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REVIEW

Application of Photostimulation Therapy in Cognitive Function of Alzheimer's Disease Patients: A Scoping Review

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Background: Alzheimer's disease patients often experience cognitive decline during disease progression, impacting their quality of life. Photostimulation therapy, as a non-invasive neuromodulation method, has been increasingly used in the adjunctive management of Alzheimer's patients in recent years. Despite the increasing number of related studies, a systematic review and comprehensive evaluation are still lacking.

Objective: This review systematically summarizes the current application of photostimulation therapy in Alzheimer's disease patients, outlines its implementation characteristics, outcome indicators, intervention effects and mechanisms of action in cognitive function intervention, and identifies evidence gaps in current research.

Methods: Relevant studies were systematically retrieved from PubMed, Web of Science, Cochrane Library, Embase, CINAHL, CNKI, CBM, WanFang Database, and VIP Database from their inception to January 5, 2026. Data from the included literature were extracted and analyzed.

Results: A total of 21 studies were included. Photostimulation therapy primarily includes light stimulation, 40 Hz rhythm-related light stimulation, photobiological modulation and their combined therapies, as well as transcatheter intracranial laser therapy. This therapy has potential value in improving cognitive function or delaying cognitive decline and may affect sleep/rhythm and behavioral symptoms. Its potential mechanisms involve neural oscillation modulation, circadian rhythm reconstruction, and improvement of synaptic plasticity. However, existing evidence exhibits significant heterogeneity in study design, sample size, intervention parameters, and outcome indicators.

Conclusion: Photostimulation therapy has shown promising potential in cognitive function intervention for Alzheimer's disease patients, but current evidence is still largely in the exploratory stage. Future research should focus on multi-center, large-sample, and standardized studies to determine the optimal parameter combinations for different stages and scenarios, and to optimize individualized intervention protocols to improve clinical efficacy.

Plain Language Summary: Investigates the effectiveness and limitations of photostimulation therapy in improving cognitive function in Alzheimer's disease patients and summarizes its mechanisms of action. The results show that photostimulation therapy shows promising potential in improving cognitive function in Alzheimer's patients, and its mechanism of action involves multiple aspects. However, existing evidence exhibits heterogeneity in terms of study design and sample size, necessitating future multi-center, large-sample, and standardized studies.

Keywords: photostimulation therapy, alzheimer's disease, cognitive function, mechanism of action, scoping review

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive decline, accounting for approximately 60–70% of all dementia cases. Clinically, it is often accompanied by a series of symptoms such as memory

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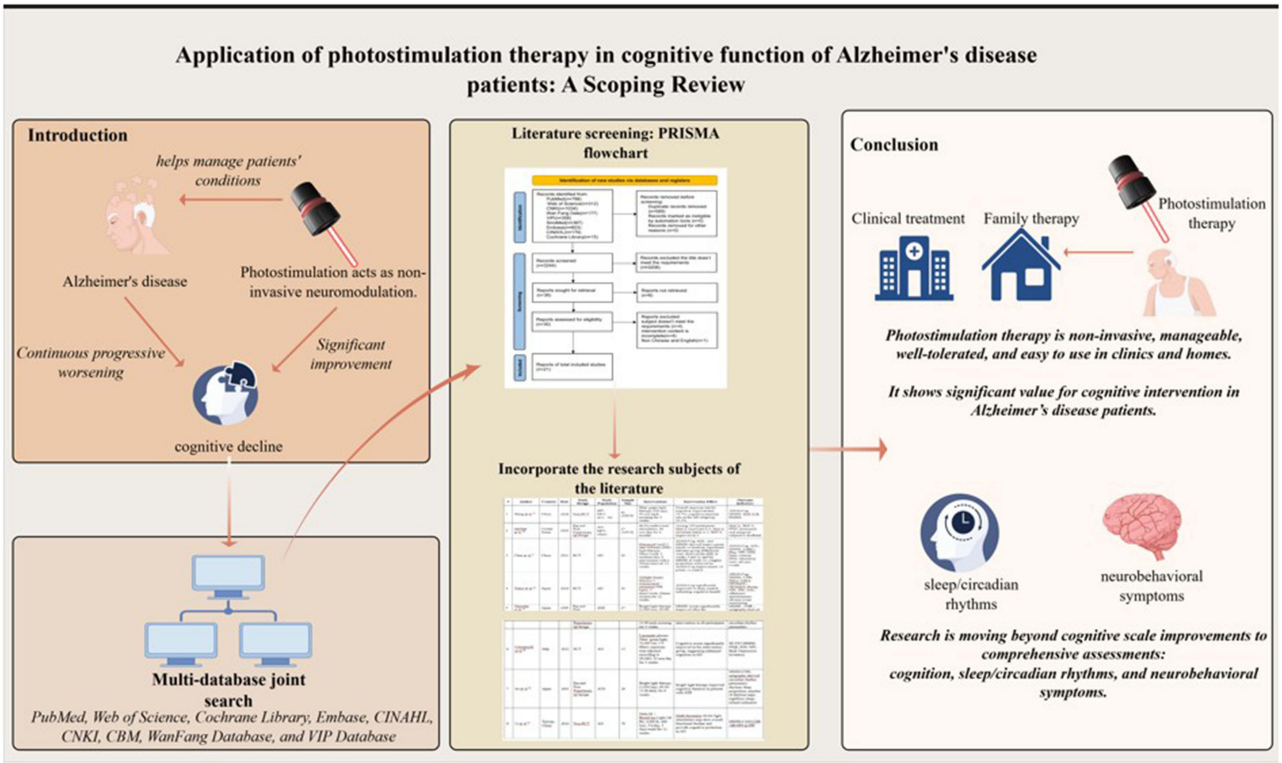
Graphical Abstract



impairment, executive function decline, language impairment, and abnormal mental and behavioral states, ultimately leading to impaired daily living abilities and long-term care dependence, it is the leading cause of dementia.[1] With the accelerating aging of the population, AD has become an increasingly serious global health problem, and its disease burden is continuously rising.[2] Data from the World Health Organization (WHO) and Alzheimer's Disease International (ADI) shows that approximately 57 million people worldwide suffered from dementia in 2021, with more than 60% living in low- and middle-income countries, and nearly 10 million new cases each year. The Global Burden of Disease Study (GBD 2019) projects this number to surge to 152.8 million by 2050.[3] Cognitive impairment not only affects patients' quality of life but also places a continuous emotional, time, and role burden on family caregivers, further highlighting the importance of exploring safe and implementable intervention strategies.[4,5] Against this backdrop, how to delay cognitive decline, improve functional outcomes, and optimize long-term management has become a key issue in Alzheimer's disease research and clinical practice.

AD is a chronic and complex disease involving multiple pathophysiological changes. Its pathogenesis is multifaceted, with the main pathological features being amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs), as well as related astrogliosis, microglial activation, and cerebral amyloid angiopathy.[6] These pathological changes lead to an imbalance in excitatory and inhibitory synaptic transmission in neurons, resulting in unbalanced neuronal activity, impaired neural network function, and consequently affecting the occurrence of gamma oscillations in the brain.[7,8] Currently, the main drug treatment options for AD are cholinesterase inhibitors and excitatory amino acid receptor antagonists such as memantine. In recent years, progress has also been made in anti-amyloid immunotherapy for early-stage Alzheimer's disease. However, these drugs cannot slow neuronal damage or stop disease progression, and may produce significant side effects, especially in the elderly.[9] Overall, while existing treatments can improve symptoms or slow disease progression to some extent, they still have limitations such as limited benefits, restricted patient populations, high monitoring requirements, and risks of adverse reactions, and have not yet fully met the long-term management needs of patients. Therefore, finding an effective, safe, and low-side-effect non-pharmacological therapy is of great clinical significance.

Photostimulation therapy is a non-invasive neuromodulation technique based on photobiomodulation mechanisms. It utilizes light signals of specific wavelengths, intensities, and frequencies to act on visual and non-visual photoreceptor pathways,[10] regulating brain neural oscillations, controlling the sleep-wake cycle, and influencing neurotransmitter release and neuroplasticity, thereby improving cognitive function and behavioral symptoms.[11,12] Due to its non-invasiveness, ease of operation, and good patient tolerance, this therapy has gained some application in diseases such as sleep disorders and seasonal affective disorder.[13,14] In recent years, it has been gradually introduced into the auxiliary management of AD and related cognitive impairments.[15] Studies have shown that light-related interventions have potential applications in individuals with cognitive impairment or dementia, but their evidence base and focus remain significantly limited. Some systematic reviews focus on a broader range of elderly individuals with cognitive impairment or dementia, primarily evaluating the overall effects of traditional light therapy on sleep, behavioral and psychiatric symptoms, mood, and cognition. However, there is a relative lack of targeted analysis on the core theme of cognitive function in Alzheimer's disease patients.[16] Other reviews primarily focus on photobiological modulation (PBM), or simultaneously discuss the potential roles of PBM and visual stimulation in the pathology and cognitive decline of Alzheimer's disease. The results suggest a promising approach, but also point out significant differences in existing studies regarding intervention types, parameter settings, study subjects, and outcome indicators, indicating that clinical translational evidence remains insufficient.[17,18] Currently, no studies have systematically described the application and mechanism of action of photostimulation therapy in the cognitive function of Alzheimer's disease patients from a comprehensive review perspective.

In summary, while research on photostimulation therapy in Alzheimer's disease and related cognitive impairments has been increasing in recent years, existing evidence remains fragmented. Different studies exhibit significant differences in intervention types, parameter settings, implementation scenarios, outcome indicators, and mechanism exploration. A systematic review of its application in cognitive function intervention for Alzheimer's patients is still lacking. Given the diverse research designs and significant heterogeneity of existing evidence in this field, a comprehensive review is more suitable for integrating different types of research. Scope reviews, as a comprehensive form of evidence used to systematically describe the current state of research, identify evidentiary features, and identify research gaps, have been widely applied in various research fields such as symptom management, critical care nursing, and advanced nursing practice.[19–22] Therefore, this study employs a comprehensive review approach to systematically review and analyze the current application and existing problems of photostimulation therapy in the cognitive function of Alzheimer's patients, summarize its main intervention forms, integrate key parameter characteristics, cognitive and related comprehensive outcomes, intervention effects and mechanisms of action, and identify evidence gaps in current research, providing a reference for future research design and clinical applications.

Materials and Methods

Defining the Research Question

This scoping review was conducted following the "PCC" methodological framework published by the Joanna Briggs Institute (JBI)[23] in Australia. Follow the Preferred Reporting Items (PRISMA-ScR) guidelines for extended-scope evaluations of systematic reviews and meta-analyses.[24] The protocol had been registered with Open Science Framework (OSF, DOI:10.17605/OSF.IO/8MB34).

The population of this review is patients with Alzheimer's disease; the concept is the application and mechanisms of photostimulation therapy in the cognitive function of Alzheimer's disease patients; and the context is the cognitive function of Alzheimer's disease patients. Therefore, the main research questions of this study are: What are the main intervention forms and key parameter characteristics of photostimulation therapy used in AD patients? What is the efficacy of photostimulation therapy on the cognitive function of AD patients? What are the clues and evidence gaps regarding the neurobiological mechanisms associated with cognitive changes related to photostimulation therapy?

Search Strategy

The System Searched PubMed, Web of Science, Cochrane Library, Embase, CINAHL, SinoMed, CNKI, Wanfang Database, and VIP Database, with a timeframe of database construction to January 2026. The search strategy was developed collaboratively by

researchers. The Chinese search focused on Alzheimer's disease and cognitive outcomes, with keywords including "Alzheimer's disease/Alzheimer's type dementia/Alzheimer's dementia/dementia/senile dementia" "cognitive function/cognitive impairment/memory/attention/executive function/neuropsychological tests" and free terms including "light stimulation/phototherapy/light therapy/bright light therapy/blue light/blue-enriched white light/blue-green light/timed light exposure/phase-customized phototherapy/circadian rhythm light exposure/light exposure/flickering light/Rhythmic Light/Gamma Light/40 Hz Light Stimulation/40 hertz/Photobiomodulation/transcranial photobiomodulation/intranasal photobiomodulation/transcranial + intranasal photobiomodulation/red light/near-infrared"; the English search terms are "Alzheimer's disease/Alzheimer dementia/Alzheimer-type dementia""Light therapy/Photostimulation therapy/bright light therapy/blue-enriched white light/circadian light""photobiomodulation/PBM/near-infrared/NIR/red light/rhythmic light/gamma light/40 Hz""cognitive function/cognition/memory/executive function""MMSE/ADAS-Cog/MoCA".

Searches were conducted using a combination of subject and free word and manual searches while snowballing through the included literature. The search timeframe was from database construction to January 5, 2026. The retrieval strategies for each database are shown in Table 1.

Table 1 Search Strategy

Database	Search Term and Strategy	No. Matches
PubMed #1 #2 #3 #4	Search ("Alzheimer Disease"[Mesh] OR "Alzheimer's disease" OR "Alzheimer dementia" OR "Alzheimer-type dementia") Search ("Phototherapy"[Mesh] OR "light therapy" OR "photostimulation therapy" OR "bright light therapy" OR photobiomodulation OR PBM OR "near-infrared" OR "red light" OR "40 Hz" OR "gamma light") Search ("Cognition"[Mesh] OR "Cognitive Dysfunction"[Mesh] OR "cognitive function" OR cognition OR memory OR "executive function" OR MMSE OR ADAS-Cog OR MoCA) Search #1 AND #2 AND #3	788
Web of Science #1 #2 #3 #4	Search TS=("Alzheimer's disease" OR "Alzheimer dementia" OR "Alzheimer-type dementia") Search TS=("light therapy" OR "photostimulation therapy" OR "bright light therapy" OR photobiomodulation OR PBM OR "near-infrared" OR "red light" OR "40 Hz" OR "gamma light") Search TS=("cognitive function" OR cognition OR memory OR "executive function" OR MMSE OR ADAS-Cog OR MoCA) Search #1 AND #2 AND #3	312
CNKI	SU=("Alzheimer's disease" + "Alzheimer dementia" + "Alzheimer-type dementia") * ("photostimulation" + "light therapy" + "phototherapy" + "bright light therapy" + "photobiomodulation" + "transcranial photobiomodulation" + "near-infrared" + "red light" + "40 Hz light stimulation") * ("cognitive function" + "cognitive impairment" + "memory" + "attention" + "executive function" + "MMSE" + "ADAS-Cog" + "MoCA")	1034
WanFang Date	Subject: (("Alzheimer's disease" OR "Alzheimer dementia" OR "Alzheimer-type dementia") AND ("photostimulation" OR "light therapy" OR "phototherapy" OR "bright light therapy" OR "photobiomodulation" OR "transcranial photobiomodulation" OR "near-infrared" OR "red light" OR "40 Hz light stimulation") AND ("cognitive function" OR "cognitive impairment" OR "memory" OR "attention" OR "executive function" OR "MMSE" OR "ADAS-Cog" OR "MoCA"))	177
VIP	K=(("Alzheimer's disease" OR "Alzheimer dementia" OR "Alzheimer-type dementia") AND ("photostimulation" OR "light therapy" OR "phototherapy" OR "bright light therapy" OR "photobiomodulation" OR "transcranial photobiomodulation" OR "near-infrared" OR "red light" OR "40 Hz light stimulation") AND ("cognitive function" OR "cognitive impairment" OR "memory" OR "attention" OR "executive function" OR "MMSE" OR "ADAS-Cog" OR "MoCA"))	358

(*Continued*)

Table 1 (Continued).

Database	Search Term and Strategy	No. Matches
SinoMed	(("Alzheimer's disease" OR "Alzheimer dementia" OR "Alzheimer-type dementia") AND ("photostimulation" OR "light therapy" OR "phototherapy" OR "bright light therapy" OR "photobiomodulation" OR "transcranial photobiomodulation" OR "near-infrared" OR "red light" OR "40 Hz light stimulation") AND ("cognitive function" OR "cognitive impairment" OR "memory" OR "attention" OR "executive function" OR "MMSE" OR "ADAS-Cog" OR "MoCA"))	367
Embase #1 #2 #3 #4	Search ("alzheimer disease"/exp OR "Alzheimer's disease" OR "Alzheimer dementia" OR "Alzheimer-type dementia") Search ("phototherapy"/exp OR "light therapy" OR "photostimulation therapy" OR "bright light therapy" OR photobiomodulation OR PBM OR "near-infrared" OR "red light" OR "40 Hz" OR "gamma light") Search ("cognition"/exp OR "cognitive function" OR cognition OR memory OR "executive function" OR MMSE OR ADAS-Cog OR MoCA) Search #1 AND #2 AND #3	603
CINAHL #1 #2 #3 #4	Search ("Alzheimer's disease" OR "Alzheimer dementia" OR "Alzheimer-type dementia") Search ("light therapy" OR "photostimulation therapy" OR "bright light therapy" OR photobiomodulation OR PBM OR "near-infrared" OR "red light" OR "40 Hz" OR "gamma light") Search ("cognitive function" OR cognition OR memory OR "executive function" OR MMSE OR ADAS-Cog OR MoCA) Search #1 AND #2 AND #3	179
Cochrane Library #1 #2 #3 #4	Search Title Abstract Keyword: "Alzheimer's disease" OR "Alzheimer dementia" OR "Alzheimer-type dementia" Search Title Abstract Keyword: "light therapy" OR "photostimulation therapy" OR "bright light therapy" OR photobiomodulation OR PBM OR "near-infrared" OR "red light" OR "40 Hz" OR "gamma light" Search Title Abstract Keyword: "cognitive function" OR cognition OR memory OR "executive function" OR MMSE OR ADAS-Cog OR MoCA Search #1 AND #2 AND #3	15

Note: #1-#4 indicate sequential search steps within each database. The asterisk (*) indicates truncation/wildcard searching, where supported by the database, to retrieve words with different endings or variations. Search strategies were adapted according to the indexing system and search interface of each database while maintaining consistent core concepts across databases.

Abbreviations: MeSH, Medical Subject Headings; TS, topic search; MH, CINAHL subject heading; ti, title; ab, abstract; kw, keyword; exp, exploded subject heading; SU, subject; K, keyword field; CBM, Chinese Biomedical Literature Database; CNKI, China National Knowledge Infrastructure; VIP, VIP Database.

Literature Inclusion and Exclusion Criteria

This study established inclusion and exclusion criteria based on the JBI-recommended PCC (Population, Concept, Context) framework.

Inclusion criteria:

(1) The study subjects are Alzheimer's disease patients, without restrictions on gender, region or age range;
(2) The intervention method is centered on light stimulation therapy, which can be used alone or in combination with other non-invasive/sensory stimulation/behavioral interventions to more comprehensively reflect the current status of practical application in this field;
(3) It can be implemented in any setting, including medical institutions, care facilities, and home settings;
(4) Studies must report at least one cognitive function-related outcome, such as overall cognition, memory, attention, executive function, or relevant neuropsychological test results, to ensure consistency between the review topic and the research question.
(5) The literature types are original studies, including randomized controlled trials, experimental-like studies, mixed-method studies, case-control studies, cohort studies, longitudinal studies, and case reports, in order to systematically review the current state of research, identify evidence characteristics, and identify research gaps;
(6) The language is Chinese or English.

Exclusion criteria:

(1) The intervention is not centered on light stimulation therapy, but rather other sensory stimulation or non-light stimulation interventions are used as the main treatment;
(2) No cognitive function-related outcome measures were reported;
(3) Non-original research such as reviews, systematic reviews, conference abstracts, research protocols, editorials/commentaries;
(4) Duplicate publications;
(5) Inability to obtain the full text.

Literature Screening and Data Extraction

The retrieved literature was imported into Zotero software for deduplication. Two researchers independently screened the studies according to the inclusion and exclusion criteria, followed by a second screening based on the full text. Disagreements were resolved through discussion or by consulting a third researcher. A data extraction table was created to document the application strategies and intervention effects of phototherapy in the cognitive function of AD patients. Two researchers independently extracted the basic information and data from the included literature. Any discrepancies or questions during the extraction process were resolved through discussion with a third researcher. The extracted information included the first author, country of publication, publication year, study design, study population, sample size, intervention measures, intervention effects, and outcome indicators.

Methodological Quality Assessment

This is a scoping review study, primarily aimed at systematically describing the current research status, application characteristics, and evidence gaps of photostimulation therapy in cognitive function intervention for Alzheimer's disease patients, rather than providing a quantitative synthesis of intervention effects or forming a definitive judgment on efficacy. Therefore, in accordance with the methodological recommendations of PRISMA-ScR and JBI comprehensive reviews, this study did not conduct a formal risk of bias or methodological quality assessment on the included literature.

Results

Results of Literature Search and Screening

The preliminary search yielded 3833 documents, with 3244 documents remaining after de-weighting, and 21 documents were finally included after reading the titles, abstracts, and full texts,[11,15,25–43] of which 2 were in Chinese,[42,43] and 19 were in English.[11,15,25–41] The flowchart of literature screening is shown in Figure 1. The basic characteristics of the included literature are shown in Table 2.

Basic Characteristics of Included Literature

Twenty-one papers published between 2000 and 2024 were included. Among them, 5 were from China,[25,27,36,42,43] 4 from the United States,[26,32,34,35] 4 from Russia,[33,38,39,41] 3 from Japan,[15,28,30] 1 from Canada,[37] 1 from Italy,[29] 1 from Taiwan,China,[31] 1 from South Korea,[11] and 1 from Austria.[40] The included literature included 9 randomized controlled trials,[11,15,27,29,34,36,40,42,43] 2 non-randomized controlled trials,[25,31] 7 Pre and Post Experimental design,[26,28,30,33,38,39,41] 2 case reports,[32,35] and 1 case series study.[37] The basic characteristics of the included literature are shown in Table 2.

Research Subjects of Included Literature

The study subjects included patients with Alzheimer's disease and related dementias. Specifically, there were 11 studies focusing on Alzheimer's disease patients,[11,15,27,29,31,32,35–37,42,43] 2 studies on Alzheimer's-type dementia patients,[28,30] and 8 studies that included both Alzheimer's disease patients and other cognitive/dementia populations (such as aMCI, vascular dementia, or other non-AD dementias) but independently reported outcomes related to Alzheimer's disease patients.[25,26,33,34,38–41] The basic characteristics of the included literature are shown in Table 2.

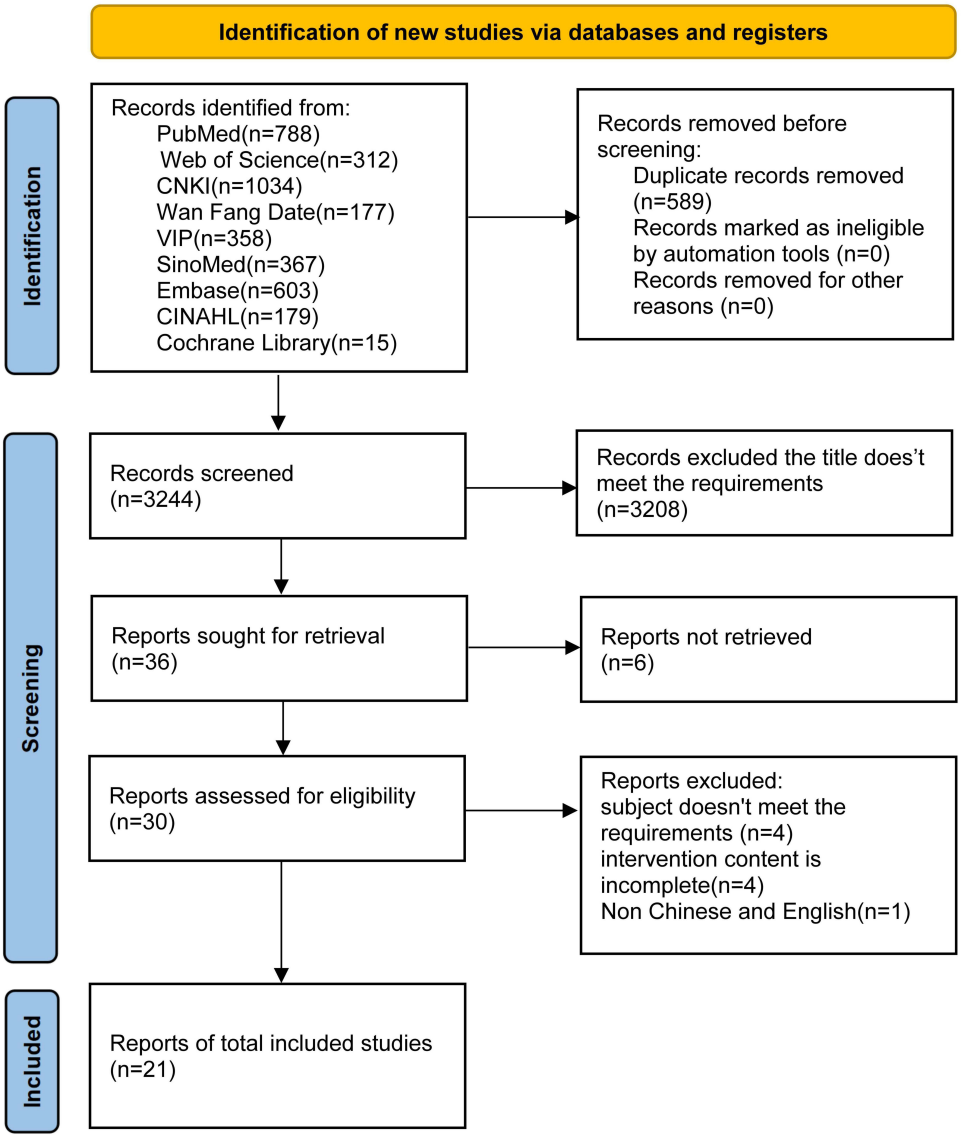


Figure 1 Literature retrieval and screening process.

Characteristics of Photostimulation Therapy as an Intervention in AD Patients

Among the 21 included studies, photostimulation therapy interventions can be mainly categorized into three types: (1) Light stimulation therapy: including bright light, blue-enriched white light/blue light or blue-green light, and customized light exposure based on circadian rhythm phase.[11,25,28–30,40,43] (2) Rhythm-related photostimulation therapy: including 40 Hz rhythmic light exposure, multi-lamp light environments, 40 Hz blue light irradiation, and combined auditory-visual sensory stimulation.[26,31,42] (3) Photobiomodulation-related therapies include those using red-near-infrared light, delivered via transcranial, intranasal, and transcranial-intranasal combinations of photobiomodulation (PBM) and combined therapies,[15,27,32,34–37] as well as transcatheter intracerebral laser photobiomodulation therapy (PBMT).[33,38,39,41] The overall parameter range shows that the spectrum/wavelength is mainly concentrated in the blue light range (approximately 464–510 nm) and the red light-near-infrared range (approximately 630–810 nm). Light exposure therapy is mostly characterized by illuminance (approximately 3000–10000 lx) or ocular illuminance (approximately 30 lx),[11,28–30,40] while photobiomodulation is mostly reported in terms of power density/energy density (mW/cm^2, J/cm^2)[27,29]. Frequency parameters mainly involve 40 Hz rhythmic light or pulsed PBM interventions.[26,31,32,34,42] The duration of a single exposure is commonly 20–60 min,[11,25,26,28,29] and the treatment course is mostly 2–24 weeks, including studies with

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Table 2 The Basic Characteristics of the Included Literature (n=21)

#	Author	Country	Date	Study Design	Study Population	Sample Size	Interventions	Intervention Effect	Outcome Indicators
1	Wang et al[25]	China	2024	Non-RCT	AD,MCI, SCI,HC	42 (AD=6)	Blue–green light therapy (500 nm), 50 min each morning for 4 weeks	Overall response rate for cognitive improvement: 16.7%; cognitive response rate in the AD subgroup: 33.3%	ADAS-Cog; MMSE; MoCA-B; HAMA
2	McNett et al[26]	United States	2023	Pre and Post Experimental design	AD,MCI, others	27 (AD=6)	40-Hz audiovisual stimulation, 60 min/day for 6 months	Among AD participants: MoCA improved in 2; MoCA remained stable in 3; BOCA improved in 3	MoCA; BOCA; EEG; participant and caregiver subjective feedback
3	Chen et al[27]	China	2021	RCT	AD	20	Donepezil (oral) + near-infrared (NIR) light therapy; 5days/week; 2 sessions/day; 6 min/session with a 30min interval; 12 weeks	ADAS-Cog, ADL, and MMSE showed improvement trends vs baseline; significant between-group differences were observed for ADL at weeks 4 and 12 and for MMSE at week 12; a higher proportion achieved an ADAS-Cog improvement ≥4 points vs control	ADAS-Cog; ADL; MMSE; CIBIC-Plus; NPI; GDS; brain volume; EEG; laboratory tests; adverse events
4	Yokoi et al[15]	Japan	2024	RCT	AD	30	Vielight Neuro Gamma 4 (transcranial + intranasal NIR light), 3 times/week, 20min/session for 12 weeks	ADAS-Cog significantly improved vs sham control, indicating cognitive benefit	ADAS-Cog; MMSE; CDR; PGI-I; CGI-I; DEMQOL; DEMQOL-Proxy; NPI; ZBI; ADL; adherence questionnaire; adverse event monitoring
5	Yamader et al[28]	Japan	2000	Pre and Post Experimental design	ATD	27	Bright light therapy (3,000 lux), 09:00–11:00 each morning for 4 weeks	MMSE scores significantly improved after the intervention in all participants	MMSE; CDR; actigraphy-derived circadian rhythm parameters
6	Cremascoli et al[29]	Italy	2022	RCT	AD	13	Luminette glasses (blue–green light, 10,000 lux, UV filter); exposure time adjusted according to DLMO; 20 min/day for 4 weeks	Cognitive scores significantly improved in the intervention group, suggesting enhanced cognition in AD	SE; TST; MMSE; PSQI; ESS; NPI; Beck Depression Inventory
7	Ito et al[30]	Japan	2001	Pre and Post Experimental design	ATD	28	Bright light therapy (3,000 lux), 09:00–11:00 daily for 8 weeks	Bright light therapy improved cognitive function in patients with ATD	MMSE; CDR; actigraphy-derived circadian rhythm parameters; daytime sleep proportion; number of daytime naps; nighttime sleep-related indicators
8	Li et al[31]	Taiwan, China	2024	Non-RCT	AD	78	Delta M + BrainCare Light (40 Hz, 4,000 K, 400 lux), 5 h/day, 5 days/week for 12 weeks	Multi-luminaire 40-Hz light stimulation may slow overall functional decline and provide cognitive protection in AD	MMSE; CASI; CDR-SB; NPI-Q; ZBI

9	Horner et al[32]	United States	2020	Case report	AD	1	Transcranial photobiomodulation (PBM) plus ketogenic diet for 10 weeks; 810-nm NIR at 40 Hz, 3 times/week, 20 min/session	Ketogenic diet combined with PBM markedly improved cognition in a patient with mild AD	MoCA; 1-min animal naming test; metabolic biomarkers; blood ketone levels; adverse event monitoring
10	Kim et al[11]	South Korea	2021	RCT	AD	25	Timed blue-enriched white light for 2 weeks; 1 h each morning using Litebook (peak 464nm); corneal illuminance 30 lux	Timed blue-enriched white light improved cognitive function in AD	PSQI; MMSE-KC; objective sleep parameters; depression scale; neuropsychiatric questionnaire; caregiver burden scale
11	Maksimovich et al[33]	Russia	2024	Pre and Post Experimental design	Dementia	404 (AD=48)	Transcatheter intracerebral laser photobiomodulation therapy (PBMT)	PBMT improved cognition and reduced dementia severity in AD; promoted intracerebral angiogenesis and neuroregeneration	CDR; TDR; MMSE; MRI; MRA; CT; cerebral blood-flow related measures
12	Iosifescu et al[34]	United States	2023	RCT	AD and aMCI	125	808-nm transcranial photobiomodulation (t-PBM)	t-PBM improved cognition or slowed cognitive decline	RBANS-Update; ACE-III; NAART35; LPC; FNAME-12; TMT(A&B); Stroop Color–Word Test; LNS; UDSNB 3.0
13	Salehpour et al[35]	United States	2019	Case Report	AD	1	Multimodal photob-iomodulation, 2 sessions/day, 25 min/session for 4 weeks	Marked cognitive improvement; reversal of olfactory dysfunction; improved instrumental activities of daily living; reduced caregiver stress	MoCA; WMQ; AST; peanut-butter odor detection test; IADL; PSM; CSAQ
14	Huang et al[36]	China	2020	RCT	AD	60	Red-light therapy (630 nm): transcranial LED helmet +Transabdo-minal abdominal LED exposure; 5 times/week, 30min/session for 24 weeks	Improved cognition, mood, neuropsychiatric symptoms, and activities of daily living; reduced formaldehyde level; improved brain function	ADAS-cog; MMSE; GDS; NPI; BI; fMRI
15	Saltmarche et al[37]	Canada	2017	Case Series Report	AD	5	810-nm NIR photobiomodulation (transcranial + intranasal LED): in-clinic Neuro device 1–2 times/week (20min/session) plus daily home intranasal "810" device (25min/session) for 12 weeks	Significant cognitive improvement; improved daily function and sleep; reduced anxiety, anger outbursts, and wandering; no adverse events reported	MMSE; ADAS-cog; patient- and caregiver-reported changes in quality of life and functional outcomes
16	Maksimovich et al[38]	Russia	2021	Pre and Post Experimental design	AD and BD	65 (AD=48)	Transcatheter intracerebral laser photobiomodulation therapy (PBMT)	In AD, microcirculation improved; temporal lobe volume increased by 10–20%; dementia severity decreased; cognition recovered; effects persisted for 2–10 years	CDR; TDR; MMSE; brain CT; MRI; SG; REG; MUGA
17	Maksimovich et al[39]	Russia	2023	Pre and Post Experimental design	AD and VP	85 (AD=48)	Transcatheter intracerebral laser photobiomodulation therapy (PBMT;632.8 nm)	In AD, angiogenesis was stimulated; collateral capillary regeneration occurred; arteriovenous shunts closed; temporal lobe volume increased by 10–20%; dementia severity decreased; cognition recovered; effects persisted for 2–15 years	CDR; TDR; MMSE; brain CT; MRI; SG; REG; MUGA

(*Continued*)

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Table 2 (Continued).

#	Author	Country	Date	Study Design	Study Population	Sample Size	Interventions	Intervention Effect	Outcome Indicators
18	Graf et al[40]	Austria	2001	RCT	AD and VD	23 (AD=11)	Bright light therapy (BLT; 3,000 lux), 17:00–19:00 daily for 10 days	Cognitive function significantly improved; body temperature rhythm (BTR) phase was delayed by 56min	MMSE; nocturnal body temperature rhythm (BTR) recording
19	Maksimovich et al[41]	Russia	2023	Pre and Post Experimental design	AD and non-AD dementia	350 (AD=48)	Transcatheter intracerebral laser photobiomodulation therapy (PBMT)	In AD, microcirculation improved; temporal lobe volume increased by 10–20%; dementia severity decreased; cognition recovered; effects persisted for 2–10 years	CDR; TDR; MMSE; brain CT; MRI; SG; REG; MUGA
20	Yanan Lin[42]	China	2024	RCT	AD	155	40- Hz blue-light exposure (LED; maximum power density >600 mW/cm^2), 5 times/week, 30 min/session for 4 weeks	Cognition significantly improved: MMSE total score and domain scores (orientation, immediate recall, attention/calculation, etc.) were higher than baseline and than the usual-care group; ADL total score was lower than baseline and than the usual-care group	MMSE; ADL; FBG; lipids; inflammatory markers
21	Conglong Qiu et al[43]	China	2021	RCT	AD	108	Haloperidol injection plus light therapy (TBX43036 device; 5,000 lx), direct exposure 07:00–09:00, 120 min/day for 14 days	The light-therapy group showed the fastest delirium symptom relief; ADL improved second only to the rTMS group; MMSE improved but less than in the rTMS and donepezil groups; no serious adverse events	MMSE; ADL; CAM

Abbreviations: AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; ATD, Alzheimer-type dementia; BD, Binswanger disease; HC, healthy controls; MCI, mild cognitive impairment; SCI, subjective cognitive impairment; VD, vascular dementia; VP, vascular pathology; PBM, photobiomodulation; PBMT, photobiomodulation therapy; NIR, near-infrared; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; CDR, Clinical Dementia Rating; ADL, activities of daily living; NPI, Neuropsychiatric Inventory; PSQI, Pittsburgh Sleep Quality Index; ZBI, Zarit Burden Interview.

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follow-up periods of 6 months or longer.[26,38,39] To facilitate comparison of the implementation characteristics of photostimulation therapy in different studies, this study further summarized the key parameters of various interventions, including wavelength, intensity/illuminance, frequency, duration of a single intervention, and treatment course length. Specific results are shown in Table 3.

Table 3 Summary of Key Photostimulation Parameters in the Included Studies

Author	Intervention Type	Wavelength/ Spectrum	Intensity/ Illuminance/ Power Density	Frequency/ Pulse	Session Duration	Treatment Course	Remarks
Wang et al[25]	Blue-green light therapy	500 nm	NR	NR	50 min/day	4 weeks	Morning exposure
McNett et al[26]	40 Hz audio-visual sensory stimulation	NR	NR	40 Hz	60 min/day	6 months	Multisensory stimulation
Chen et al[27]	Near-infrared light plus donepezil	Near-infrared	NR	NR	6 min/session, twice daily, 30-min interval	12 weeks	5 days/week
Yokoi et al[15]	Transcranial + intranasal PBM	Near-infrared	NR	NR	20 min/session	12 weeks	3 times/week
Yamader et al[28]	Bright light therapy	NR	3,000 lx	NR	120 min/day	4 weeks	09:00–11:00
Cremascoli et al[29]	Blue-green light glasses	Blue-green light	10,000 lx	NR	20 min/day	4 weeks	Individually timed based on DLMO
Ito et al[30]	Bright light therapy	NR	3,000 lx	NR	120 min/day	8 weeks	09:00–11:00
Li et al[31]	Multi-luminaire 40 Hz lighting environment	4,000 K	400 lx	40 Hz	5 h/day	12 weeks	5 days/week
Horner et al[32]	Transcranial PBM + ketogenic diet	810 nm near-infrared	NR	40 Hz	20 min/session	10 weeks	3 times/week
Kim et al[11]	Blue-enriched white light	Peak 464 nm	Corneal illuminance 30 lx	NR	1 h/day	2 weeks	Morning exposure
Maksimovich et al[33]	Transcatheter intracerebral laser PBMT	NR	NR	NR	NR	NR	Precise parameters not reported in the manuscript
Iosifescu et al[34]	Transcranial PBM	808nm	NR	42 Hz; duty cycle 33%	NR	NR	Session duration and course not clearly reported
Salehpour et al[35]	Multi-modal PBM	NR	NR	NR	25 min/session, twice daily	4 weeks	Case study
Huang et al[36]	Red light therapy (transcranial helmet + transabdominal)	630 nm	NR	NR	30 min/session	24 weeks	5 times/week
Saltmarche et al[37]	Transcranial + intranasal PBM	810 nm near-infrared	NR	NR	Clinic: 20 min/ session; home intranasal: 25 min/ day	12 weeks	Clinic visits 1–2 times/week
Maksimovich et al[38]	Transcatheter intracerebral laser PBMT	NR	NR	NR	NR	NR	Follow-up 2–10 years; precise treatment parameters not reported

(*Continued*)

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Table 3 (Continued).

Author	Intervention Type	Wavelength/ Spectrum	Intensity/ Illuminance/ Power Density	Frequency/ Pulse	Session Duration	Treatment Course	Remarks
Maksimovich et al[39]	Transcatheter intracerebral laser PBMT	632.8 nm	NR	NR	NR	NR	Follow-up 2–15 years; precise dose parameters not reported
Graf et al[40]	Bright light therapy	NR	3,000 lx	NR	120 min/day	10 days	17:00–19:00
Maksimovich et al[41]	Transcatheter intracerebral laser PBMT	NR	NR	NR	NR	NR	Follow-up 2–10 years; precise treatment parameters not reported
Yanan Lin[42]	40 Hz blue light stimulation	Blue light	Maximum power density >600 mW/cm^2	40 Hz	30 min/session	4 weeks	5 times/week
Conglong Qiu et al[43]	Light stimulation combined therapy	NR	5,000 lx	NR	120 min/day	14 days	07:00–09:00, direct exposure to the light source

Light Stimulation Therapy

Seven studies employed light stimulation therapy.[11,25,28–30,40,43] The intervention methods primarily included bright light, blue-enriched white light/blue light, and blue-green light. Most studies were implemented in care settings such as hospital wards or nursing homes, and the emphasis was on operability and compliance management. Studies have shown that the timing of light exposure may be a key factor affecting the consistency of intervention efficacy. Yamadera et al[28] reported that patients' MMSE index was significantly improved from baseline after continuous intervention with 3000 lx bright light from 9:00 to 11:00 in the morning for 4 weeks, and the changes in diurnal rhythm parameters were recorded simultaneously, which is consistent with the reports of 3 other studies.[29,30,40] Compared to traditional bright light, blue light-enriched illumination places more emphasis on regulating non-visual photoreceptor pathways.Kim et al[11] used a timed blue light-enriched white light intervention with a spectral peak of 464 nm, administered for one hour each morning for two weeks. This study specifically emphasized integrating the light therapy into daily care routines to improve clinical feasibility and adherence.Wang et al[25] used 500 nm blue-green light for 50 minutes daily for 4 weeks, suggesting that future research designs should clearly define stratification and subgroup analysis to further standardize the intervention protocol. Conglong Qiu et al[43] used 5000 lx light stimulation as part of a combined treatment plan, requiring patients to look directly at the light source for 120 minutes each morning for 14 days. The results showed that the degree of cognitive improvement might be confounded by the various intervention measures in the combined treatment.

Rhythm-Related Photostimulation Therapy

Three studies employed 40 Hz rhythmic photostimulation therapy.[26,31,42] The intervention methods mainly included combined auditory and visual sensory stimulation, exposure to a 40 Hz multi-lamp light environment, and 40 Hz blue light irradiation.A common feature of these studies was the use of a fixed frequency as the core dosage element, ensuring the effectiveness of light stimulation through device-based or environmental exposure.McNett et al[26] used the AlzLife 40 Hz auditory-visual sensory stimulation therapy, 60 minutes daily, for 6 months, suggesting improvements in MoCA or BOCA scores in some individuals within a sample including a subgroup with AD. Li et al[31] used multi-lamp 40 Hz light stimulation in a real-world care environment, with parameters of 4000K and 400 lx, 5 hours daily, 5 days a week, for 12 weeks, providing a reproducible parameter framework and implementation reference for non-pharmacological intervention in a "real-world" setting.In addition, Lin Yanan[42] conducted a randomized controlled study of 40 Hz blue light irradiation, 5 times a week, 30 minutes each time, for 4 weeks. The study suggested that patients' metabolic and inflammatory indicators may change with the duration of the intervention, providing clinical clues for subsequent mechanism validation.

Photobiological Modulation-Related Therapies

Eleven studies employed photobiological modulation-related therapies. Seven studies[15,27,32,34–37] used PBM therapy interventions, including transcranial, intranasal, and combined transcranial and intranasal delivery routes, primarily employing red light or near-infrared wavelengths, with power density/energy density, pulse frequency, single session duration, and treatment course as core dosimetric elements.

Yokoi et al[15] used the Vielight Neuro Gamma 4 device for transcranial and intranasal near-infrared PBM therapy, three times a week for 20 minutes each time, for 12 weeks, and simultaneously monitored patients' quality of life, neuropsychiatric symptoms, and adverse events. Chen et al[27] combined near-infrared light therapy with donepezil medication, with short-duration irradiation twice daily, 5 days a week, for 12 weeks. This study suggested that PBM therapy, as a non-pharmacological intervention for AD, warrants further validation of its efficacy.In home-based interventions, the case series by Saltmarche et al[37] used daily intranasal transcranial PBM therapy at home, providing feasibility evidence for subsequent, more rigorous controlled studies. In a case study, Horner et al[32] combined 810 nm, 40 Hz near-infrared transcranial PBM therapy with a ketogenic diet, reporting improvements in MoCA scores and naming tests, and simultaneously recording changes in metabolism-related indicators.Iosifescu et al[34] conducted a randomized controlled study of transcranial near-infrared PBM therapy on 125 patients, using a pulsed mode with parameters of 42 Hz and a 33% duty cycle, and setting predefined outcomes and metabolic assessments. The study showed that PBM therapy is progressing from an exploratory to a standardized approach.Furthermore, the randomized controlled study of 630 nm red light by Huang et al[36] and the case report by Salehpour et al[35] both suggested that multimodal PBM therapy may be associated with improvements in cognition, olfaction, and quality of life, providing hypotheses for subsequent mechanism-outcome efficacy validation. Four studies[33,38,39,41] employed PBMT therapy, highlighting its potential to intervene in pathological processes related to cerebral microcirculation. However, its invasiveness and limited generalizability restrict its widespread use, and the evidence is mostly presented in before-and-after comparison formats. Maksimovich et al[33,38,39,41] reported in different cohorts that PBMT therapy led to a decrease in the severity of dementia and improvement in MMSE scores in AD patients, accompanied by imaging evidence such as increased temporal lobe volume and improved cerebral microcirculation. Some studies suggested that the effects could last for several years.It should be noted that due to the non-randomized design, insufficient controls, and significant sample heterogeneity of these studies, the current evidence is more suitable for suggesting research directions and feasibility. Its clinical value still needs further verification under standardized procedures, improved safety monitoring, and long-term follow-up.

Application Effectiveness Evaluation

In the 21 included studies, commonly used scales for cognitive outcomes included MMSE, ADAS-Cog, MoCA, and CASI. Some studies also evaluated dementia severity grading, including the Clinical Dementia Rating, activities of daily living, behavioral and psychological symptoms, and emotional outcomes, supplemented by sleep-wake cycle indicators or objective monitoring parameters to comprehensively reflect the intervention effects.

Different Patterns of Light Stimulation May Affect Cognitive Function in AD Patients

Seven studies[11,25,28–30,40,43] have shown that light therapy has a significant effect on cognitive outcomes in AD patients, and cognitive changes often synchronize with sleep-wake rhythm outcomes. Yamadera et al[28] conducted a 4-week intervention with 3000 lx morning bright light in 27 patients with Alzheimer's-type dementia. The results showed a significant improvement in MMSE scores compared to before the intervention, and changes in circadian rhythm parameters were observed. Ito et al[30] provided the same light intensity but extended the bright light intervention to 8 weeks in 28 patients. Their study also showed improved cognitive function accompanied by changes in rhythm-related indicators such as daytime sleepiness.In a randomized controlled study, Cremascoli et al[29] used individualized DLMO-timed blue-green light glasses in 13 AD patients, and the study showed improvements in cognitive scores and sleep efficiency. Kim et al[11] treated 25 patients with mild to moderate AD with 1 hour of timed blue-enriched white light every morning for 2 weeks, and the results showed an improving trend in relevant cognitive scales and subjective and objective sleep indicators. In addition to the above studies, Wang et al[25] applied 500nm blue-green light continuously for 4 weeks in 42 subjects (including 6 AD patients), reporting an observable cognitive improvement rate in the AD subsample and suggesting that baseline cognitive level may affect the

direction of the response. Graf et al[40] treated 23 dementia patients (including 11 AD patients) with 3000 lx bright light in the evening for 10 days, and the results showed increased MMSE scores, improved cognitive function, and changes in body temperature rhythm phase. Conglong Qiu et al[43] compared 5000 lx morning light combined with conventional medication and other treatments in 108 AD patients with delirium. The results showed that the light therapy group had faster relief of delirium symptoms and improved MMSE scores.

Rhythm-Based Photostimulation Therapy Can Improve Cognitive Function in AD Patients

Three studies[26,31,42] have shown that 40Hz rhythmic light stimulation is feasible in individuals with AD patients and related dementias, and demonstrates signals of cognitive function protection. McNett et al[26] conducted a pre and post intervention controlled study on 27 subjects (including 6 AD patients) using a 40 Hz multisensory protocol (including light stimulation therapy) for 6 months. The results showed generally acceptable subject compliance, and a trend towards improvement or slower decline in cognitive function outcomes. Li et al[31] further indicated in a study of exposure to a multi-lamp 40 Hz light environment that long-term, regular frequency-modulated light environments can be implemented in real-world care settings, and observed a slower rate of overall functional decline and cognitive protection signals in patients. Yanan Lin[42] compared 40 Hz blue light intervention with conventional treatment in 155 AD patients. The results showed that the total MMSE score and scores in subdomains such as orientation, immediate recall, attention, and calculation improved after treatment compared to before treatment, suggesting that frequency parameters may influence the degree of improvement in cognitive function. Future research should validate the effects of this therapy on core cognitive outcomes in a larger sample and determine the appropriate population and minimum effective dose.

Photobiomodulation-Related Therapies Can Improve Cognitive Function and Behavioral and Psychological Symptoms in AD Patients

Eleven studies[15,27,32–39,41] have shown that transcranial, intranasal, or combined transcranial and intranasal PBM therapies can improve cognitive outcomes in AD patients, with some studies[15,27,32,34,36–38,41] also showing beneficial effects on daily function and behavioral and psychological symptoms. In a randomized controlled trial, Chen et al[27] combined near-infrared light therapy with conventional medication in 20 AD patients, showing an improving trend in outcomes such as ADAS-Cog, MMSE, and ADL in the intervention group compared to baseline, and significantly better results than the control group at some time points. Yokoi et al[15] conducted a transcranial and intranasal PBM sham-controlled trial in 30 individuals with mild dementia due to AD, showing significant improvement in ADAS-Cog compared to the sham control group. Huang et al[36] conducted a 24-week randomized controlled trial in 60 patients with mild to moderate AD using a transcranial helmet and abdominal belt therapy with 630 nm red light irradiation, with ADAS-Cog as the primary outcome, and also evaluating NPI and Barthel indices. The results suggested improvements in cognition, mood, and daily function with acceptable safety, and also reported clues to changes in biomarkers related to formaldehyde metabolism. In a randomized study of transcranial PBM in 125 AD patients by Iosifescu et al,[34] the results showed improved cognition or slowed decline, and reported good tolerability, providing a reference for subsequent parameter standardization and widespread application In small sample case series and case studies, Saltmarche et al[37] applied transcranial and intranasal PBM therapy to 5 subjects, showing improvements in cognitive scales, accompanied by improved sleep, reduced anxiety, and reduced behavioral symptoms such as anger outbursts Salehpour et al[35] and Horner et al[32] separately reported improvements in cognitive and quality of life-related outcomes after multimodal PBM therapy intervention at the case level.

Furthermore, Maksimovich et al[33,38,39,41] explored PBMT therapy intervention in large-sample before-and-after controlled studies, showing a decrease in dementia severity, improved cognitive function, and imaging evidence of increased temporal lobe volume and improved cerebral microcirculation. It is important to emphasize that studies on PBM and PBMT therapies differ significantly in wavelength, power density/energy density, pulse frequency, treatment duration, and combined interventions, and high-quality studies are still needed to further verify their therapeutic effects.

Safety and Adverse Events

Across the 21 included studies, the overall results showed that light therapy was generally safe and well-tolerated, with no serious adverse events directly related to the intervention.Adverse reactions were mostly mild and transient, including eye or head discomfort, fatigue, or reactions during the sleep-wake cycle adjustment period.[11,15,27,36,42,43] Some studies

emphasized the importance of adherence monitoring and caregiver support during long-term interventions in home or healthcare settings.[31,37] In terms of evidence quality, the safety conclusions were limited by small sample sizes, insufficient follow-up, and inconsistent definitions and reporting of adverse events. Future studies should incorporate adverse event grading, adherence, and actual dose exposure into the predefined protocol, and simultaneously record relevant risk factors.

The Mechanisms by Which Photostimulation Therapy Improves Cognitive Function in AD Patients

Sleep-Wake Pathways

Multiple neuroscience and sleep medicine studies indicate that phototherapy can influence cognitive processes such as attention, executive function, and memory through the intrinsically photosensitive retinal ganglion cells (ipRGCs)-suprachiasmatic nucleus (SCN) pathway and its projections to downstream nuclei involved in arousal, mood, and cognition. Mahoney et al[44] emphasized that timed light exposure can directly regulate cognitive-related brain network activity without being entirely dependent on circadian rhythm resetting. Sleep and circadian rhythm disturbances are common in the progression of AD and may conversely promote the accumulation of Aβ and Tau-related pathology and neuroinflammation, thus forming a vicious cycle. Musiek et al[45] pointed out that sleep-wake and circadian rhythm abnormalities often appear in the early stages of the disease and are closely related to Aβ dynamics, synaptic homeostasis, and clearance processes. Another study found that[46] sleep fragmentation and rhythm disruption may impair memory consolidation and reduce glymphatic clearance efficiency, thereby accelerating neurodegenerative changes. Therefore, light stimulation therapy provides a more stable physiological basis for cognitive function by providing sufficient daytime light phase signals, enhancing rhythm stability, and improving nighttime sleep continuity.[47,48]

Neural Network Synchronization and Gamma Oscillations

Gamma-band neural oscillations are closely associated with higher-level cognitive processes such as attention, working memory, and information integration. Iaccarino et al[49] proposed in animal model studies that 40Hz sensory rhythmic stimulation can induce cortical gamma oscillations and alter microglial cell states, accompanied by a decrease in Aβ load, providing a testable mechanistic framework for immune and pathological regulation. Subsequently, Martorell et al[50] further showed that multisensory stimulation can induce gamma synchronization in brain regions, reduce pathology, and improve learning and memory performance, suggesting that multimodal input may enhance the tractability and inter-regional synchronization of neural networks. Recent translational research has expanded its focus from "increasing gamma power" to "clearance pathways and vascular-glial coupling". Murdock et al[51] reported in Nature that multisensory 40 Hz stimulation can promote cerebrospinal fluid inflow and interstitial fluid outflow, enhance AQP4 polarization, and expand meningeal lymphatic vessels. Experimentally inhibiting glymphatic clearance eliminated the Aβ reduction effect, suggesting that 40 Hz rhythm may regulate metabolic waste transport through vascular pulsation and the glial-lymphatic system.

Therefore, rhythm-related photostimulation therapy mainly regulates neuroimmune responses by inducing gamma synchronization and functional connectivity remodeling, and may improve pathological load through glymphatic and vascular dynamics, thus providing a more favorable microenvironment for cognitive function.

Mitochondrial Bioenergetics, Oxidative Stress, and Neural Plasticity

Currently, the mechanism of action of PBM therapy is generally believed to involve photons in the red-near-infrared spectrum being primarily absorbed by cytochrome coxidase (CCO) in the mitochondrial respiratory chain. This absorption relieves the reversible inhibition of CCO by nitric oxide, enhancing electron transfer efficiency and thereby increasing mitochondrial membrane potential and ATP synthesis. This process is accompanied by moderate activation of reactive oxygen species/nitric oxide signaling, further triggering downstream transcription and cytoprotective pathways. De Freitas et al[52] systematically proposed the "CCO-NO dissociation-bioenergetic enhancement" model, and Kashiwagi et al[53] further pointed out from the perspective of NO signaling that PBM can enhance the bioavailability of NO, improve endothelial function and vascular tone, thus providing a crucial link for cerebral blood flow perfusion and metabolic regulation.

At the nervous system level, PBM is thought to improve cognitive function by improving mitochondrial function and energy supply, inhibiting oxidative stress and chronic neuroinflammation, and promoting synaptic plasticity and neurotrophic factor expression. Hamblin et al[54] showed the anti-inflammatory effects of PBM in various inflammatory models and its regulation of immune cell phenotypes. Yan et al[55] further emphasized that PBM can act on multiple aspects of neurovascular coupling, helping to restore metabolic matching between neurons, blood vessels, and glial cells. Therefore, PBM interventions such as transcranial or intranasal administration improve cognitive function not through a single target, but as a result of the combined effects of enhanced energy metabolism, inflammation modulation, and improved hemodynamics.

Cerebral Microcirculation, Angiogenesis, and Neurogenesis

Vascular dysfunction and reduced cerebral perfusion are considered important accompanying pathologies in the development and progression of AD, and are associated with cognitive decline, white matter damage, and impaired metabolic clearance[53] Studies suggest that PBM can improve local perfusion and optimize oxygen or glucose delivery through NO-mediated vasodilation and improved endothelial function.

Simultaneously, PBM's modulation of neurovascular coupling (NVC) may improve the matching of neural activity and blood flow response, thereby supporting task-related cognitive processing. In addition to short-term blood flow effects, some studies[55] suggest that PBM can induce angiogenesis-related signaling, promote neurogenesis and synaptic remodeling, providing a basis for longer-term cognitive function recovery.

Discussion

To facilitate interpretation of the heterogeneous evidence identified in this review, we summarized the current application framework of photostimulation therapy in Alzheimer's disease into an integrated conceptual figure As shown in Figure 2, the therapeutic landscape can be understood from three interconnected dimensions: the practical intervention pathways used in clinical and care settings, the wavelength- or modality-specific biological mechanisms, and the closed-loop process linking assessment, parameter selection, intervention delivery, multidimensional outcome evaluation, and subsequent optimization. This integrative framework helps explain why photostimulation therapy is increasingly being viewed not merely as a strategy for improving cognitive scores, but as a broader management approach targeting cognition, sleep/circadian rhythm regulation, and neuropsychiatric or functional outcomes in patients with Alzheimer's disease.

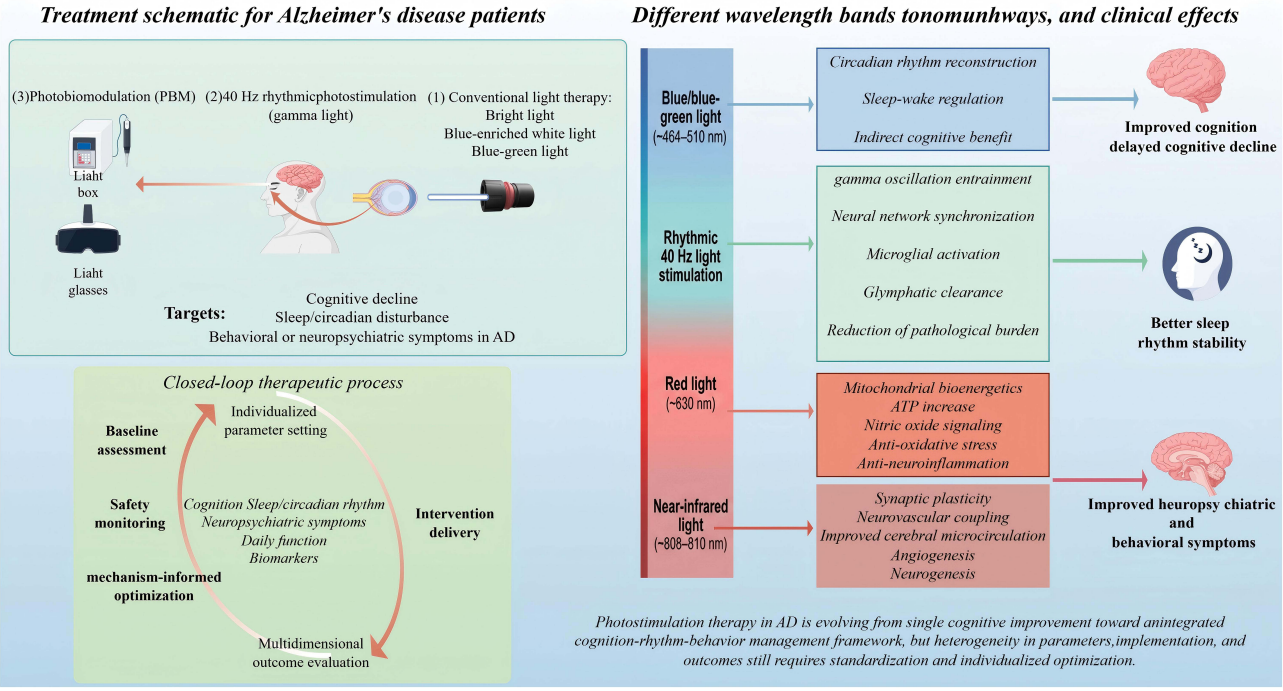

Figure 2 The pathways and clinical effects of photostimulation therapy in Alzheimer's disease.

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The Application of Photostimulation Therapy in Cognitive Intervention for AD Patients is Gradually Shifting from Focusing Solely on Cognitive Improvement to Evaluating Comprehensive Outcome Indicators

In previous studies, photostimulation therapy often used cognitive scales such as MMSE and ADAS-Cog as primary outcome measures. In recent years, researchers have emphasized the interplay between cognitive decline in AD patients and sleep-wake rhythm disturbances, daytime sleepiness, depression, and behavioral and psychological symptoms of dementia (BPSD). Using a single scale to assess treatment efficacy may not reflect the comprehensive effects of the intervention in a care setting. A meta-analysis of randomized controlled trials by Aini et al[47] showed that photostimulation therapy in dementia patients not only improved cognitive function but also potentially improved sleep and reduced depression and neuropsychiatric behavioral problems, indicating a comprehensive effect and beneficial impact on patients. However, this multidimensional efficacy evaluation is not consistently observed in all studies. A systematic review and meta-analysis by Lu et al[56] also observed improvements in cognitive outcomes in AD patients, but no consistent significant differences were found in BPSD-related indicators such as NPI and some objective sleep indicators, suggesting that the choice of outcome measures and baseline characteristics of the population significantly affect the evaluation of intervention effects.

The American Academy of Sleep Medicine (AASM), in its guidelines for circadian rhythm sleep-wake disorders,[14] suggests considering photostimulation therapy for irregular sleep-wake rhythm disorders in elderly individuals with dementia. This reflects, to some extent, that the academic and clinical communities are incorporating light therapy into a discussion framework of integrated "rhythm-function-cognition" management. Therefore, future research and clinical assessments should, while retaining core cognitive scales, simultaneously include multidimensional outcome measures such as circadian rhythm, sleep quality, and neuropsychiatric symptoms to systematically elucidate the comprehensive effects of light therapy in the management of AD.

The Application of Photostimulation Therapy in AD Patients is Becoming Increasingly Diverse, but There is Heterogeneity in the Reported Intervention Content and Parameters

(1) The qualifications of operators and implementation teams vary across different studies and settings. Compared to traditional lighting environment interventions, photostimulation therapy interventions often require precise settings of wavelength, illuminance, power density, frequency, and exposure time, as well as equipment calibration, compliance monitoring, and adverse reaction management. This places higher demands on the training and standardized procedures of the implementation team. Furthermore, transcranial/intranasal PBM and other pathways involve more complex delivery methods and safety monitoring. The lack of unified training standards and qualification requirements can easily lead to variations in implementation, thus affecting efficacy assessment and safety evaluation. (2) Standardized operating procedures still have gaps. Current research shows significant variations in key parameters and reporting methods, including spectrum, wavelength, illuminance, power density, frequency, single session duration, cumulative dose, treatment length, irradiation time, delivery route, intervention setting, control conditions, and compliance records. Even within the same category of intervention, different studies do not consistently define and quantify dosage, making it difficult to directly compare research conclusions. Future research should further clarify standardized procedures for photostimulation therapy interventions, establishing unified standards for core parameters, calibration and monitoring methods, compliance recording, adverse reaction management, and discontinuation criteria to reduce heterogeneity and improve the quality of evidence.

Heterogeneity Analysis of Intervention Methods, Study Design, and Outcome Indicators in Studies Related to Photostimulation Therapy

(1) The heterogeneity of existing studies is reflected in the intervention methods. Photostimulation therapy is not a single technology, but includes multiple forms such as bright phototherapy, blue-enriched white light/blue-green light, 40 Hz rhythmic visual stimulation, and transcranial or intranasal photobiological modulation. Different studies have significant differences in wavelength, illuminance or power density, frequency, single intervention duration, treatment course length,

irradiation phase, delivery route, and whether it is combined with other treatments, making the actual exposure conditions of photostimulation therapy in different studies not entirely comparable. A systematic review has pointed out[16] that phototherapy studies lack a unified approach in terms of light source type, dose, irradiation duration, and timing, which not only increases the complexity of result interpretation but also limits the generalization of optimal intervention parameters. At the same time, the methodological guidelines for non-pharmacological intervention studies emphasize[57,58] that intervention materials, implementation procedures, parameter settings, implementers, and compliance information should be reported as completely as possible to improve the reproducibility and clinical translatability of the study. Therefore, in addition to exploring the advantages of different photostimulation pathways, future studies should promote the standardized reporting of key parameters and intervention procedures.

(2) Heterogeneity in study design is an important factor affecting the interpretation of existing evidence. Currently, the field is still dominated by exploratory research, with randomized controlled trials, non-randomized controlled trials, pre- and post-control studies and case reports coexisting. Different studies have significant differences in sample size, control settings, blinding implementation, follow-up duration and combined intervention control. More importantly, Alzheimer's disease itself has significant heterogeneity in clinical phenotype, pathological burden, progression rate and comorbidities, which makes it difficult to directly compare treatment responses between different studies.[59] Current methodological research on the evolution of randomized controlled trial design for Alzheimer's disease further shows that[60] trials in this field are gradually shifting towards larger samples, long-term follow-up and refined stratified designs to improve the ability to detect slow and subtle changes in efficacy. Therefore, for non-pharmacological interventions such as photostimulation therapy, future research should not only expand the sample and extend the observation period, but also pay more attention to the stratified control of disease stage, pathological state, care scenario and combined treatment.

(3) The heterogeneity of outcome indicators increases the difficulty of integrating different research results. Although most studies use scales such as MMSE, ADAS-Cog, and MoCA to assess cognitive changes, different scales are inconsistent in terms of measurement dimensions, applicable stages, and sensitivity to changes. The meaning of "cognitive improvement" is not exactly the same in different studies. The latest systematic review shows that[61] the sensitivity of commonly used progression indicators in Alzheimer's disease clinical trials to changes varies, and a single cognitive scale fails to fully reflect the disease process or intervention benefits. At the same time, the expert framework on "clinically meaningful outcomes" in Alzheimer's disease clinical trials points out that[62] outcome evaluation should not be limited to the cognitive scale itself, but should also be combined with functional status, behavioral symptoms, and outcomes that patients and caregivers are truly concerned about. Core outcome studies of non-pharmacological interventions for dementia also suggest that[63] there is still a certain misalignment between existing measurement tools and outcomes that stakeholders value. Therefore, subsequent studies should further strengthen the combined reporting of function, sleep/circadian rhythm, mental and behavioral symptoms, and patient-centered outcomes on the basis of retaining core cognitive outcomes, so as to improve the comparability and clinical interpretability between studies.

Limitations

This review systematically summarizes the current application and mechanisms of photostimulation therapy in cognitive function intervention for Alzheimer's disease patients, but certain limitations remain. First, this study only includes Chinese and English literature, excluding relevant studies in other languages, potentially introducing language bias and affecting the comprehensiveness of the evidence retrieval. Second, the overall sample size of the included studies is relatively limited, with some studies still primarily employing small-sample exploratory designs, and a few only reporting results from Alzheimer's disease subgroups, which to some extent limits the stability of the research conclusions. Furthermore, the included studies exhibit significant heterogeneity in study design, intervention methods, and outcome indicators, increasing the difficulty of cross-study comparisons and suggesting that current evidence is more suitable for mapping research profiles, identifying potential intervention signals, and summarizing research trends, rather than making definitive judgments on the relative efficacy of different photostimulation modalities. Finally, the nature of this review study dictates that it primarily focuses on the systematic review of evidence and the identification of research gaps, rather than the quantitative synthesis of intervention effects. Therefore, this study did not conduct a formal risk of

bias or methodological quality assessment of the included literature, and further validation is needed in future high-quality studies with rigorous design, sufficient samples, and standardized reporting.

Conclusion

Photostimulation therapy, with its advantages of being non-invasive, highly manageable, generally well-tolerated, and easily applicable in both clinical and home settings, has demonstrated significant value in the cognitive function intervention of AD patients. Currently, research in this field is shifting from focusing solely on improvements in cognitive scales to a comprehensive assessment of "cognition-sleep/circadian rhythm-neurobehavioral symptoms" outcomes. However, the existing evidence is still in the exploratory stage. The included studies are highly heterogeneous in terms of study design, intervention methods, parameter settings and outcome indicators, and some studies have limited sample sizes, which to some extent limits the cross-comparison of results and their clinical application. Future research should further refine research design and reporting standards, prioritizing multi-center, large-sample, rigorously controlled, and well-followed randomized controlled trials to clarify the applicable boundaries and optimal parameter combinations for different population stages, scenarios, and types of photostimulation. Simultaneously, research can incorporate objective rhythm indicators, neurophysiological or imaging indicators, and biomarkers. When necessary, symptom network analysis or hierarchical models can be introduced to identify key symptoms and interventional points at different stages, thereby developing more targeted and individualized photostimulation intervention plans to improve intervention efficacy and continuously enhance the scientific validity and application value of photostimulation therapy in the cognitive function of Alzheimer's patients.

Data Sharing Statement

All data relevant to the study are included in the article or available upon reasonable request from the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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