

Perspective

A Clearance-Repair-Activation Framework for Alzheimer's Disease: A Perspective and Validation Roadmap

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ABSTRACT: Alzheimer's disease (AD) is a heterogeneous clinicobiological syndrome involving impaired protein clearance, neuroinflammation, synaptic and cellular injury, network dysfunction, and progressive functional decline. Amyloid-directed antibodies provide an evidence-based treatment backbone for selected patients with early symptomatic AD, but adjunctive strategies may be needed to address other disease mechanisms. This Perspective proposes a clearance-repair-activation framework for hypothesis-driven research. Clearance includes established pharmacological treatment and risk management as well as investigational drainage approaches; lymphaticovenous anastomosis (LVA) and deep cervical lymphaticovenous anastomosis (dcLVA) are considered only as research options within this broader domain. Repair includes neural stem-cell (NSC), induced pluripotent stem-cell-derived, engineered-cell, and secretome-based strategies, for which AD evidence remains predominantly preclinical. Activation encompasses invasive and non-invasive stimulation, sensory entrainment, neurofeedback, brain-computer interface (BCI) monitoring, and cognitive rehabilitation; BCI is positioned mainly as an experimental monitoring and adaptive rehabilitation platform. We define falsifiable links between clearance and repair readiness and between repair markers and activation responsiveness, consider adaptive and parallel alternatives to fixed sequencing, and integrate disease stage, heterogeneity, regulation, and combination-trial design. Informatics is limited to trial infrastructure and safety governance. The validation roadmap specifies success criteria, stop rules, interaction testing, clinically meaningful outcomes, and long-term surveillance.

Keywords: Alzheimer's disease, clearance-repair-activation, lymphaticovenous anastomosis, neural stem cells, brain-computer interface, validation roadmap

1. Scope and Clinical Context

AD is now understood through biomarker-defined and stage-aware models that encompass amyloid, tau, neurodegeneration, vascular injury, inflammation, synaptic failure, and network dysfunction [1,2]. Lecanemab and donanemab have demonstrated clinical efficacy in selected patients with early symptomatic AD

and provide the current disease-modifying treatment backbone in that setting [3,4]. The proposed framework asks whether future clearance, repair, and activation interventions can add value as adjunctive, staged, or combination strategies within contemporary care.

Clearance, repair, and activation denote three biological tasks: modifying disease-relevant molecular, inflammatory, vascular, or drainage burdens; restoring trophic, synaptic, cellular, or microenvironmental

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capacity; and engaging residual or repaired circuits through neuromodulation, neurofeedback, sensory entrainment, or rehabilitation. Their proposed dependencies are hypotheses that require direct testing.

2. Evidence Hierarchy and Relation to Multimodal AD Care

Claims are classified as human clinical evidence, animal-model evidence, computational or engineering evidence, mechanistic inference, or proposed hypothesis. Animal studies can support mechanisms but may not predict human efficacy, whereas computational methods can

organize data and generate predictions but cannot replace biological validation.

The framework extends, but is more specific than the general principle that multifactorial AD may require combination therapy [5]. Current multimodal care includes symptomatic drugs, amyloid-directed therapy, vascular-risk management, sleep and lifestyle interventions, cognitive rehabilitation, and supportive care. The proposed advance is to test whether clearance changes improve repair readiness, whether repair markers modify activation response, and whether combinations add value beyond their individual components (Fig. 1).

Clearance-repair-activation framework for Alzheimer's disease

Arrows show a proposed testing sequence, not an established causal pathway or proven therapeutic effect.

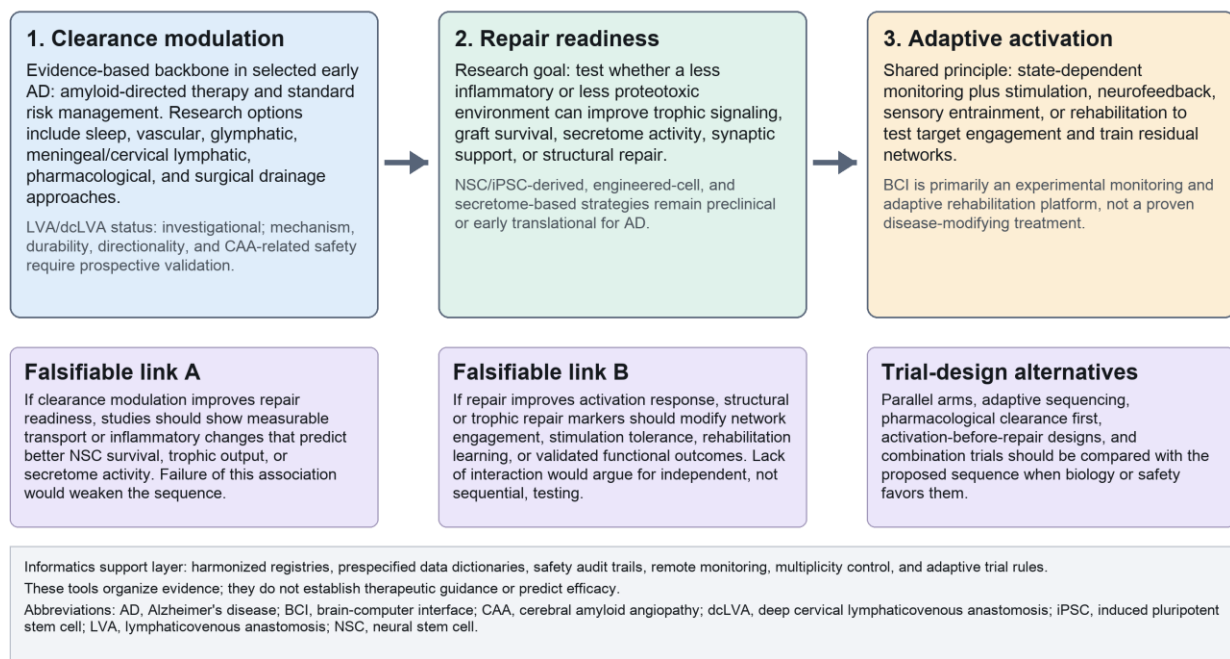


Figure 1. Clearance-repair-activation testing framework. Arrows represent a proposed research sequence and not established biological causality or proven therapeutic efficacy.

Table 1 summarizes the maturity of major evidence domains. A central rule is that the evidence label should travel with the claim. A cerebrospinal fluid (CSF) biomarker change should not be described as removal of total parenchymal amyloid or tau unless supported by imaging, tissue, or validated quantitative evidence. Likewise, target engagement, decoding accuracy, or network entrainment should not be presented as clinical efficacy unless accompanied by prespecified clinical and functional outcomes.

3. Biological Rationale and Falsifiable Intermediate Links

The framework is biologically meaningful only if its intermediate links are testable. The first hypothesis is that reducing inflammatory or proteotoxic stress, improving drainage-related transport markers, or stabilizing vascular and sleep-related clearance conditions improves repair readiness, measured by NSC survival, trophic output, secretome activity, or synaptic-support markers. Support would require prespecified clearance measures to predict repair endpoints after adjustment for disease stage, amyloid and tau burden, vascular burden, apolipoprotein

E (APOE) genotype, and background treatment; unchanged repair outcomes despite verified clearance target engagement would weaken the hypothesis.

Table 1. Evidence classification for the clearance-repair-activation framework.

Domain	Current support	Evidence class	Key limitation and implication
AD as a multifactorial and staged syndrome	Biomarker frameworks, anti-amyloid trials, and clinical literature support stage-aware care.	Human clinical evidence	Supports adjunctive and combination research but does not validate a new sequence.
Established and investigational clearance modulation	Amyloid-directed antibodies have trial evidence in selected early AD; glymphatic, meningeal lymphatic, sleep, vascular, pharmacological, and drainage concepts have variable evidence.	Human clinical evidence for selected antibodies; animal, imaging, and mechanistic evidence for many drainage concepts	Each clearance method requires its own target-engagement and safety evidence; CSF change must be separated from parenchymal protein removal.
LVA/dcLVA for AD	Uncontrolled clinical reports and mechanistic proposals exist, but sham-controlled randomized evidence is lacking and recent regulatory restrictions have been described.	Preliminary human observations; mechanistic inference; regulatory concern	Should be treated as one investigational clearance method, not as an established first component.
Repair by NSC or induced pluripotent stem-cell-derived cells, engineered cells, or secretome strategies	AD models suggest trophic, synaptic, and immunomodulatory effects; translational manufacturing and safety literature is expanding.	Animal-model and early translational evidence	Human AD efficacy, dose, graft survival, immunogenicity, ectopic growth, tumor risk, and durability remain unresolved.
Activation through DBS, non-invasive stimulation, sensory entrainment, neurofeedback, BCI, and rehabilitation	DBS has early AD trial experience; non-invasive and behavioral approaches vary widely; BCI evidence in AD is mainly experimental.	Early human, engineering, and rehabilitation evidence	Modalities should be subdivided by mechanism, invasiveness, risk, regulatory status, and endpoint.
Informatics, digital biomarkers, federated learning, and digital twins	Digital-health and federated-learning literature supports data harmonization, monitoring, and privacy-preserving research.	Computational and engineering evidence	Useful for trial infrastructure and safety audit; not proof of treatment guidance or efficacy prediction.
Complete clearance-repair-activation framework	Derived from component-level rationale and explicit intermediate hypotheses.	Proposed hypothesis	No preclinical or clinical validation of the complete sequence; should advance only through staged testing with stop rules.

The second hypothesis is that structural or trophic repair increases residual-network responsiveness to stimulation, neurofeedback, sensory entrainment, or cognitive rehabilitation. Readouts could include synaptic markers, trophic factors, electrophysiological plasticity, connectivity, rehabilitation learning curves, and validated functional scales. The critical test is an interaction: activation after repair should produce a larger target-engagement or functional signal than activation alone. Absence of interaction would favor independent or parallel evaluation.

A clearance-repair-activation order is biologically plausible if a less proteotoxic or inflammatory environment improves repair and if trophic or synaptic readiness enhances activation response, but the order should remain a design variable. Alternatives include pharmacological clearance before investigational drainage, neuromodulation or rehabilitation before cell therapy to identify residual network capacity, parallel intervention when delay is undesirable, and adaptive resequencing after nonresponse, intolerance, or safety signals.

4. Clearance Modulation and the Investigational Status of LVA/dcLVA

The clearance component should be interpreted broadly. Brain solute transport is influenced by perivascular exchange, astroglial water handling, sleep, vascular pulsatility, meningeal lymphatics, cervical lymphatic drainage, blood-brain barrier function, peripheral immune state, and disease-modifying pharmacology [6-11]. For selected early AD patients, amyloid-directed antibodies already provide a clinically tested clearance-oriented intervention [3,4]. Future surgical, pharmacological, sleep-related, vascular, or lymphatic strategies should therefore be evaluated as adjunctive or comparator approaches rather than as replacements for established therapy.

LVA and dcLVA are research approaches within this wider clearance field. Uncontrolled reports and mechanistic proposals do not establish efficacy, durable flow directionality, or clinical benefit in AD. Recent literature and official Chinese regulatory communication describe restrictions on applying deep cervical lymphatic or lymph-node venous anastomosis to AD because efficacy and safety remain insufficiently established [12-16]. This regulatory status constrains translational feasibility.

Mechanistic studies should avoid converting hydraulic analogies into clinical proof. Equations involving pressure gradients, hydraulic resistance, or tissue tortuosity may generate predictions, but they do not show that an operation changes human intracranial or extracranial transport in a sustained and directional manner. Prospective studies would need anatomical lymphatic mapping, venous pressure assessment, standardized sleep and vascular-state recording, serial CSF sampling, amyloid and tau imaging when appropriate, and explicit analysis of lymphatic valves, venous pressure variation, vascular pulsatility, aquaporin-4 (AQP4) polarization, cerebral amyloid angiopathy (CAA), antithrombotic therapy, and anti-amyloid antibody exposure.

CAA is especially important because it may alter both transport interpretation and procedural safety. APOE epsilon4 status, microhemorrhage burden, superficial siderosis, anticoagulant or antiplatelet use, and recent or planned amyloid-directed therapy may affect hemorrhagic risk and amyloid-related imaging abnormality risk. A clearance trial should therefore define CAA-related exclusions, use independent safety review, and distinguish CSF concentration changes from total brain amyloid or tau removal.

5. Repair Strategies: From NSC Rationale to Modern Regenerative Constraints

The repair component addresses the possibility that clearance alone may be insufficient after synaptic loss, neuronal dysfunction, and network disconnection have progressed. NSC transplantation improved cognition in transgenic AD models through trophic and synaptic mechanisms, including brain-derived neurotrophic factor (BDNF)-dependent effects, and human NSC transplantation has shown biological activity in animal models [20,21]. These findings justify continued research, but they do not establish neuronal replacement, circuit reconstruction, immune remodeling, or cognitive recovery in human AD.

The NSC field has also changed since early transplantation studies. Relevant translational questions now include induced pluripotent stem-cell-derived neural progenitors, engineered cells with controlled trophic or immunomodulatory output, extracellular-vesicle or secretome-based approaches, scalable manufacturing, batch comparability, potency assays, genomic stability, immunogenicity, route of delivery, biodistribution, graft persistence, ectopic growth, and long-term tumor surveillance [22,23]. These issues are not technical details that can be deferred indefinitely; they determine whether a repair strategy is reproducible, regulatable, and interpretable.

Direct evidence that clearance modulation improves graft survival or secretome effects is lacking. Studies should compare repair after verified clearance target engagement with repair alone using prespecified measures of graft persistence, cell phenotype, trophic output, local inflammation, synaptic support, imaging safety, and stage-appropriate function.

6. Activation: Subdividing Heterogeneous Modalities

Activation includes modalities with distinct mechanisms, risks, and endpoints. Deep brain stimulation (DBS) is invasive and has early AD trial experience, including fornix-targeted studies [24,25], whereas non-invasive stimulation, sensory entrainment, neurofeedback, and cognitive rehabilitation require separate evaluation. BCI systems may record neural states, decode electrophysiological features, and guide adaptive feedback or rehabilitation, but AD-specific therapeutic evidence is limited.

The shared principle that justifies grouping these methods is adaptive functional engagement: measuring a neural or behavioral state, applying a stimulation or training rule, and testing whether target circuits show reproducible engagement with acceptable risk. This principle permits subdivision rather than conflation.

Invasive stimulation should be evaluated for surgical and neuropsychiatric risk; non-invasive stimulation for dosing, durability, and sham control; sensory entrainment for state engagement and adherence; neurofeedback and BCI for decoding reliability and training transfer; and cognitive rehabilitation for task learning and functional generalization [26,27].

BCI is positioned primarily as an experimental monitoring and adaptive rehabilitation platform. Signal quality, decoding stability, connectivity change, stimulation tolerance, training performance, and adherence are target-engagement measures, not clinical efficacy. Efficacy assessment should emphasize the Clinical Dementia Rating-Sum of Boxes (CDR-SB), validated activities-of-daily-living measures, neuropsychiatric and caregiver-relevant outcomes, and safety rather than relying mainly on the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA).

7. Stage-Specific Selection and AD Heterogeneity

Patient selection should be stage specific and explicitly hypothetical. In early symptomatic AD with biomarker confirmation, the most plausible research context is adjunctive testing on the background of evidence-based therapy, with careful attention to anti-amyloid eligibility, amyloid-related imaging abnormality (ARIA) risk, and CAA. Clearance modulation or activation may be studied as add-on target engagement or functional-support strategies; invasive surgery or cell therapy would require a high safety bar. In mild-to-moderate AD, repair and adaptive rehabilitation questions may be more relevant, but declining capacity, comorbidity, and caregiver burden become increasingly important. In advanced neurodegeneration, invasive approaches are less likely to have a favorable benefit-risk balance, and research should focus on safety, comfort, caregiver outcomes, and clearly justified target engagement rather than disease reversal.

AD heterogeneity should be embedded into eligibility, stratification, and interpretation. APOE genotype, CAA, cerebrovascular disease, Lewy body co-pathology, limbic-predominant age-related transactive response DNA-binding protein 43 (TDP-43) encephalopathy, hippocampal sclerosis, frailty, renal or cardiovascular disease, immunosuppression, and medication burden may all influence safety and response [17-19]. These variables can determine whether a participant is suitable for anti-amyloid therapy, a drainage study, cell therapy, invasive stimulation, or non-invasive rehabilitation. They also affect interpretation of negative results because non-AD co-pathology may obscure target engagement even when a component intervention performs as intended.

8. Informatics as Trial Infrastructure, Not Therapeutic Guidance

Digital biomarkers, knowledge graphs, federated learning, audit trails, and digital twins may support registry design, data harmonization, longitudinal monitoring, privacy-preserving collaboration, prespecified analysis, and safety review [28-31]. Current evidence does not support their use to select individual treatment, predict efficacy, or optimize sequencing. Informatics is therefore treated as trial infrastructure and safety governance, with a harmonized registry as a more realistic near-term goal than a predictive digital twin.

9. Validation Roadmap and Combination-Trial Statistics

Because the components differ in maturity and risk, progression should require predefined success criteria, stop rules, and independent safety review (Table 2). Reproducible change requires directionally consistent prespecified effects across independent sites or cohorts with confidence intervals and defined missing-data handling. Safety thresholds should be benchmarked against comparable interventions. Graft survival should be supported by convergent imaging, molecular, histological when feasible, and safety evidence. Added value requires a controlled biological or functional signal beyond the best-performing component.

Pairwise combination testing requires a statistical plan before entering a full sequence. Factorial designs can estimate main effects and interactions when components can be assigned independently. Sequential multiple-assignment randomized trials may be appropriate when response to one stage determines the next stage. Multiplicity control is required because biomarker, target-engagement, safety, and functional endpoints will be tested in parallel. Sample size should be based on the interaction or added-benefit estimate, not only on component-level effects. Adverse-event attribution should be prespecified because surgical, cellular, device, pharmacological, and rehabilitation components may produce overlapping complications.

Later-phase trials should prioritize clinically meaningful and functional outcomes. MMSE and MoCA may remain descriptive or secondary cognitive measures, but they should not be treated as proof of structural neural recovery. Outcomes such as CDR-SB, activities of daily living, neuropsychiatric symptoms, caregiver burden,

safety, and long-term functional trajectory are more relevant for regulatory and clinical interpretation.

Table 2. Staged validation roadmap with operational success criteria and stop rules.

Stage	Primary question	Operational success criteria	Stop rules
1. Clearance mechanism	Does the selected clearance method engage a plausible target?	Prespecified transport, imaging, vascular, sleep, lymphatic, CSF, or amyloid/tau measures change in the expected direction in at least two independent cohorts or sites; CSF and parenchymal endpoints are reported separately.	No directional signal, inconsistent measurements, excessive variability, or inability to separate concentration change from true burden change.
2. Clearance safety	Can safety be confirmed for the intended AD subgroup?	Serious adverse events remain below predefined thresholds; CAA, APOE, anticoagulation, anti-amyloid exposure, and vascular-risk exclusions are validated by independent monitoring.	Hemorrhage, venous complications, infection, ARIA interaction, or cognitive/functional worsening exceeds thresholds.
3. Repair feasibility	Can the repair product be manufactured, delivered, and monitored reproducibly?	Potency, identity, sterility, genomic stability, dose, delivery route, biodistribution, graft/secretome persistence, immune monitoring, and tumor surveillance are prespecified and independently audited.	Poor viability or survival, ectopic growth, uncontrolled immune reaction, manufacturing drift, or absent biological signal.
4. Activation target engagement	Which activation modality engages a target network with acceptable risk?	Sham or active-control design shows reproducible target engagement, training transfer, adherence, and tolerability; clinical efficacy endpoints are not inferred from engagement alone.	Device instability, neuropsychiatric or neurological adverse events, no engagement signal, or unacceptable participant burden.
5. Pairwise combinations	Does a two-component combination add value beyond components?	Factorial or sequential randomized designs test main effects and interactions with prespecified multiplicity control, adequate sample size, and adverse-event attribution.	No additive or interaction signal, attribution becomes impossible, or combined toxicity exceeds component-level expectations.
6. Full framework feasibility	Can the complete framework be implemented without excessive burden?	Protocol adherence, staged eligibility, component-level target engagement, caregiver feasibility, and safety remain acceptable before any efficacy claim.	Failure of any essential component, excessive dropout, excessive burden, or unfavorable risk-benefit balance.
7. Biomarker-stratified randomized trial	Does the selected strategy improve meaningful outcomes?	Randomization is stratified by stage, biomarkers, APOE/CAA risk, and background therapy; blinded assessment includes CDR-SB, activities of daily living, neuropsychiatric, caregiver, biomarker, and safety outcomes with confidence intervals.	Futility, harm, lack of clinically meaningful difference, or loss of equipoise.
8. Long-term surveillance	Are benefits durable, safe, and economically defensible?	Registry follow-up captures delayed tumor, immune, vascular, device, cognitive, functional, cost-effectiveness, and access-equity outcomes.	Late safety signal, non-durable benefit, unsustainable cost, or inequitable access.

10. Ethical, Regulatory, and Reporting Safeguards

Participants with AD may have fluctuating decision-making capacity, and caregivers may feel pressure to

pursue experimental interventions. Consent should address capacity, caregiver understanding, uncertainty, independent safety oversight, and withdrawal rules, while

avoiding language that implies established efficacy or neural restoration.

Regulatory review should proceed component by component. Surgical drainage, cellular therapy, invasive or adaptive stimulation, artificial intelligence (AI)-supported data systems, and privacy-preserving networks may each require separate manufacturing, device, surgical, data-protection, and adverse-event reporting pathways. Conflict-of-interest statements should cover LVA centers, cell-product developers, BCI or stimulation manufacturers, software vendors, data-platform operators, and any commercialization interests.

Reporting should include baseline values, sample size, comparator, follow-up duration, confidence intervals, missing-data handling, adverse-event definitions, target-engagement endpoints, clinical efficacy endpoints, and negative or conflicting results. Figures and tables should label claims as clinically demonstrated, preclinically supported, computationally proposed, mechanistic inference, or hypothesis.

11. Conclusion

The clearance-repair-activation framework is a stage-aware research hypothesis. Its value will depend on component-level target engagement and safety, reproducible evidence for the proposed inter-stage links, and controlled demonstration that combinations add biological or functional benefit beyond existing evidence-based AD care.

Conflict of Interest

The authors declare that they have no competing financial or non-financial interests related to this manuscript.

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AI Statement

The authors used OpenAI Codex [exact model/version, accessed in 2026] for English-language editing, reducing repetition, manuscript organization, and typography/layout adjustments for Figure 1. The authors reviewed all AI-assisted changes and take full responsibility for the final content.

References

- [1] Alzheimer's Association (2026). 2026 Alzheimer's disease facts and figures. *Alzheimers Dement*, 22:e71345.
- [2] Jack CR Jr, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. (2024). Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*, 20:5143-5169.
- [3] van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. (2023). Lecanemab in early Alzheimer's disease. *N Engl J Med*, 388:9-21.
- [4] Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. (2023). Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*, 330:512-527.
- [5] Cummings JL, Zhou Y, Yang Y, Zhong K, Fonseca J, Osse AL, et al. (2026). Alzheimer's disease drug development pipeline: 2026. *Alzheimers Dement (N Y)*, 12:e70251.
- [6] Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med*, 4:147ra111.
- [7] Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. (2015). Structural and functional features of central nervous system lymphatic vessels. *Nature*, 523:337-341.
- [8] Da Mesquita S, Louveau A, Vaccari A, Smirnov I, Cornelison RC, Kingsmore KM, et al. (2018). Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature*, 560:185-191.
- [9] Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, et al. (2014). Impairment of paravascular clearance pathways in the aging brain. *Ann Neurol*, 76:845-861.
- [10] Holter KE, Kehlet B, Devor A, Sejnowski TJ, Dale AM, Omholt SW, et al. (2017). Interstitial solute transport in 3D reconstructed neuropil occurs by diffusion rather than bulk flow. *Proc Natl Acad Sci U S A*, 114:9894-9899.
- [11] Ray LA, Iliff JJ, Heys JJ (2019). Analysis of convective and diffusive transport in the brain interstitium. *Fluids Barriers CNS*, 16:6.
- [12] National Health Commission of China (2025). Notice on the prohibition of deep cervical lymphaticovenous anastomosis for the treatment of Alzheimer's disease, No. 282. (in Chinese).
- [13] Li G, Jiao S, Zhou Y, Cheng X (2026). Deep cervical lymphaticovenous anastomosis for Alzheimer's disease: theoretical foundations, regulatory suspension, and translational challenges. *Front Aging*, 7:1849207.
- [14] Zhang R, Liu YY, Xia X, Li X (2025). Unvalidated efficacy and significant risks hinder clinical use of deep cervical lymphatic-venous anastomosis for Alzheimer's disease. *Front Aging Neurosci*, 17:1671741.
- [15] Tang C, Zheng X, Li H, et al. (2025). Deep cervical lymphatic-venous anastomosis in dementia: a clinical and mechanistic evaluation. *Int J Surg*, 112:9002-9014.

- [16] Tu WJ, Li J, Meng F (2025). From enthusiasm to evidence: advancing scientific validation of deep cervical lymphatic-venous anastomosis for Alzheimer's disease. *Int J Surg*, 111:9869-9871.
- [17] Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ (2020). Cerebral amyloid angiopathy and Alzheimer disease: one peptide, two pathways. *Nat Rev Neurol*, 16:30-42.
- [18] Robinson JL, Lee EB, Xie SX, Rennert L, Suh E, Bredenberg C, et al. (2018). Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. *Brain*, 141:2181-2193.
- [19] Nelson PT, Dickson DW, Trojanowski JQ, Jack CR, Boyle PA, Arfanakis K, et al. (2019). Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. *Brain*, 142:1503-1527.
- [20] Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Muller FJ, Loring JF, et al. (2009). Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. *Proc Natl Acad Sci U S A*, 106:13594-13599.
- [21] McGinley LM, Kashlan ON, Bruno ES, Chen KS, Hayes JM, Kashlan SR, et al. (2018). Human neural stem cell transplantation improves cognition in a murine model of Alzheimer's disease. *Sci Rep*, 8:14776.
- [22] Attaluri S, Jaimes Gonzalez J, Kirmeni M, Vogel AD, Upadhy R, Kodali M, et al. (2023). Intranasally administered extracellular vesicles from human induced pluripotent stem cell-derived neural stem cells quickly incorporate into neurons and microglia in 5xFAD mice. *Front Aging Neurosci*, 15:1200445.
- [23] Aboody K, Capela A, Niazi N, Stern JH, Temple S (2011). Translating stem cell studies to the clinic for CNS repair: current state of the art and the need for a rosetta stone. *Neuron*, 70:597-613.
- [24] Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, et al. (2010). A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol*, 68:521-534.
- [25] Lozano AM, Fosdick L, Chakravarty MM, Leoutsakos JM, Munro C, Oh E, et al. (2016). A phase II study of fornix deep brain stimulation in mild Alzheimer's disease. *J Alzheimers Dis*, 54:777-787.
- [26] Grover S, Wen W, Viswanathan V, Gill CT, Reinhart RMG (2022). Long-lasting, dissociable improvements in working memory and long-term memory in older adults with repetitive neuromodulation. *Nat Neurosci*, 25:1237-1246.
- [27] Sabbagh M, Sadowsky C, Tousi B, Agronin ME, Alva G, Armon C, et al. (2020). Effects of a combined transcranial magnetic stimulation and cognitive training intervention in patients with Alzheimer's disease. *Alzheimers Dement*, 16:641-650.
- [28] Kourtis LC, Regele OB, Wright JM, Jones GB (2019). Digital biomarkers for Alzheimer's disease: the mobile/wearable devices opportunity. *NPJ Digit Med*, 2:9.
- [29] Piau A, Wild K, Mattek N, Kaye J (2019). Current state of digital biomarker technologies for real-life, home-based monitoring of cognitive function for mild cognitive impairment to mild Alzheimer disease and implications for clinical care: systematic review. *J Med Internet Res*, 21:e12785.
- [30] Rieke N, Hancox J, Li W, Milletari F, Roth HR, Albarqouni S, et al. (2020). The future of digital health with federated learning. *NPJ Digit Med*, 3:119.
- [31] Bjornsson B, Borrebaeck C, Elander N, Gasslander T, Gawel DR, Gustafsson M, et al. (2020). Digital twins to personalize medicine. *Genome Med*, 12:4.