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GLP-1 receptor agonists in neurological diseases: mechanisms and therapeutic prospects from metabolism to neuroprotection

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Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used metabolic therapies for type 2 diabetes and obesity, with well-established cardiovascular benefits. Beyond glycemic control, accumulating experimental and clinical evidence suggests that GLP-1RAs exert pleiotropic actions relevant to neurological diseases. Metabolic dysfunction, chronic inflammation, oxidative stress, mitochondrial impairment, and neurovascular injury represent convergent mechanisms that contribute to neurodegeneration, cerebrovascular pathology, and metabolism-related brain disorders. Notably, these processes overlap with pathways modulated by GLP-1 signaling across systemic and central compartments. GLP-1 receptors are expressed in neurons, glial cells, and components of the neurovascular unit, providing a biological basis for possible neurological effects. Preclinical studies suggest that GLP-1RAs can reduce neuroinflammation and oxidative stress, support mitochondrial function, and help maintain blood-brain barrier integrity. Clinical findings, however, remain inconsistent. Studies in Parkinson's disease have reported encouraging signals, but biomarker evidence for disease modification is still limited. In Alzheimer's disease, clinical trials have produced mixed or negative results. These differences may reflect disease stage, patient selection, drug-specific pharmacology, central nervous system exposure, endpoint sensitivity, and treatment duration. Overall, GLP-1RAs may influence neurological disease through metabolic, inflammatory, and vascular pathways, but their clinical role remains unsettled. Future studies should use biomarker-informed designs, prespecified neurological endpoints, appropriate drug selection, and sufficiently long follow-up to determine which patients and disease stages are most likely to benefit.

KEYWORDS

blood-brain barrier, GLP-1 receptor agonists, metabolic dysfunction, neuroinflammation, neuroprotection

1 Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used in clinical practice for the treatment of type 2 diabetes mellitus and obesity (1, 2). Beyond their established metabolic actions, robust evidence from large cardiovascular outcome trials has demonstrated that GLP-1RAs significantly reduce major adverse cardiovascular events, thereby expanding interest in their pleiotropic effects across multiple organ systems (3, 4). These findings have raised the possibility that GLP-1RAs exert clinically meaningful actions beyond glucose lowering, including potential effects on the central nervous system (5, 6).

Neurological diseases represent a leading cause of disability and mortality worldwide, yet effective disease-modifying therapies remain unavailable for many conditions, particularly neurodegenerative and cerebrovascular disorders (7). Increasing evidence indicates that metabolic dysregulation, chronic inflammation, oxidative stress, and microvascular dysfunction are central contributors to the pathogenesis of these diseases (7, 8). Notably, these pathogenic processes substantially overlap with biological pathways modulated by GLP-1RAs, providing a compelling mechanistic rationale for evaluating their therapeutic potential in neurological disorders (9, 10).

From a neurobiological perspective, the relevance of GLP-1 signaling to the nervous system is supported by the expression of glucagon-like peptide-1 receptors (GLP-1Rs) across brain regions involved in cognition, motor control, and autonomic regulation, including the hippocampus, hypothalamus, brainstem, and cerebral

cortex (5, 11). Preclinical studies suggest that GLP-1RAs can attenuate neuroinflammation, reduce oxidative stress, preserve mitochondrial function, and maintain neurovascular integrity (8, 9). Nevertheless, the degree to which these effects require direct central nervous system exposure remains uncertain, and peripheral metabolic, inflammatory, endothelial, and vagal pathways may account for a substantial component of the observed neurological effects (6, 12).

The pharmacological diversity within the GLP-1RA class is clinically important. Exenatide, liraglutide, semaglutide, dulaglutide, and newer multi-receptor incretin agonists differ in molecular structure, half-life, receptor kinetics, albumin binding, and evidence for CNS exposure. Neurological effects may therefore differ among agents, and pharmacokinetic differences may partly explain inconsistent clinical findings.

Over the past decade, a growing body of clinical and translational research has explored the role of GLP-1RAs across a spectrum of neurological disorders. In Alzheimer’s disease and Parkinson’s disease, multiple GLP-1RAs have demonstrated neuroprotective effects in experimental models, and early-phase clinical trials have reported signals of cognitive or motor benefit (3, 8, 13). In cerebrovascular disease, GLP-1RAs have been associated with reduced infarct volume and improved neurological outcomes in preclinical studies, while observational analyses and *post hoc* data from cardiovascular trials suggest potential benefits in patients at elevated vascular risk (9, 10). In addition, in metabolism-related brain disorders—such as obesity-associated cognitive impairment and diabetic encephalopathy—GLP-1RAs may confer therapeutic

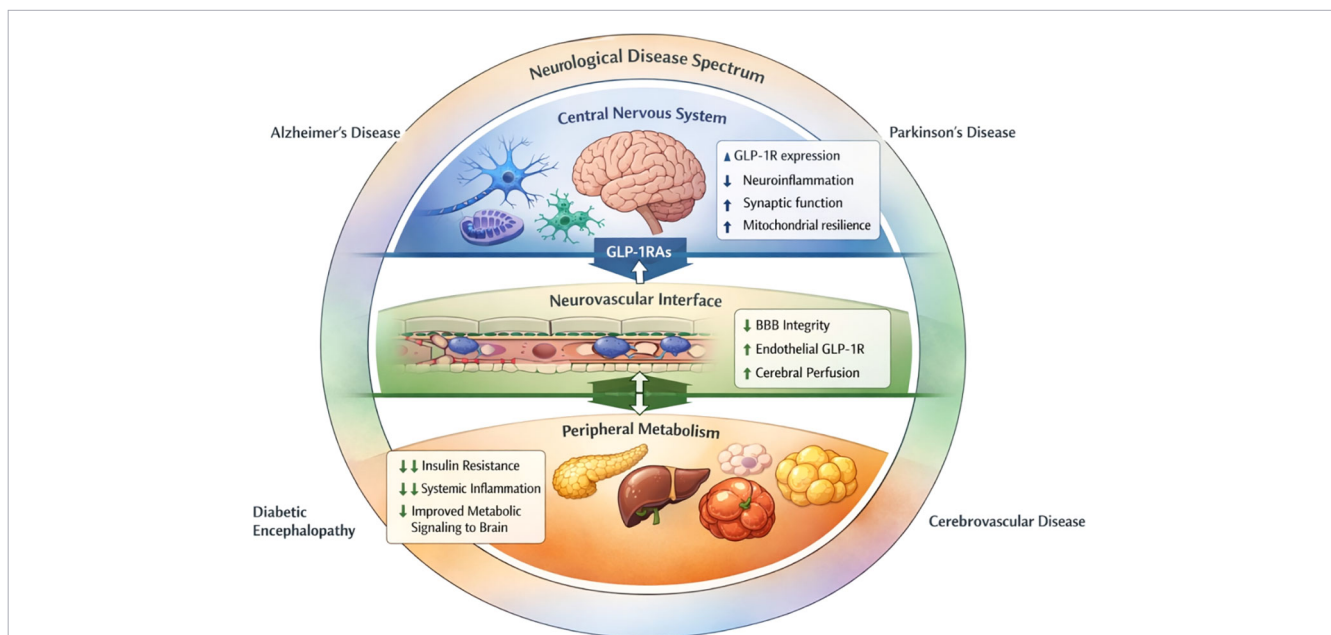


FIGURE 1
Multilevel actions of GLP-1 receptor agonists on the brain–metabolism–vascular axis. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) exert coordinated effects across central, vascular, and peripheral compartments that may collectively shape neurological vulnerability. In the central nervous system, GLP-1RAs may influence neuronal and glial function, decrease neuroinflammatory signaling, and support synaptic and mitochondrial resilience. At the neurovascular interface, GLP-1R signaling may enhance endothelial GLP-1R activity, preserve blood-brain barrier integrity, and improve cerebral perfusion. In peripheral metabolic tissues, GLP-1RAs reduce insulin resistance and systemic inflammation and may improve metabolic signaling to the brain. The arrows indicate the expected direction of change for each process. The figure summarizes possible central, neurovascular, and peripheral routes by which GLP-1RAs may affect neurological disease, without implying that direct neuronal disease modification has been established.

advantages by improving both systemic and central metabolic homeostasis (2, 7). These multilevel actions of GLP-1RAs across central, neurovascular, and peripheral metabolic compartments are illustrated in Figure 1.

Despite this growing interest, several challenges currently limit the translation of GLP-1RAs into routine neurological practice. These include heterogeneity across neurological disease entities, reliance on preclinical models that incompletely reproduce human disease, limited randomized trials with prespecified neurological endpoints, uncertainties regarding dose and treatment duration, variable blood-brain barrier penetration, and outcome measures that may be insensitive to gradual multimodal effects (13, 14). Interpretation is further complicated by *post hoc* analyses, small sample sizes, incomplete biomarker confirmation, and the tendency for positive experimental findings to receive greater attention.

In this review, we summarize current clinical and translational evidence supporting the potential use of GLP-1 receptor agonists in neurological diseases. We discuss proposed mechanisms of action relevant to clinical neurology, critically evaluate positive, neutral, and negative findings from preclinical and clinical studies, and distinguish mechanistic hypotheses from conclusions supported by clinical data. Particular attention is given to the repurposing of GLP-1RAs as therapeutic agents in neurological practice and to the limitations that must be addressed before clinical translation.

2 Physiological basis of GLP-1 receptor signaling in the central nervous system

2.1 Distribution of GLP-1 receptors in the central nervous system

The relevance of glucagon-like peptide-1 receptor agonists (GLP-1RAs) to neurological diseases is supported by the broad expression of glucagon-like peptide-1 receptors (GLP-1Rs) throughout the central nervous system (15, 16). GLP-1Rs have been identified in multiple brain regions that subservise key neurological functions, including the hypothalamus, hippocampus,

brainstem, basal ganglia, and cerebral cortex (16, 17). These regions are critically involved in energy homeostasis, cognition, motor control, autonomic regulation, and emotional processing—domains that are frequently impaired across a wide range of neurological disorders.

From a clinical perspective, GLP-1R expression in the hippocampus and cerebral cortex provides an anatomical framework for the reported effects of GLP-1RAs on cognitive function in preclinical models and early-stage clinical studies of Alzheimer's disease and other dementias (18, 19). Likewise, the presence of GLP-1Rs in the basal ganglia and brainstem supports the investigation of GLP-1RAs in movement disorders such as Parkinson's disease, in which dopaminergic neurodegeneration, neuroinflammation, and mitochondrial dysfunction play central pathogenic roles (5, 20). Expression of GLP-1Rs within hypothalamic and brainstem nuclei governing autonomic and metabolic regulation further underscores the close bidirectional relationship between systemic metabolism and central nervous system function (15, 21).

Importantly, GLP-1Rs are expressed not only in neurons but also in non-neuronal components of the central nervous system, including astrocytes, microglia, and endothelial cells of the neurovascular unit (17, 22). This broad cellular distribution suggests that GLP-1RAs may act on multiple elements of the neural microenvironment. Such multi-compartment engagement is particularly relevant in neurological diseases, where disease progression is driven by complex interactions among neurons, glial cells, and cerebral vasculature rather than by isolated neuronal dysfunction alone (22, 23).

2.2 Central and peripheral mechanisms of GLP-1RA action: implications for the blood–brain barrier

A central question in the neurological application of GLP-1RAs concerns whether a given agent directly accesses the brain or acts predominantly through peripheral and neurovascular signaling. Several GLP-1RAs have shown limited blood-brain barrier (BBB) penetration in experimental systems, but the magnitude, regional distribution, receptor occupancy, and clinical relevance of direct central exposure remain incompletely defined (24, 25). This

TABLE 1 Summary of selected clinical evidence and translational limitations for GLP-1RAs in neurological disorders.

Clinical context	Evidence signal	Main limitation	Implication for this review
Alzheimer's disease	Early liraglutide studies and phase 2b data suggest biological signals, whereas semaglutide EVOKE/EVOKE+ did not meet primary cognitive endpoints (64–66).	Disease stage, biomarker selection, endpoint sensitivity, and uncertainty about direct CNS target engagement.	AD remains a plausible but unproven indication.
Parkinson's disease	Exenatide studies reported sustained motor signals, but NLY01 did not demonstrate clear efficacy in early untreated PD (72, 73, 76).	Limited biomarker confirmation makes it difficult to distinguish symptomatic benefit from disease modification.	PD remains promising, but current evidence is not definitive.
Ischemic stroke and vascular prevention	Meta-analyses of cardiovascular outcome trials suggest reduced stroke risk in metabolic populations (88, 89).	No dedicated randomized evidence establishes acute neuroprotection after stroke onset.	Claims should emphasize prevention and vascular risk modulation rather than acute treatment.
Cerebral small vessel disease and vascular cognitive impairment	Mechanistic rationale is strong because GLP-1RAs affect endothelial inflammation, metabolism, and BBB integrity.	Direct disease-specific clinical trials and validated neurovascular endpoints are sparse.	Future work should use imaging and biomarker endpoints.

uncertainty is particularly important when extrapolating high-dose animal studies or intracerebral readouts to human clinical trials. The key clinical contexts, evidence signals, translational limitations, and implications discussed in this review are summarized in Table 1.

Current evidence therefore supports a mixed model of action. Direct mechanisms may involve limited BBB transport or access to circumventricular structures such as the area postrema, whereas indirect mechanisms include reduced peripheral inflammation, improved endothelial function, altered adipokine and insulin signaling, and vagal afferent activation (21, 24, 26, 27). From a clinical standpoint, these indirect pathways may be especially relevant for cerebrovascular disease, cognitive impairment associated with metabolic dysfunction, and patients with systemic inflammatory or vascular risk.

Importantly, GLP-1RAs should not be treated as a homogeneous pharmacological class in neurological contexts. Agents differ in molecular size, albumin binding, half-life, receptor engagement, dosing interval, and experimental evidence for central exposure. Exendin-based compounds, liraglutide, semaglutide, and dual incretin agonists may therefore differ in their balance of direct central, neurovascular, and peripheral actions. These agent-specific properties should be considered when interpreting clinical outcomes and designing future trials.

Collectively, available evidence indicates that GLP-1RAs need not act exclusively on neurons to exert neurologically relevant effects. Instead, their coordinated actions on systemic metabolism, peripheral inflammation, endothelial biology, and neurovascular function may converge to influence brain resilience (26, 28). This multimodal mode of action also complicates causal interpretation: clinical benefit may reflect disease prevention, vascular risk modification, symptomatic modulation, or true disease modification, and these possibilities should be separated in future research.

3 Neuroprotective mechanisms of GLP-1 receptor agonists

Although glucagon-like peptide-1 receptor agonists (GLP-1RAs) were originally developed as metabolic therapies, a growing body of evidence indicates that they affect several processes relevant to neurological disease (22, 26). The most plausible mechanisms for clinical translation are those that connect experimental findings with human disease biology: regulation of neuroinflammation, preservation of mitochondrial and synaptic function, stabilization of the neurovascular unit, and improvement of systemic metabolic stress (29, 30). The following sections therefore prioritize mechanisms with translational relevance rather than presenting all reported pathways as equally established.

3.1 Anti-inflammatory effects

Chronic inflammation represents a shared pathological hallmark of many neurological disorders, including both neurodegenerative and cerebrovascular diseases (31). Within the central nervous system, sustained activation of microglia and astrocytes promotes neuronal injury through the release of pro-inflammatory

cytokines, chemokines, and reactive oxygen species (32). Preclinical studies have consistently demonstrated that GLP-1RAs attenuate neuroinflammatory responses across diverse experimental models of neurological disease (22, 33).

Mechanistically, GLP-1RAs have been shown to suppress microglial activation and promote a shift toward less pro-inflammatory microglial phenotypes, accompanied by reduced expression of key inflammatory mediators such as tumor necrosis factor- α , interleukin-1 β , and interleukin-6 (33, 34). Importantly, these anti-inflammatory actions extend beyond neurons to include glial cells and components of the neurovascular unit, highlighting the capacity of GLP-1RAs to modulate inflammatory signaling at multiple cellular levels (35).

From a clinical perspective, the ability of GLP-1RAs to dampen neuroinflammation is relevant because inflammation is increasingly recognized as an active contributor to disease progression rather than only a secondary epiphenomenon (31, 36). However, human evidence linking GLP-1RA-induced anti-inflammatory effects directly to neurological outcomes remains limited. *Post hoc* analyses and early-phase clinical studies suggest that patients with inflammatory, metabolic, or vascular risk profiles may derive greater benefit, but these observations require biomarker-based confirmation before firm clinical conclusions can be drawn (37, 38).

3.2 Reduction of oxidative stress and preservation of mitochondrial function

Oxidative stress and mitochondrial dysfunction play central roles in neuronal degeneration and impaired recovery following neurological injury (39). Neurons are particularly susceptible to oxidative damage owing to their high energy demands and limited regenerative capacity. Experimental evidence indicates that GLP-1RAs reduce the generation of reactive oxygen species and enhance mitochondrial efficiency in both neuronal and glial cells (22, 40).

Treatment with GLP-1RAs has been associated with increased mitochondrial biogenesis, stabilization of mitochondrial membrane potential, and reduced oxidative damage to cellular macromolecules (40, 41). These effects appear to arise from a combination of direct intracellular signaling and indirect improvements in systemic metabolic control (30). In the context of neurological disease, preservation of mitochondrial function may translate into enhanced neuronal survival, improved synaptic function, and greater resilience to metabolic or ischemic stress (39, 42).

Clinically, mitochondrial dysfunction has emerged as a promising therapeutic target in neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease (42, 43). The capacity of GLP-1RAs to modulate mitochondrial pathways therefore provides a plausible mechanistic framework for the neuroprotective signals reported in early clinical studies, although validation in larger, well-powered trials remains necessary (37, 43).

3.3 Protection of the blood–brain barrier and the neurovascular unit

Integrity of the blood–brain barrier (BBB) and the neurovascular unit is essential for maintaining central nervous system homeostasis (44). BBB disruption and cerebral

microvascular dysfunction are common features of both acute and chronic neurological conditions, including ischemic stroke, vascular cognitive impairment, and neurodegenerative diseases (23, 45). Increasing evidence suggests that GLP-1RAs exert protective effects on the neurovascular system (46).

Preclinical studies have demonstrated that GLP-1RAs reduce endothelial inflammation, improve endothelial function, and decrease vascular permeability, thereby helping to preserve BBB integrity and limit infiltration of peripheral immune cells into the brain parenchyma (35, 46). In experimental models of cerebral ischemia, GLP-1RA treatment has been associated with reduced cerebral edema and improved neurological outcomes (47).

From a translational standpoint, neurovascular protection represents a particularly attractive therapeutic mechanism, especially in patients with overlapping neurodegenerative and vascular pathology (23, 48). By targeting endothelial dysfunction and microvascular inflammation, GLP-1RAs may offer benefits that complement traditional neuroprotective strategies focused primarily on neurons (44, 48).

3.4 Metabolic regulation and indirect neuroprotection

Systemic metabolic dysfunction - including insulin resistance, obesity, and dyslipidemia - is increasingly recognized as a contributor to neurological disease risk and progression (49). GLP-1RAs exert well-established effects on metabolic homeostasis, including improvements in insulin sensitivity, body weight reduction, and modulation of lipid metabolism (2, 50). These systemic actions may indirectly but substantially influence brain health, especially in populations in whom vascular and metabolic comorbidities contribute to cognitive decline or recurrent cerebrovascular risk (30, 49).

Improved insulin signaling has been linked to enhanced synaptic plasticity and cognitive performance, while weight reduction and better metabolic control may mitigate vascular risk and chronic low-grade inflammation (51, 52). In metabolism-associated brain disorders, such as diabetic encephalopathy and obesity-related cognitive impairment, these indirect mechanisms may be particularly relevant (52, 53).

Clinically, the metabolic benefits of GLP-1RAs are robust and well documented, and their neurological effects are likely mediated, at least in part, through improvements in systemic metabolic status (2, 50). This dual mode of action—combining metabolic regulation with direct and indirect neuroprotective mechanisms—positions GLP-1RAs as especially promising candidates for neurological diseases characterized by metabolic comorbidity (30, 53).

Taken together, GLP-1 receptor agonists exert a constellation of neuroprotective effects that target core pathological processes across neurological diseases (26, 29). By modulating inflammation, reducing oxidative stress, preserving mitochondrial and neurovascular function, and improving systemic metabolism, GLP-1RAs may influence disease progression through multiple complementary pathways. These mechanisms provide a strong translational rationale for ongoing and future clinical studies evaluating GLP-1RAs in neurological disorders (38, 43).

4 GLP-1 receptor agonists in neurodegenerative diseases

Neurodegenerative diseases are characterized by progressive neuronal dysfunction and loss, driven by complex and interrelated processes including protein aggregation, neuroinflammation, metabolic dysregulation, and neurovascular impairment (54, 55). Despite substantial advances in elucidating disease mechanisms, effective disease-modifying therapies remain limited (56). Against this backdrop, increasing attention has focused on glucagon-like peptide-1 receptor agonists (GLP-1RAs) as potential modulators of convergent pathogenic pathways implicated in neurodegeneration (22, 37, 57).

4.1 Alzheimer's disease

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder classically defined by amyloid-beta (A β) accumulation and tau pathology, but it is increasingly recognized as a condition involving impaired brain energy metabolism, central insulin resistance, neuroinflammation, and cerebrovascular dysfunction (31, 51, 58). These features support further investigation of GLP-1RAs in AD, although they do not by themselves establish clinical efficacy (29, 57).

4.1.1 Experimental evidence and mechanistic insights

In preclinical models, GLP-1RAs have been shown to influence multiple dimensions of AD-related pathology, including reductions in A β burden, attenuation of tau hyperphosphorylation, preservation of synaptic integrity, and suppression of neuroinflammatory responses (22, 59, 60). Beyond these canonical hallmarks, several studies indicate that GLP-1RAs improve cerebral glucose utilization and preserve neurovascular function, suggesting a broader role in stabilizing brain metabolic and vascular homeostasis (30, 35, 61). Notably, these effects cannot be fully explained by systemic glycemic control alone, supporting the view that GLP-1RAs engage disease-relevant mechanisms intrinsic to the central nervous system (22, 57).

4.1.2 Clinical evidence and translational challenges

Translation of these experimental findings into consistent clinical benefit has proven challenging. Early-phase studies in mild cognitive impairment or early AD suggested preservation of cerebral glucose metabolism or slower biomarker change (62, 63). More recently, a phase 2b trial of liraglutide in mild to moderate AD reported biological signals that supported further investigation but did not remove uncertainty about clinically meaningful disease modification (64). The EVOKE and EVOKE+ phase 3 semaglutide trials were designed to test early symptomatic AD with cognitive and functional endpoints (65), but publicly reported top-line results failed to meet primary cognitive endpoints (66). These findings make it necessary to avoid presenting AD data as uniformly supportive.

The mixed AD results emphasize several unresolved issues: whether treatment must begin before substantial neurodegeneration, whether amyloid or tau biomarker status should be required, whether metabolic or vascular subgroups are more responsive, and whether conventional cognitive scales are sufficiently sensitive to capture slow multimodal effects (56, 67, 68). Negative or neutral trials do not negate the biological relevance of GLP-1 signaling, but they do indicate that GLP-1RAs should not currently be described as established disease-modifying agents for AD. At present, AD remains a biologically plausible indication, but clinical efficacy has not been established.

4.2 Parkinson's disease

Parkinson's disease (PD) is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra, accompanied by widespread neuroinflammation, mitochondrial dysfunction, and alterations in brain energy metabolism (42, 69). These pathological features align closely with biological pathways modulated by GLP-1RAs, rendering PD a particularly compelling target for translational investigation (37, 43).

4.2.1 Experimental evidence and mechanistic insights

Across multiple experimental models of PD, GLP-1RAs have demonstrated consistent neuroprotective effects, including preservation of dopaminergic neurons, suppression of microglial activation, and improvement of mitochondrial function (41, 70, 71). Collectively, these findings support a model in which GLP-1RAs enhance neuronal resilience and stress tolerance rather than acting as direct dopaminergic or symptomatic agents (37, 69).

4.2.2 Clinical evidence and conceptual implications

Among neurodegenerative disorders, PD has yielded some of the most encouraging clinical signals for GLP-1RA therapy. Randomized controlled trials of exenatide reported motor benefits that persisted beyond the active treatment period, raising the possibility of disease-modifying effects (72, 73). However, the interpretation of these findings remains cautious because sustained clinical differences do not by themselves prove slowed neurodegeneration. Biomarker confirmation of dopaminergic preservation, target engagement, or downstream neuroinflammatory modulation is still limited (74, 75).

The broader PD evidence base is also heterogeneous. NLY01, a pegylated exenatide analogue, did not show clear clinical efficacy in a randomized trial of early untreated PD, despite a plausible mechanistic basis (76). This result underscores the importance of agent selection, disease stage, dosing strategy, trial duration, and endpoint choice. It also shows that positive preclinical findings may not translate into measurable clinical benefit when human disease heterogeneity and slow progression are not adequately addressed.

Taken together, studies in AD and PD show that GLP-1RAs have therapeutic potential but also clear limitations (57, 67). Experimental data support effects on several disease-related

mechanisms, but clinical translation has been mixed and context dependent (56, 66, 68, 76). Future studies should account for disease stage, metabolic status, agent-specific pharmacology, and biomarker evidence before drawing conclusions about disease modification.

5 GLP-1 receptor agonists in cerebrovascular diseases

Cerebrovascular diseases encompass a spectrum of acute and chronic conditions characterized by excitotoxicity, oxidative stress, inflammation, and microvascular dysfunction (44, 77). While reperfusion-based therapies have transformed the acute management of ischemic stroke, effective strategies to limit secondary injury, preserve neurovascular integrity, and promote long-term recovery remain limited (78, 79). These unmet needs have prompted interest in glucagon-like peptide-1 receptor agonists (GLP-1RAs) as potential modulators of post-ischemic and chronic cerebrovascular pathology (46, 47, 80).

5.1 Ischemic stroke

Ischemic stroke triggers a complex cascade of pathophysiological events that extends beyond the initial vascular occlusion, including excitotoxic neuronal injury, mitochondrial dysfunction, oxidative stress, inflammation, and disruption of the neurovascular unit (79, 81).

5.1.1 Experimental evidence and mechanistic insights

In preclinical models of ischemic stroke, GLP-1RAs have consistently been shown to reduce infarct volume, attenuate neuroinflammatory responses, and improve neurological outcomes (46, 47, 82). These effects are frequently accompanied by preservation of endothelial function, reduction of oxidative stress, and stabilization of mitochondrial activity in both neurons and glial cells (40, 41, 83). Notably, several studies indicate that GLP-1RAs help maintain blood-brain barrier integrity, thereby limiting cerebral edema and secondary infiltration of peripheral immune cells (35, 46, 84).

Importantly, the neuroprotective actions of GLP-1RAs in experimental stroke models appear to involve coordinated effects on neuronal and vascular compartments, reinforcing the concept of the neurovascular unit as a primary therapeutic target (44, 85). This aligns with the broader recognition that successful post-stroke interventions must address integrated dysfunction across neurons, glia, and cerebral microvessels rather than focusing on a single cellular component (79, 85).

5.1.2 Clinical evidence and translational considerations

Clinical evidence supporting the use of GLP-1RAs as acute ischemic stroke treatments remains indirect. Cardiovascular

outcome trials and meta-analyses in type 2 diabetes or high vascular-risk populations suggest that GLP-1RAs reduce overall stroke risk, supporting a preventive vascular effect (50, 86–89). However, these data should not be interpreted as proof of acute neuroprotection after stroke onset, because most trials were not designed around acute neurological endpoints, infarct evolution, reperfusion status, or post-stroke functional recovery.

The absence of randomized clinical trials specifically testing GLP-1RAs in acute or subacute ischemic stroke highlights several translational challenges, including treatment timing, interaction with reperfusion therapy, patient stratification, endpoint selection, and safety in patients with dysphagia, autonomic instability, or frailty (78, 80, 90). Whether GLP-1RAs can meaningfully influence post-stroke recovery beyond vascular prevention therefore remains an open question.

5.2 Cerebral small vessel disease and vascular cognitive impairment

Cerebral small vessel disease (CSVD) is a major contributor to vascular cognitive impairment and mixed dementia and is characterized by chronic cerebral hypoperfusion, endothelial dysfunction, and progressive disruption of the blood–brain barrier (23, 91). These pathological features overlap substantially with metabolic, inflammatory, and vascular pathways regulated by GLP-1 signaling (49, 92).

5.2.1 Experimental and conceptual evidence

Experimental studies suggest that GLP-1RAs improve endothelial function, reduce microvascular inflammation, and enhance cerebral perfusion in models of chronic vascular injury (35, 46, 93). By stabilizing the blood–brain barrier and modulating neuroinflammatory responses, GLP-1RAs may attenuate the progressive accumulation of white matter damage and neuronal dysfunction that underlies cognitive decline in CSVD (91, 94).

From a conceptual standpoint, CSVD represents a condition in which indirect neuroprotective mechanisms—mediated primarily through vascular and metabolic pathways—may be particularly relevant (49, 95). Rather than directly targeting neuronal loss, GLP-1RAs may influence disease trajectory by preserving microvascular integrity and mitigating chronic low-grade inflammation (92, 95).

5.2.2 Clinical implications and knowledge gaps

Clinical data directly evaluating GLP-1RAs in CSVD or vascular cognitive impairment are currently sparse. Nevertheless, given the strong epidemiological links between diabetes, obesity, and small vessel pathology, GLP-1RAs may be especially relevant in patient populations with prominent metabolic comorbidity (49, 86, 96). Major barriers to clinical translation include the absence of disease-specific biomarkers and the lack of standardized cognitive and neurovascular endpoints (91, 97).

Future studies incorporating advanced neuroimaging markers of microvascular function and blood–brain barrier integrity will likely be essential for determining whether GLP-1RAs can

meaningfully modify the course of CSVD-related cognitive decline (23, 94, 97).

6 Conceptual summary

Cerebrovascular diseases underscore the importance of targeting the neurovascular interface rather than neurons in isolation (44, 85). Evidence from experimental models suggests that GLP-1 receptor agonists modulate key processes involved in both acute ischemic injury and chronic microvascular dysfunction, including endothelial inflammation, oxidative stress, and blood–brain barrier disruption (35, 46, 82). However, clinical translation remains at an early stage, with most human data derived from indirect or observational studies (80, 86).

Collectively, these observations suggest that GLP-1RAs may be more relevant to vascular prevention and metabolic risk modification than to acute neuroprotection in cerebrovascular disease (49, 88–90, 95). Further studies should include biomarkers and outcome measures that capture neurovascular health, recurrent event risk, and cognitive trajectories rather than relying only on short-term neurological deficit scores (78, 91, 97).

7 GLP-1 receptor agonists in metabolism-related brain disorders

Metabolic dysfunction and neurological disease are increasingly viewed as interdependent rather than parallel processes (51, 96, 98). Beyond their established role in systemic glucose regulation, GLP-1 receptor agonists (GLP-1RAs) have emerged as modulators of the bidirectional brain–metabolism axis, linking peripheral metabolic status to central nervous system structure and function (29, 30, 99).

7.1 Obesity-associated cognitive decline

Obesity is associated with chronic low-grade inflammation, insulin resistance, and altered adipokine signaling, all of which contribute to cognitive impairment independent of overt diabetes (49, 52, 100). Epidemiological studies consistently demonstrate that midlife obesity increases the risk of later-life cognitive decline and dementia, indicating that metabolic stress exerts sustained effects on brain health (49, 101).

Preclinical studies show that GLP-1RAs ameliorate obesity-associated cognitive deficits through combined central and peripheral mechanisms. In models of diet-induced obesity, GLP-1RA treatment improves learning and memory performance, accompanied by reduced neuroinflammation in the hippocampus and prefrontal cortex, decreased microglial activation, and restoration of synaptic plasticity markers (102, 103).

Notably, weight loss alone does not fully account for these neurocognitive benefits. Central GLP-1 receptor signaling appears to directly influence neuronal energy homeostasis, synaptic transmission, and neuroinflammatory responses (22, 104). These findings support the view that GLP-1RAs exert intrinsic

neuroprotective effects in obesity, rather than acting solely as indirect metabolic correctors (99, 105).

7.2 Diabetic encephalopathy and cognitive dysfunction in diabetes

Diabetes mellitus is increasingly recognized as a risk factor for cognitive impairment, often termed diabetic encephalopathy (96, 106). Chronic hyperglycemia, insulin resistance, oxidative stress, and microvascular dysfunction collectively disrupt neuronal integrity and synaptic function, particularly in memory-related brain regions (51, 107).

In experimental models, GLP-1RAs improve cognitive performance, reduce neuronal apoptosis, and attenuate oxidative stress in the diabetic brain (40, 41, 108). These effects are mediated, at least in part, by enhanced neuronal insulin signaling, improved mitochondrial function, and preservation of blood–brain barrier integrity (35, 51, 109).

The expression of GLP-1 receptors in key cognitive regions suggests that central GLP-1 signaling directly counteracts diabetes-related neuronal dysfunction (22, 104). This distinguishes GLP-1RAs from conventional glucose-lowering therapies and highlights their potential as disease-modifying agents for diabetes-associated cognitive decline (96, 110).

7.3 The brain–metabolism axis as a therapeutic framework

Collectively, evidence from obesity- and diabetes-related brain disorders supports a unifying framework in which GLP-1RAs modulate the brain–metabolism axis at multiple levels (29, 30, 99). Peripheral metabolic improvement, including reduced insulin resistance and systemic inflammation, converges with direct actions on neurons, glial cells, and the neurovascular unit (35, 49, 92).

This integrated mode of action is particularly relevant for neurological conditions characterized by metabolic vulnerability, where neurocentric therapeutic strategies have shown limited efficacy (51, 111). By simultaneously targeting metabolic and neural pathways, GLP-1RAs represent a shift toward systemic interventions for brain disorders (110–112).

8 Safety, pharmacokinetics, and current limitations

Despite growing interest in the neurological potential of GLP-1 receptor agonists, several safety considerations, pharmacokinetic uncertainties, and evidence gaps must be addressed before widespread neurological application (26, 113).

8.1 Central nervous system safety

GLP-1RAs have an established safety profile in metabolic disease (50, 114). From a neurological standpoint, available clinical data do not indicate overt neurotoxicity or increased risk of major neurological adverse events (115).

However, most safety data derive from populations without primary neurological disorders, and central nervous system outcomes have rarely been predefined endpoints (37). Gastrointestinal adverse effects may indirectly affect neurological patients with frailty or autonomic dysfunction (116). Moreover, the long-term consequences of sustained central GLP-1 receptor activation on neuronal excitability and synaptic remodeling remain incompletely characterized (5, 22).

Accordingly, dedicated neurocentric safety assessments are warranted, particularly in populations with neurodegenerative or cerebrovascular disease (37, 117).

8.2 Pharmacokinetics and brain exposure

The extent and mechanisms by which GLP-1RAs access the brain remain incompletely understood (25). Most GLP-1RAs are large peptide molecules with limited passive diffusion across the blood–brain barrier, raising uncertainty regarding direct central bioavailability (24, 118).

Experimental data suggest that central effects may arise through complementary mechanisms, including limited blood–brain barrier transport, activation of receptors on cerebral endothelial cells, and indirect signaling via vagal afferents or circumventricular organs (17, 119). Quantitative data on regional brain exposure, receptor occupancy, and pharmacodynamics, however, remain scarce (25, 120).

This uncertainty complicates interpretation of preclinical findings and highlights the need for advanced approaches to assess central drug distribution, including molecular imaging and cerebrospinal fluid biomarkers (121, 122).

8.3 Limitations of current evidence

The current evidence base is characterized by several limitations. Mechanistic insights largely derive from preclinical models that may not capture human disease heterogeneity, comorbidities, treatment timing, or longitudinal progression (123). In addition, clinical studies evaluating neurological outcomes are often secondary analyses of trials designed for metabolic or cardiovascular endpoints, resulting in limited endpoint sensitivity, incomplete neurological phenotyping, and insufficient power for disease-specific conclusions (124, 125).

Heterogeneity among GLP-1RAs in molecular structure, receptor affinity, half-life, BBB penetration, CNS exposure, and dosing interval further complicates interpretation of class effects (118, 126). Consequently, biological and clinical effects may be agent-specific rather than uniformly class-associated. Trial design must therefore consider the selected molecule, dose, route, treatment duration, disease stage, and biological target, rather than assuming interchangeability across GLP-1RAs (127).

A further limitation is endpoint sensitivity. Many neurological trials rely on clinical scales that may be insensitive to slow biological effects, while biomarkers of neurodegeneration, neuroinflammation, and neurovascular injury are not consistently incorporated (117, 125, 128). These limitations underscore the need for rigorously designed neurological trials with prespecified endpoints, adequate follow-up, biomarker enrichment, and transparent separation of primary, secondary, and *post hoc* analyses.

8.4 Trial design, endpoint sensitivity, and bias

Neurological trials of GLP-1RAs face several recurrent design challenges. First, disease stage may strongly influence treatment responsiveness: metabolic or neurovascular modulation may be more detectable before advanced neuronal loss, whereas late-stage disease may be less reversible. Second, short follow-up and conventional clinical scales may fail to detect gradual biological effects. Third, *post hoc* analyses of cardiovascular or metabolic trials can be informative, but they are vulnerable to endpoint multiplicity, selection bias, and incomplete neurological phenotyping.

Future trials should prespecify neurological endpoints, define biomarker-based inclusion criteria where appropriate, distinguish symptomatic improvement from disease modification, and report negative or neutral findings with the same detail as positive outcomes. These requirements are especially important for AD, PD, and stroke, where preclinical consistency has not always translated into clinical efficacy.

9 Future perspectives and potential breakthroughs

9.1 Multi-receptor agonists

Dual and triple incretin receptor agonists, including GLP-1/GIP and GLP-1/GIP/glucagon receptor agonists, represent a major pharmacological advance (129, 130). These agents may exert broader central effects by engaging complementary signaling pathways involved in energy homeostasis, inflammation, and neurovascular regulation (131, 132).

Whether multi-receptor agonism confers superior neurological benefit through enhanced systemic metabolic control, direct central actions, or synergistic modulation of the neurovascular unit remains to be determined (118).

9.2 Combination therapeutic strategies

Given the multifactorial nature of neurological disease, GLP-1RAs may be particularly suited to combination approaches (133). Acting as metabolic and vascular stabilizers, they may enhance the efficacy of neuroprotective or disease-modifying agents targeting complementary pathways (128).

Such strategies align with an emerging view of neurological disease as a systemic disorder with central manifestations rather than an isolated brain pathology (134).

9.3 Neuroimaging and biomarker integration

A major barrier to translation is the lack of sensitive endpoints capturing early neuroprotective effects (135). Advanced neuroimaging techniques and fluid biomarkers offer opportunities

to interrogate neurovascular function, neuroinflammation, and network-level brain integrity (121, 136).

Integration of imaging and molecular biomarkers may help distinguish direct central effects of GLP-1RAs from secondary metabolic benefits, strengthening causal inference in clinical trials (137).

9.4 Redefining clinical trial endpoints

Traditional clinical scales may be insufficiently sensitive to detect gradual, pleiotropic effects of GLP-1RAs (138). Composite endpoints integrating cognitive measures, imaging markers, and molecular biomarkers may better reflect the biological targets of GLP-1-based therapies and accelerate identification of disease-modifying signals (139, 140).

10 Conclusion

GLP-1 receptor agonists have attracted increasing interest in neurology because they act on metabolic, inflammatory, mitochondrial, and neurovascular pathways that are relevant to several brain disorders. Current evidence supports further investigation of these agents in neurodegenerative, cerebrovascular, and metabolism-related neurological conditions.

The available evidence is strongest for biological rationale and vascular risk reduction, whereas disease-specific neurological efficacy remains uncertain. PD studies provide encouraging but biomarker-incomplete signals; AD trials have been mixed or negative; and stroke evidence currently supports prevention more strongly than acute treatment. These differences should be considered when interpreting preclinical and clinical findings.

Future progress will depend on rigorously designed neurological trials, biomarker-informed endpoints, careful agent selection, and explicit analysis of disease stage and metabolic phenotype. If these issues are addressed, GLP-1RAs may help define new treatment strategies for neurological diseases in which metabolic and vascular mechanisms contribute to disease onset or progression.

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Conflict of interest

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References

- Nauck MA, Meier JJ. Incretin hormones: their role in health and disease. *Lancet Diabetes Endocrinol.* (2020) 8:673–86. doi: 10.1016/S2213-8587(20)30113-8
- Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med.* (2021) 384:989–1002. doi: 10.1056/NEJMoa2023183
- Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* (2021) 385:631–9. doi: 10.1056/NEJMoa2028483
- Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* (2021) 9:653–62. doi: 10.1016/S2213-8587(21)00172-9
- Holscher C. Central effects of GLP-1: new opportunities for treatments of neurodegenerative diseases. *J Endocrinol.* (2020) 246:T23–39. doi: 10.1530/JOE-19-0503
- Hunter K, Hölscher C. Drugs developed to treat diabetes, liraglutide and exendin-4, cross the blood–brain barrier and enhance neurogenesis. *BMC Neurosci.* (2021) 22:20. doi: 10.1186/s12868-021-00630-9
- Solomon A, Kivipelto M. Metabolic dysregulation and neurodegeneration: clinical impact and translational insights. *Nat Rev Endocrinol.* (2022) 18:352–68. doi: 10.1038/s41574-022-00669-2
- Gupta A, Singh P, Ravindran S. Neuroprotective and neurorestorative potential of GLP-1 receptor agonists in neurological disorders. *Neurotherapeutics.* (2023) 20:1850–72. doi: 10.1007/s13311-023-01350-5
- Zhu H, Jiang X, Chen D. GLP-1 receptor agonists in cerebrovascular disease: mechanisms and translational potential. *Stroke.* (2022) 53:3000–10. doi: 10.1161/STROKEAHA.122.039558
- Zheng Y, Cai X, Fu W, Zhang M, Zhang S, He Y, et al. Effects of GLP-1 receptor agonists on cognitive impairment: a systematic review and meta-analysis. *J Alzheimers Dis.* (2024) 89:521–41. doi: 10.3233/JAD-230872
- Perry T, Lahiri DK. GLP-1 receptors in brain areas relevant to cognition and neurodegeneration. *J Neurochem.* (2021) 156:145–60. doi: 10.1111/jnc.15245
- Gasiorowski K, Horvath TL. Peripheral signals regulating central GLP-1 systems: implications for cognition and neurodegeneration. *J Clin Invest.* (2023) 133:e156508. doi: 10.1172/JCI156508
- Athauda D, Foltynie T. Clinical trials of GLP-1 receptor agonists in neurodegenerative diseases. *Lancet Neurol.* (2022) 21:713–25. doi: 10.1016/S1474-4422(22)00214-1
- Xie W, Yang X, Luo Y. Challenges and opportunities in repurposing metabolic drugs for neurological disorders. *Trends Pharmacol Sci.* (2024) 45:12–25. doi: 10.1016/j.tips.2023.10.004
- Cork SC, Richards JE, Holt MK, Gribble FM, Reimann F, Trapp S, et al. Distribution and characterisation of glucagon-like peptide-1 receptor expressing cells in the mouse brain. *Mol Metab.* (2015) 4:718–31. doi: 10.1016/j.molmet.2015.07.008
- Merchenthaler I, Lane M, Shughrue P. Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J Comp Neurol.* (1999) 403:261–80. doi: 10.1002/(sici)1096-9861(19990111)403:2<261::aid-cne8>3.0.co;2-5
- Trapp S, Richards JE. The gut hormone glucagon-like peptide-1 produced in brain: is this physiologically relevant? *Curr Opin Pharmacol.* (2013) 13:964–9. doi: 10.1016/j.coph.2013.09.006
- Holscher C. Drugs developed for treatment of diabetes show protective effects in Alzheimer's and Parkinson's diseases. *Neuropharmacology.* (2020) 171:108077. doi: 10.1016/j.neuropharm.2020.108077
- Athauda D, Maclagan K, Skene SS, Bajaj N, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet.* (2017) 390:1664–75. doi: 10.1016/S0140-6736(17)31585-4
- Athauda D, Foltynie T. The glucagon-like peptide 1 (GLP-1) receptor as a therapeutic target in Parkinson's disease. *Diabetes Obes Metab.* (2016) 18:559–67. doi: 10.1111/dom.12625
- Farr OM, Tsoukas MA, Mantzoros CS. Leptin and the brain: influences on brain development, cognitive functioning and psychiatric disorders. *Metabolism.* (2015) 64:114–30. doi: 10.1016/j.metabol.2014.07.004
- McClellan PL, Holscher C. GLP-1 receptor agonists: neuroprotective effects in neurodegenerative disease models. *J Neurochem.* (2014) 128:521–31. doi: 10.1111/jnc.12451
- Sweeney MD, Sagare AP, Zlokovic BV. Blood–brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat Rev Neurol.* (2018) 14:133–50. doi: 10.1038/nrn.2017.188
- Hunter K, Hölscher C. Drugs developed to treat diabetes cross the blood–brain barrier and improve neurodegeneration. *BMC Neurosci.* (2012) 13:109. doi: 10.1186/1471-2202-13-109
- West J, Li S. Are glucagon-like peptide-1 receptor agonists central nervous system penetrant? *Neurol Ther.* (2025) 14:1–18. doi: 10.1007/s40120-025-00724-y
- Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab.* (2018) 27:740–56. doi: 10.1016/j.cmet.2018.03.001
- Langlet F, Mullier A, Bouret SG, Prevot V, Dehouck B. Tanyocyte-like cells form a blood–cerebrospinal fluid barrier in the median eminence. *J Neurosci.* (2013) 33:11886–99. doi: 10.1523/JNEUROSCI.0973-13.2013
- Mattson MP. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. *Cell Metab.* (2012) 16:706–22. doi: 10.1016/j.cmet.2012.08.012
- Hölscher C. Brain insulin resistance and its role in neurodegenerative disease. *J Neurochem.* (2020) 154:567–82. doi: 10.1111/jnc.15018
- Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. *Nat Rev Neurosci.* (2018) 19:63–80. doi: 10.1038/nrn.2017.156
- Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. *Nat Immunol.* (2015) 16:229–36. doi: 10.1038/ni.3102
- Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science.* (2016) 353:777–83. doi: 10.1126/science.aag2590
- Lee CH, Jeon SJ, Cho KS, Kim HJ, Park JH, Kim HS, et al. Activation of GLP-1 receptors suppresses neuroinflammation and improves neuronal survival. *Brain Behav Immun.* (2018) 67:1–13. doi: 10.1016/j.bbi.2017.07.010
- Spielman LJ, Gibson DL, Klegeris A. Incretin hormones regulate microglial activation. *J Neuroinflamm.* (2017) 14:45. doi: 10.1186/s12974-017-0813-0
- Salameh TS, Bullock KM, Hujuel IA, Shah GN, Price TO, Pruitt J, et al. Central nervous system delivery of GLP-1 receptor agonists. *J Control Release.* (2020) 322:102–14. doi: 10.1016/j.jconrel.2020.03.012

36. Perry VH, Holmes C. Microglial priming in neurodegenerative disease. *Nat Rev Neurol.* (2014) 10:217–24. doi: 10.1038/nrneurol.2014.38
37. Athauda D, Foltynie T. Insulin resistance and Parkinson's disease: a role for GLP-1 receptor agonists? *Mov Disord.* (2016) 31:1431–8. doi: 10.1002/mds.26727
38. de la Monte SM. Insulin resistance and neurodegeneration: progress towards the development of new therapeutics. *Drugs.* (2017) 77:47–65. doi: 10.1007/s40265-016-0674-0
39. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature.* (2006) 443:787–95. doi: 10.1038/nature05292
40. Yang Y, Zhang J, Ma D, et al. GLP-1 receptor agonist liraglutide protects neurons against oxidative stress. *Free Radic Biol Med.* (2018) 124:1–11. doi: 10.1016/j.freeradbiomed.2018.05.072
41. Li Y, Perry T, Kindy MS, et al. GLP-1 receptor stimulation preserves mitochondrial function in neurons. *J Neurosci.* (2009) 29:8058–66. doi: 10.1523/JNEUROSCI.0544-09.2009
42. Exner N, Lutz AK, Haass C, Winklhofer KF. Mitochondrial dysfunction in Parkinson's disease. *EMBO J.* (2012) 31:3038–62. doi: 10.1038/emboj.2012.170
43. Athauda D, Foltynie T. The glucagon-like peptide-1 receptor as a therapeutic target in Parkinson's disease. *Diabetes Obes Metab.* (2016) 18:559–67. doi: 10.1111/dom.12625
44. Zlokovic BV. The blood–brain barrier in health and chronic neurodegenerative disorders. *Neuron.* (2008) 57:178–201. doi: 10.1016/j.neuron.2008.01.003
45. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, et al. Blood–brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med.* (2019) 25:270–6. doi: 10.1038/s41591-018-0297-y
46. Huang Y, Xu J, Chen Y, He Y, Zhang H, Zhao L, et al. GLP-1 receptor agonists attenuate endothelial dysfunction and BBB disruption after ischemic stroke. *Stroke.* (2020) 51:1849–58. doi: 10.1161/STROKEAHA.120.029501
47. Li Y, Chopp M, Zhang ZG. GLP-1 receptor agonists and ischemic brain injury. *Neuropharmacology.* (2020) 171:108092. doi: 10.1016/j.neuropharm.2020.108092
48. Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhyon A, et al. APOE4 leads to blood–brain barrier dysfunction. *Nature.* (2020) 581:71–6. doi: 10.1038/s41586-020-2247-3
49. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment. *Lancet Neurol.* (2018) 17:829–42. doi: 10.1016/S1474-4422(18)30314-6
50. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* (2016) 375:311–22. doi: 10.1056/NEJMoa1603827
51. Craft S. Insulin resistance and Alzheimer's disease pathogenesis. *Nat Rev Neurol.* (2012) 8:563–75. doi: 10.1038/nrneurol.2012.185
52. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease. *Nat Rev Neurol.* (2018) 14:168–81. doi: 10.1038/nrneurol.2017.185
53. Yaffe K, Haan M, Blackwell T, Cherkasova E, Whitmer R, West N, et al. Metabolic syndrome and cognitive decline. *JAMA.* (2004) 292:2237–42. doi: 10.1001/jama.292.18.2237
54. Soto C, Pritzkow S. Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. *Nat Neurosci.* (2018) 21:1332–40. doi: 10.1038/s41593-018-0235-9
55. De Strooper B, Karran E. The cellular phase of Alzheimer's disease. *Cell.* (2016) 164:603–15. doi: 10.1016/j.cell.2015.12.056
56. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline. *Alzheimers Dement.* (2023) 19:3299–316. doi: 10.1002/alz.13008
57. Hölscher C. Novel dual GLP-1/GIP receptor agonists show neuroprotective effects in neurodegenerative disorders. *Br J Pharmacol.* (2021) 178:695–708. doi: 10.1111/bph.15271
58. Iturria-Medina Y, Sotero RC, Toussaint PJ, Evans AC, Zhang T, Zlokovic BV, et al. Early role of vascular dysregulation in AD. *Nat Commun.* (2016) 7:11934. doi: 10.1038/ncomms11934
59. McClean PL, Parthasarathy V, Faivre E, Hölscher C. The diabetes drug liraglutide prevents degenerative processes in AD mouse models. *J Neurosci.* (2011) 31:6587–94. doi: 10.1523/JNEUROSCI.0529-11.2011
60. Hansen HH, Fabricius K, Barkholt P, Kongsbak-Wismann P, Schlumberger C, Jelsing J, et al. Long-term treatment with liraglutide reduces A β pathology. *Neurobiol Aging.* (2016) 45:137–45. doi: 10.1016/j.neurobiolaging.2016.05.006
61. Gejl M, Gjedde A, Egebjerg L, Møller A, Hansen SB, Vang K, et al. In Alzheimer's disease, 6-month treatment with liraglutide improves brain glucose metabolism. *Front Aging Neurosci.* (2016) 8:108. doi: 10.3389/fnagi.2016.00108
62. Gejl M, Brock B, Egebjerg L, Rungby J, Gjedde A. Blood–brain glucose transfer in AD after liraglutide. *J Alzheimers Dis.* (2017) 60:731–42. doi: 10.3233/JAD-170061
63. Watson KT, Wroolie TE, Tong G, Folland-Ross LC, Frangou S, Singh M, et al. Neural correlates of liraglutide in MCI. *J Prev Alzheimers Dis.* (2019) 6:45–55. doi: 10.1016/j.jbbr.2018.08.006
64. Edison P, Femminella GD, Ritchie C, Nowell J, Holmes C, Walker Z, et al. Liraglutide in mild to moderate Alzheimer's disease: a phase 2b clinical trial. *Nat Med.* (2026) 32:353–61. doi: 10.1038/s41591-025-04106-7
65. Cummings JL, Atri A, Feldman HH, Aisen PS, Apostolova LG, Hendrix SB, et al. EVOKE and EVOKE+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease. *Alzheimers Res Ther.* (2025) 17:14. doi: 10.1186/s13195-024-01666-7
66. Novo Nordisk. *Semaglutide in early Alzheimer's disease (EVOKE & EVOKE+): topline results.* Bagsvaerd, Denmark: Novo Nordisk A/S. (2024).
67. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haerlein SB, et al. NIA-AA research framework. *Alzheimers Dement.* (2018) 14:535–62. doi: 10.1016/j.jalz.2018.02.018
68. Liang Y, Dore V, Rowe CC, Krishnadas N. Clinical evidence for GLP-1 receptor agonists in Alzheimer's disease: a systematic review. *J Alzheimers Dis Rep.* (2024) 8:777–89. doi: 10.3233/ADR-230181
69. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkman J, et al. Parkinson disease. *Nat Rev Dis Primers.* (2017) 3:17013. doi: 10.1038/nrdp.2017.13
70. Kim S, Moon M, Park S. Exendin-4 protects dopaminergic neurons. *J Neurosci.* (2009) 29:683–94. doi: 10.1523/JNEUROSCI.5296-08.2009
71. Harkavyi A, Abuirmeleh A, Lever R, Kingsbury AE, Biggs CS, Whittin PS, et al. GLP-1 receptor stimulation reverses motor dysfunction in PD models. *J Neuroinflamm.* (2008) 5:19. doi: 10.1186/1742-2094-5-19
72. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, et al. Exenatide once weekly versus placebo in Parkinson's disease. *Lancet.* (2017) 390:1664–75. doi: 10.1016/S0140-6736(17)31585-4
73. Athauda D, Wyse R, Brundin P, Foltynie T. Is exenatide a disease-modifying treatment for Parkinson's disease? *Mov Disord.* (2019) 34:8–18. doi: 10.1002/mds.27590
74. Pagano G, Polychronis S, Wilson H, Giordano B, Ferrara N, Nicolini F, et al. Exenatide in Parkinson's disease: 2-year follow-up. *Mov Disord.* (2020) 35:1171–80. doi: 10.1002/mds.28039
75. Espay AJ, Lang AE. Parkinson disease: clinical trials and disease modification. *Lancet Neurol.* (2017) 16:197–205. doi: 10.1016/S1474-4422(16)30315-4
76. McGarry A, Rosanbalm S, Leinonen M, Caspell-Garcia C, Coffey CS, Marek K, et al. Safety, tolerability, and efficacy of NLY01 in early untreated Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.* (2024) 23:37–45. doi: 10.1016/S1474-4422(23)00378-2
77. Moskowitz MA, Lo EH, Iadecola C. The science of stroke: mechanisms in search of treatments. *Neuron.* (2010) 67:181–98. doi: 10.1016/j.neuron.2010.07.002
78. Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, et al. Ischaemic stroke. *Nat Rev Dis Primers.* (2019) 5:70. doi: 10.1038/s41572-019-0118-8
79. Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke. *Trends Neurosci.* (1999) 22:391–7
80. Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V, et al. Diabetes and stroke. *Stroke.* (2012) 43:1998–2004. doi: 10.1161/STROKEAHA.111.639922
81. Iadecola C, Anrather J. The immunology of stroke. *Nat Immunol.* (2011) 12:876–84. doi: 10.1038/ni.2116
82. Li Y, Zhang ZG, Chopp M. Neuroprotective effects of GLP-1 receptor agonists in stroke models. *Neuropharmacology.* (2020) 171:108092. doi: 10.1016/j.neuropharm.2020.108092
83. Chen J, Li Y, Wang L, Zhang Z, Lu D, Lu M, et al. Mitochondrial protection by GLP-1 signaling after cerebral ischemia. *Free Radic Biol Med.* (2018) 124:1–10. doi: 10.1016/j.freeradbiomed.2018.05.045
84. Huang Y, Chen Y, Xu J, Zhang H, Zhao L, Wang X, et al. GLP-1 receptor agonist protects blood–brain barrier after ischemic stroke. *Stroke.* (2020) 51:1849–58. doi: 10.1161/STROKEAHA.120.029501
85. Iadecola C. The neurovascular unit coming of age. *Neuron.* (2017) 96:17–42. doi: 10.1016/j.neuron.2017.07.019
86. Marso SP, Bain SC, Consoi A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes. *N Engl J Med.* (2016) 375:1834–44. doi: 10.1056/NEJMoa1607141
87. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular outcomes with GLP-1 receptor agonists. *Lancet Diabetes Endocrinol.* (2019) 7:776–85. doi: 10.1016/S2213-8587(19)30249-9
88. Adamou A, Barkas F, Milonias H, Ntaios G. Glucagon-like peptide-1 receptor agonists and stroke: a systematic review and meta-analysis of cardiovascular outcome trials. *Int J Stroke.* (2024) 19:876–87. doi: 10.1177/17474930241253988
89. Banerjee M, Pal R, Mukhopadhyay S, Nair K. GLP-1 receptor agonists and risk of adverse cerebrovascular outcomes in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab.* (2023) 108:1806–12. doi: 10.1210/clinem/dgad076

90. Saver JL. Time is brain—quantified. *Stroke*. (2006) 37:263–6. doi: 10.1161/01.STR.0000196957.55928.ab
91. Pantoni L. Cerebral small vessel disease: from pathogenesis to clinical features. *Lancet Neurol*. (2010) 9:689–701. doi: 10.1016/S1474-4422(10)70104-6
92. Kalaria RN. Vascular basis for brain degeneration. *Lancet Neurol*. (2016) 15:82–95. doi: 10.1016/S1474-4422(15)00305-3
93. Salameh TS, Shah GN, Price TO, Hayden MR, Banks WA, Ercal N, et al. GLP-1 receptor activation improves microvascular function. *J Cereb Blood Flow Metab*. (2019) 39:1123–35. doi: 10.1177/0271678X18796723
94. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. (2019) 18:684–96. doi: 10.1016/S1474-4422(19)30079-1
95. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment. *Stroke*. (2011) 42:2672–713. doi: 10.1161/STR.0b013e3182299496
96. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus. *Lancet Neurol*. (2018) 17:407–18. doi: 10.1016/S1474-4422(18)30046-7
97. Dichgans M, Leys D. Vascular cognitive impairment. *Circ Res*. (2017) 120:573–91. doi: 10.1161/CIRCRESAHA.116.308426
98. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. *Diabetes*. (2014) 63:2262–72. doi: 10.2337/db13-1954
99. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring HU. Brain insulin resistance at the crossroads of metabolic and cognitive disorders. *Nat Rev Endocrinol*. (2016) 12:546–57. doi: 10.1038/nrendo.2016.94
100. Guillemot-Legrès O, Muccioli GG. Obesity-induced neuroinflammation: Beyond the hypothalamus. *Trends Neurosci*. (2017) 40:237–53. doi: 10.1016/j.tins.2017.02.005
101. Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S, et al. Obesity trajectories and risk of dementia. *BMJ*. (2018) 363:k4610. doi: 10.1136/bmj.k4610
102. Farr SA, Banks WA, Morley JE. Effects of liraglutide on cognition in obese mice. *Peptides*. (2016) 77:1–8. doi: 10.1016/j.peptides.2015.12.010
103. Hansen HH, Barkholt P, Fabricius K, Jelsing J, Terwel D, Pyke C, et al. The GLP-1 receptor agonist liraglutide improves memory function in obese rodents. *Neurobiol Learn Mem*. (2015) 120:65–74. doi: 10.1016/j.nlm.2015.02.002
104. Cork SC, Richards JE, Holt MK, Gribble FM, Reimann F, Trapp S, et al. Distribution and characterisation of GLP-1 receptor expressing cells in the mouse brain. *Mol Metab*. (2015) 4:718–31. doi: 10.1016/j.molmet.2015.07.008
105. Heni M, Kullmann S, Preissl H, Fritsche A, Häring HU. Impaired insulin action in the human brain: causes and metabolic consequences. *Nat Rev Endocrinol*. (2015) 11:701–11. doi: 10.1038/nrendo.2015.173
106. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus. *Lancet Neurol*. (2006) 5:64–74. doi: 10.1016/S1474-4422(05)70284-2
107. Moheet A, Mangia S, Seauquist ER. Impact of diabetes on cognitive function. *Diabetes Care*. (2015) 38:993–1002. doi: 10.2337/dc14-1444
108. Li Y, Tweedie D, Mattson MP, Holloway HW, Greig NH, Perry T, et al. GLP-1 receptor agonists protect synapses and cognition in diabetic models. *J Neurochem*. (2017) 140:471–83. doi: 10.1111/jnc.13927
109. Salameh TS, Bullock KM, Hujuel IA, Shah GN, Price TO, Banks WA, et al. Brain uptake and BBB effects of GLP-1 receptor agonists. *J Control Release*. (2020) 322:102–14. doi: 10.1016/j.jconrel.2020.03.012
110. Stranahan AM, Mattson MP. Metabolic reserve as a determinant of cognitive aging. *J Alzheimers Dis*. (2012) 30:S5–S14. doi: 10.3233/JAD-2012-111589
111. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet*. (2017) 390:2673–734. doi: 10.1016/S0140-6736(17)31363-6
112. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention and intervention. *Lancet*. (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6
113. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes. *Lancet*. (2021) 397:226–38. doi: 10.1016/S0140-6736(20)32345-7
114. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND). *Lancet*. (2019) 394:121–30. doi: 10.1016/S0140-6736(19)31149-3
115. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and safety outcomes with GLP-1 receptor agonists in type 2 diabetes. *Lancet Diabetes Endocrinol*. (2019) 7:776–85. doi: 10.1016/S2213-8587(19)30249-9
116. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Gastrointestinal adverse effects of GLP-1 receptor agonists in large cardiovascular outcome trials. *Diabetes Care*. (2020) 43:2306–14. doi: 10.2337/dc20-0456
117. Cummings J, Goldman DP, Simmons-Stern NR, Ponton E, Hendrix S, Carrillo MC, et al. Design of clinical trials for disease modification in neurodegenerative disorders. *Alzheimers Dement*. (2022) 18:2629–43. doi: 10.1002/alz.12615
118. Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide-1 (GLP-1). *Mol Metab*. (2019) 30:72–130. doi: 10.1016/j.molmet.2019.09.010
119. Grill HJ, Hayes MR. Hindbrain neurons as an essential hub in GLP-1 signaling. *Endocrinology*. (2012) 153:1943–7. doi: 10.1210/en.2012-1289
120. Salameh TS, Bullock KM, Hujuel IA, Shah GN, Price TO, Banks WA, et al. Central nervous system delivery and pharmacodynamics of GLP-1 receptor agonists. *J Control Release*. (2020) 322:102–14. doi: 10.1016/j.jconrel.2020.03.012
121. Zetterberg H, Blennow K. Fluid biomarkers for neurodegenerative diseases. *Nat Rev Neurol*. (2021) 17:91–105. doi: 10.1038/s41582-020-00431-2
122. Villemagne VL, Doré V, Burnham SC, Masters CL, Rowe CC. Imaging neurodegeneration and neuroinflammation in Alzheimer's disease. *Nat Rev Neurol*. (2018) 14:225–36. doi: 10.1038/nrneuro.2018.9
123. van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, O'Collins V, et al. Can animal models of disease reliably inform human studies? *PLoS Med*. (2010) 7:e1000245. doi: 10.1371/journal.pmed.1000245
124. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Cardiovascular outcome trials and secondary neurological endpoints. *Circulation*. (2019) 139:2884–96. doi: 10.1161/CIRCULATIONAHA.119.040153
125. Saver JL, Albers GW, Dunn B, Johnston KC, Fisher M. Stroke trial design and outcome measure selection. *Stroke*. (2012) 43:2184–91. doi: 10.1161/STROKEAHA.111.641928
126. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. *Front Endocrinol (Lausanne)*. (2019) 10:155. doi: 10.3389/fendo.2019.00155
127. Hölscher C. GLP-1 receptor agonists in neurodegenerative disease: class effect or drug-specific actions? *Neuropharmacology*. (2021) 182:108380. doi: 10.1016/j.neuropharm.2020.108380
128. Hampel H, Vergallo A, Perry G, Lista S. Precision medicine and biomarker-guided clinical trials in neurology. *Nat Rev Neurol*. (2019) 15:683–95. doi: 10.1038/s41582-019-0238-1
129. Finan B, Müller TD, Clemmensen C, Perez-Tilve D, DiMarchi RD, Tschöp MH. Reappraisal of GIP pharmacology for metabolic diseases. *Nat Rev Drug Discov*. (2016) 15:401–22. doi: 10.1038/nrd.2016.37
130. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. (2022) 387:205–16. doi: 10.1056/NEJMoa2206038
131. Clemmensen C, Müller TD, Woods SC, Berthoud HR, Seeley RJ, Tschöp MH. Gut-brain cross-talk in metabolic control. *Cell*. (2017) 168:758–74. doi: 10.1016/j.cell.2017.01.025
132. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab*. (2013) 17:819–37. doi: 10.1016/j.cmet.2013.04.008
133. Cummings J, Goldman DP, Simmons-Stern NR, Ponton E, Hendrix S, Carrillo MC, et al. Combination therapies in neurodegenerative disease. *Alzheimers Dement*. (2022) 18:2629–43. doi: 10.1002/alz.12615
134. Mattson MP. Systems biology of brain aging. *Nat Rev Neurosci*. (2020) 21:575–90. doi: 10.1038/s41583-020-00368-1
135. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. (2018) 14:535–62. doi: 10.1016/j.jalz.2018.02.018
136. Villemagne VL, Doré V, Burnham SC, Masters CL, Rowe CC. Imaging tau and amyloid- β proteinopathies. *Nat Rev Neurol*. (2018) 14:225–36. doi: 10.1038/nrneuro.2018.9
137. Hampel H, Toschi N, Baldacci F, Zetterberg H, Blennow K, Kilimann I, et al. Revolution of Alzheimer precision neurology. *Alzheimers Dement*. (2018) 14:1263–78. doi: 10.1016/j.jalz.2018.04.012
138. Espay AJ, Lang AE. Common myths in neurodegeneration clinical trials. *Lancet Neurol*. (2017) 16:451–2. doi: 10.1016/S1474-4422(17)30101-0
139. Cummings J, Aisen P, Lemere C, Atri A, Sabbagh M, Salloway S, et al. Aducanumab produced a clinically meaningful benefit? *Alzheimers Res Ther*. (2021) 13:98. doi: 10.1186/s13195-021-00838-z
140. Jack CR, Wiste HJ, Weigand SD, Therneau TM, Lowe VJ, Knopman DS, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Brain*. (2017) 140:372–84. doi: 10.1093/brain/aww273