR)	Complexity, Disfluency	LR, ERNIE, BERT	83.1	83.5	83.0	83.0	Model fusion
	Wang et al., 2021	Speech, Text (ASR)	X-vector, Linguistic	CNN + attention	80.3	81.9	80.1	81.0	Model fusion
	Pan et al., 2021	Speech	Wav2vec	RF	74.7	75.0	74.6	74.5	-
CCC	Nasreen et al., 2021a	Speech	Acoustic, Interactional	SVM, LR	90.0	90.5	90.0	89.5	Interactional features
ADReSS-M	Jin et al., 2023	Speech	Acoustic, Disfluency	Swin transformer, RF	86.7	-	-	-	Model fusion
	Tamm et al., 2023	Speech	eGeMAPS	attention pooling+MLP	82.6	88.9	-	80.0	Fine tuning
	Mei et al., 2023	Speech	Low-pass filtered speech	Wav2vec2	73.9	-	-	-	Fine tuning
	Shah et al., 2023	Speech, Text (ASR)	Duration, Pause, Confidence score, Meta	LR	69.6	-	-	-	Feature combination
	Chen et al., 2023	Speech	IS10	SVM	69.6	69.2	75.0	72.0	Paralinguistic features

classifier, regardless of which ASR systems being used, achieving F_1 scores of 93.9% and 91.7%, respectively. Syed et al. (2020) fused the top-10 performing embedding models based on transcripts and achieved an accuracy of 85.4%. Syed et al. (2021) proposed a label fusion system based on deep textual embeddings and LR classifier. By fusing high specificity and high sensitivity models, the paper achieved an accuracy of 84.51%. Qiao et al. (2021) employed model stacking to combine two LRs using complexity and disfluency features respectively, and two models, i.e. BERT and ERNIE, resulting 83.1% accuracy. Wang et al. (2021) fused three CNN-attention networks based on linguistic features and x-vectors using an attention layer followed by a softmax layer, and achieved a good performance. Jin et al. (2023) proposed a complementary and simultaneous ensemble (CONSEN) algorithm to combine the results of prediction and regression tasks, and yielded state-of-the-art performance on the ADReSS-M dataset.

4.3.3. Transfer learning

When it comes to multilingual or low-resource AD detection, transfer learning proves to be a powerful approach for efficiently leveraging patterns from similar tasks and achieving remarkable

performance. Recent studies such as Mei et al. (2023), Tamm et al. (2023) have demonstrated the effectiveness of this approach by utilizing pre-training on English datasets and fine-tuning on Greek datasets, resulting in impressive performance for cross-lingual AD detection. This utilization of transfer learning shows its potential in addressing the challenges posed by multilingual and low-resource scenarios in AD detection research.

4.3.4. ASR improvement

Some research tried to improve ASR performance or extract ASR-related features (Pan et al., 2021) for better performance. Ye et al. (2021) exploited a range of techniques to improve ASR performance for older adults to achieve an accuracy of 88%. It is noticed that when using the ground truth transcripts rather than ASR outputs, a comparable or worse performance was obtained with a F_1 score of 87%. Wang et al. (2022a) employed ASR optimization using neural architecture search, cross-domain adaptation and fine-grained elderly speaker adaptation and multi-pass rescoring based system combination with hybrid TDNN.

4.3.5. Combined optimization methods

Many studies have improved the system performance by exploiting more than one kind of optimization methods. For example, Sarawgi et al. (2020) extracted three diverse features and used model fusion strategies, resulting in an accuracy of 88% on Pitt dataset and 83.3% on the ADReSS dataset. Wang et al. (2022a) employed ASR optimization and model fusion strategies based on BERT and RoBERTa features. As a result, the paper achieved state-of-the-art performance with a F_1 score of 92% on the Pitt dataset. Martinc et al. (2021) accounted for temporal aspects of both linguistic and acoustic features by combining ADR with bag-of-n-gram features, and used late fusion via majority vote of 5 classifiers, including Xgboost, RF, SVM, LR and LDA. As a result, the system obtained an appreciable performance with an accuracy of 93.8%.

From Table 2, it is seen that linguistic features extracted from text modality consistently outperform acoustic features extracted from speech. For instance, in the work by Pan et al. (2021), the accuracy of acoustic-only and linguistic-only approaches was reported as 74.65% and 84.51% respectively. Rohanian et al. (2021) revealed that utilizing text modality alone yielded better results than using audio modality, with an accuracy of 74% and 68%, respectively. Then, incorporating diverse features from multiple modalities generally leads to improved performance. For instance, Martinc et al. (2021) demonstrated that the best performance was achieved by combining speech and text modalities, even when text-only features were available. Rohanian et al. (2021) indicated that a multimodal LSTM model with gating outperformed single modality models (0.79 vs. 0.74). Wang et al. (2021) utilized both audio and linguistic features to yield a best performance for AD detection.

Moreover, it is evident that optimization strategies play a crucial role in determining the performance of the studies. Among the various methods employed, model fusion has emerged as an effective approach to achieve better performance in the majority of cases. This demonstrates the significance of optimization strategies and highlights the potential benefits of integrating multiple models for enhanced accuracy and reliability in AD detection studies.

Recently, end-to-end models can directly build a mapping from data to the result label and have achieved promising performance in other fields such as speech processing (Watanabe et al., 2018; He et al., 2019; Yasuda et al., 2021), NLP (Libovický and Helcl, 2018; Xie et al., 2022), CV (Feng et al., 2019; Coquenet et al., 2022). They are also exploited to detect AD recently, such as fine-tuned BERT (Balagopalan et al., 2020), degraded version of generative Transformer (GPT-D) (Li et al., 2022a). However, limited by the size of the publicly available data, the performance of large models does not show significant improvement compared to the utilization of a feature extraction and classification pipeline, with accuracy of 85% lower than the state-of-the-art accuracy of 93.8% (Wang et al., 2022b) on the ADReSS dataset.

5. Discussion

ML or DL-based classification models have achieved promising results for the automatic detection of AD. However, there are still some challenges that need to be addressed.

5.1. Few-shot and diverse data

There are very few public datasets available until now, with only a limited number of participants, mainly due to the challenges of recording large quantities of audio from AD patients and obtaining expert annotations. Considering the complexity of AD detection, large-scale datasets are necessary for more effective, scalable and powerful models. Moreover, the datasets show a large diversity of accents, languages, neuropsychological tests, background noise and device channels, and thus the best model on one dataset may not have a stable performance on another dataset. Some technologies, such as transfer learning, self-supervised learning or unsupervised learning, data augmentation, provide the potential to address this issue. For example, a recent study by Chen et al. (2023) demonstrated the extraction of paralinguistic features and the feature transfer across English and Greek languages for multilingual AD detection, showing promising results. Additionally, combining an ASR system with speech augmentation and speech enhancement techniques enhances robustness to noise. Beyond the latest studies, more research is required for this challenge.

5.2. Model explainability

Although many classification models for AD detection are still based on statistical machine learning algorithm, as shown in Table 2, it can be expected that DL-based methods will be exploited by more studies as the size of the dataset increases in the future because of powerful ability of information representation. However, many of the DL-based models appear as a black box. Thus, it is hard to analyze learned representations and give AD patients any meaningful interpretation, which is often undesirable in medical domain. Some work introduced interpretable NNs to provide interpretation information. For example, Pan et al.

(2020) designed SincNet by defining the filters as a collection of parameterized Sinc functions. By analyzing the output of SincNet, a better interpretation of the frequency-related information is gained for cognitive decline assessment. Laguarta and Subirana (2021) introduced the biomarker saliency map to track and visualize progression of AD for the model explainability. However, the explanation provided may not meet the expectations of patients, as they often require a more comprehensive and easily understandable explanation. Additionally, clinicians, who require a deeper and more specialized understanding, also have distinct needs for explanation. Catering to these different requirements for explanation introduces complexity into the model's design and implementation. Recently, there are also many work for interpretable DL used in various fields (Liao et al., 2019; Preuer et al., 2019; Li et al., 2022b), such as drug discovery, glaucoma diagnosis, surveillance of COVID-19, and so on, which can be also used for AD-related tasks to make the model results meaningful.

5.3. Model reliability for short recordings

The detection of AD theoretically requires long-term monitoring. However, for most researchers only public datasets are available, and their durations lasting between seconds and minutes. Therefore, the question arises whether such short recordings can provide reliable AD detection results. There is work, such as Laguarta and Subirana (2021), to provide long-term analysis by adding more biomarkers with longitudinal recordings, such as cough. However, the lack of available longitudinal data prevents more researchers from studying this topic.

5.4. More modality fusion

This paper reviews automatic detection methods of AD from spontaneous speech, which contains two modalities: audio and text. The use of these two modalities is basically only to extract features separately and then cascade or build separate classification models and fuse them, without aligning the information between modalities. These fusion methods cannot well handle the relationship and interdependence between modalities. Besides, other efficient modalities are also used for AD detection, such as video (MacWhinney et al., 2011), MRI (Chyzhyk et al., 2012; Altinkaya et al., 2020; Noor et al., 2020) and functional MRI images (Wagner, 2000; Ibrahim et al., 2021), video games (Castiblanco et al., 2022), biomakers (Laguarta and Subirana, 2021) and so on. Sheng et al. (2022) fused information from speech and eye-tracking, and achieved a better performance. Pan et al. (2021) designed five models based on BERT, with acoustic features only as model input and combined linguistic features and acoustic features as model input. The detection results showed that the the performance of bimodal-based models outperforms speech only. Future research can use information from more modalities to learn the relationship and interdependence through joint multimodal learning methods.

5.5. Distinguishing diseases with similar symptoms

AD is characterized by a range of cognitive and behavioral symptoms, including memory impairment, cognitive decline, emotional and behavioral changes, agitation, aggression, and impairment in daily living activities. These symptoms share similarities with several other medical conditions, which can lead to confusion during early AD diagnosis. For instance, MCI is an early stage of cognitive decline that can be associated with AD but can also occur independently or as a precursor to other types of dementia. Depressive symptoms are also common in AD but can manifest in various other medical conditions as well. Lewy Body Dementia (LBD) is a degenerative brain disorder similar to AD, characterized by the presence of Lewy bodies in brain cells. LBD patients may exhibit AD-like memory problems along with visual hallucinations and motor issues. Thus, Careful differentiation of these similar symptoms is crucial during the early stages of AD diagnosis to establish an accurate assessment. Research by Fraser et al. (2016b) demonstrated the efficiency of MFCC features and SVM classifier in detecting dementia from depression. Pérez-Toro et al. (2023) utilized modified ForestNets to discriminate between AD and depression in AD patients. However, their study did not provide a definitive conclusion regarding the primary distinguishing speech-based symptoms for classifying dementia from other conditions with similar symptoms.

6. Conclusions

The paper focuses on the development of automatic AD detection from spontaneous speech, leveraging theoretical basis of the language dysfunction of patients. Compared to other modalities such as MRI, speech-based methods offer non-invasive, convenient and scalable solutions. In this paper, we describe three key components for AD detection in detail, including data collection, feature extraction, and classification models. We also summarize optimization methods and the state-of-the-art performance on several public datasets, with a focus on the last three years. However, AD detection systems face many challenges, and future research can be directed toward improving reliability and accuracy, including increasing dataset sizes or exploring few-shot learning methods, designing interpretable neural networks, establishing long-term monitoring mechanisms (e.g., using wearable devices for real-time monitoring of elderly activities), incorporating multiple modalities and adopting multimodal fusion methods.

The inclusion of cognitive assessments, such as MMSE scores, in longitudinal studies will further advance our understanding of disease progression and its correlation with speech patterns. Future research should consider conducting specialized reviews on AD progression, providing deeper insights into advancements and complementing our current understanding. These efforts will contribute to the development of effective diagnostic tools and treatment strategies for AD.

Author contributions

Conceptualization: XQ and WB. Methodology, writing—original draft preparation, and project administration: XQ. Investigation: QZ. Writing—review and editing: QZ and JD. Visualization: JD. Supervision: WB. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the Scientific Research Innovation Project of China University of Political Science and Law (10821424), the Open Projects Program of State Key Laboratory of Multimodal Artificial Intelligence Systems, the National Natural Science Foundation of China (NSFC) (61603390), and the Fundamental Research Funds for the Central Universities.

Conflict of interest

QZ is employed by AI Speech Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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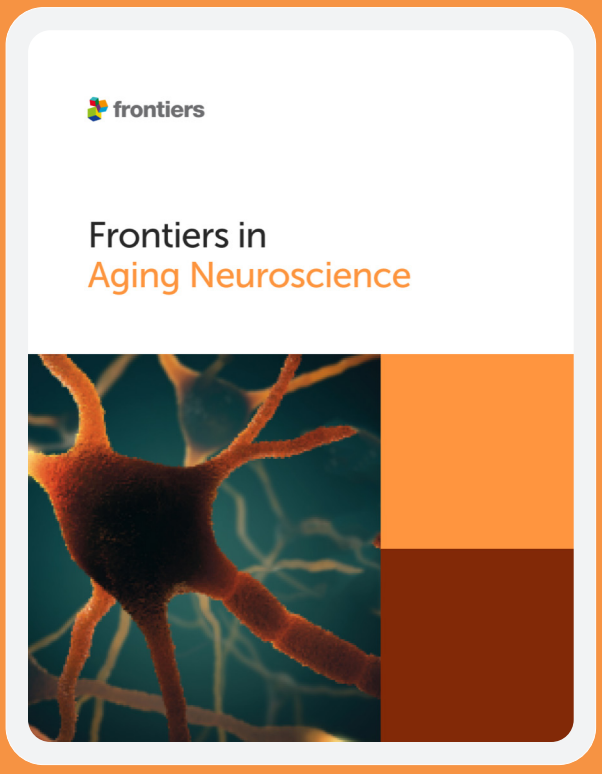

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