RJNMSR
Review Journal of Neurological & Medical Sciences Review

Volume 4, Issue 6, 2026

THE BIOMARKER-PRIMED RECOVERY MODEL: SYNERGISTIC MODULATION OF THE IDOL-LRP1 PATHWAY AND METABOLIC FLUX TO OPTIMIZE FUNCTIONAL MOTOR REHABILITATION IN ALZHEIMER'S DISEASE

Muhammad Yaseen[1], Maryam Afzal[2], Muhammad Ubaid U Allah[3], Maheen Hidayat[4], Nimra Zahoor[5], Eeman Fatima[*6], Raheem Chaudhary[7], Romaisa Fatima[8], Maria Manan[9], Abu Sulman[10], Muhammad Saad Naeem[*11]

[1,2]*Islamabad Medical and Dental College Islamabad*
[3]*Department of Pharmacy, Faculty of Health and Pharmaceutical Sciences University of Agriculture Faisalabad*
[4]*Department of Physiotherapy, Faculty of Rehabilitation and Allied Health Sciences, Shaheed Benazir Bhutto Dewan University*
[5,6,8]*Department of Pharmacy, Lyallpur Institute of Advance Studies*
[7]*Department of Pharmacy, The University of Faisalabad*
[9]*Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Government College University Faisalabad*
[10,*11]*Department of Pharmacy, Faculty of Health and Pharmaceutical Sciences University of Agriculture Faisalabad*

[*6]ef7378784@gmail.com, [*11]drd54595@gmail.com

Corresponding Author: *
Eeman Fatima,
Muhammad Saad Naeem

DOI:https://doi.org/10.5281/zenodo.20826651

Received	Accepted	Published
24 April 2026	06 June 2026	21 June 2026

ABSTRACT

Multimodal neurorehabilitation, driven by biomarkers, is an important step towards treating Alzheimer's disease, as it overcomes the weaknesses of single-target therapy. This integrative approach is based on molecular priming, metabolic optimization, and precision-based rehabilitation to boost neuroplasticity and functional recovery. The main focus of this plan is the regulation of the IDOL-LRP1 system, which promotes amyloid-beta clearance and synaptic integrity, and the application of GLP-1 receptor agonists in order to normalize cerebral energy metabolism and mitochondrial activity. Neural priming is a critical notion, since it equips the biological substrate to react more favourably to the rehabilitative interventions. Planned protocols that involve high-intensity interval training and robot-assisted gait training also enhance synaptic remodelling and integration of motor pathways. Moreover, bio-digital integration with wearable sensors and adaptive feedback systems will provide an opportunity to monitor patient performance in real-time, as well as constantly adjust the intensity of the therapy. This individual treatment means that rehabilitation is related to biological readiness of the patient and offers the maximum of therapeutic effects. All in all, these strategies are not only able to maximize quick recovery, but also long-term sustainability of cognitive and motor improvements, which is a promising trend in future neurorestorative therapies.

Keywords: *IDOl-LRP1, Neurodegeneration, Alzheimer's disease, Rehabilitation.*

INTRODUCTION

By 2026, therapeutic provision of the Alzheimer disease (AD) has experienced a significant change whereby the use of single pharmacological agents is no longer seen as a viable option, but integrated, multimodal bio-rehabilitative models are being the preferred choice. The decades of therapeutic approaches were more or less dedicated to the specific pathological hallmarks, i.e., amyloid-2 plaques and tau protein tangles .z{Abe, 2019 #50} Although these methods have been useful in understanding disease pathobiology, their clinical utility has been low, and they have typically only shown a moderate effect with regards to symptomatic relief, but not much effect with regards to disease pathogenesis. The restriction has strengthened the knowledge that Alzheimer disease is a multifactorial disease that comprises multifaceted interactions between neuroinflammation, synaptic dysfunction, mitochondrial dysfunction, vascular abnormalities and systemic metabolic imbalances. Consequently, modern strategies have taken on a systems-based view that incorporates a combination of therapeutic modalities to re-establish functional capacity as opposed to focusing on discrete events at a molecular scale (Samanta et al., 2022).

This paradigm shift is based upon the fact that brain has some plasticity even when neurodegeneration occurs. Multimodal bio-rehabilitative models seek to exploit such residual plasticity through the integration of pharmacological, physical, cognitive, nutritional and neuromodulator technologies. In this regard, pharmacological agents are no longer considered as isolated therapeutic agents but as modifiers, which make the brain more responsive to behavioural and environmental stimuli. The progress in the field have artificial intelligence and multi-omics technologies has additionally made it possible to develop individualized treatment plans and customize interventions depending on a genetic, metabolic, and neurophysiological profile of a person. This combined strategy aims at not only reducing the progression of the disease but also enhancing the functional outcomes and quality of life (Clemente-Suárez et al., 2023).

In this changing paradigm, physical activity has come out as a pillar of non-pharmacological intervention. Exercise has been well known to enhance blood flow in the brain, release of neurotrophic factors like brain-derived neurotrophic factor (BDNF), and synaptic plasticity. These effects have been linked to cognitive, mood, and overall brain enhancements in early stages of the Alzheimer disease or in people at risk. A paradox however is seen when exercising is used at the late stages of the disease. Physical rehabilitation is usually associated with inconsistent or insignificant results in severely neuro degenerated patients despite its well-established advantages (Della Guardia, 2024).

It is possible to explain this paradox by the impaired integrity of neural substrate in severe Alzheimer disease. Massive neuron destruction, synaptic decline and neural network perturbation considerably impair the brain adaptive plasticity. The molecular pathways involved in activity-dependent synaptic strengthening, such as NMDA receptor signalling, regulation of calcium and mitochondrial energy production, are frequently defective. In turn, the resulting physiological stimuli of exercise might not cause the required neuroadaptive changes. In other instances, improperly calibrated or overexercise can actually cause a worsening of the stress pathways, amplify the oxidative stress and cause additional neuronal damage (Rajan, 2025).

This situation is further complicated by chronic neuroinflammation that forms an unfavourable microenvironment that suppresses neurogenesis and synaptic repair. Recruitment of microglia and an increase in pro-inflammatory cytokines like interleukin-1B and tumour necrosis factor-A disrupt neurotrophic signalling pathways, thus reducing the positive effects of exercise. Also, vascular impairment and decreased cerebral perfusion restricts oxygen and other necessary nutrients needed to sustain exercise-induced neuroplasticity. There are also behavioural and psychological issues, which result in the decreased effectiveness of exercise at advanced stages. Patients often lack interest, are hyperactive or lack motor control, and their cognitive function is impaired, so they are unable to engage in rehabilitation programs or follow structured exercise programs (Crisci, 2021).

Such constraints have motivated the development of the idea of priming, which is an essential breakthrough in the development of multimodal approaches to therapy. Priming is a technique that involves the preparation of the neural substrate by means of specific interventions, prior to the active use of behavioural therapy, which can be either exercise or cognitive training. The goal is to become more receptive to the external stimuli, and to increase the chances of making functional improvements meaningful, by optimising the internal environment of the brain (Stoykov & Madhavan, 2015). The method recognizes the ineffectiveness of rehabilitation in every situation and that the biological condition of the brain contributes a role in dictating the success of the therapy (Table 1).

Priming may be attained by a combination of pharmacological and biological medications designed to regulate major pathways that are used in the synaptic functioning, metabolism and inflammatory control. As an example, medications that augment cholinergic communication or stabilize glutamatergic signalling may augment synaptic performance, thus maximizing the outcome of the ensuing rehabilitative endeavours (Yap et al., 2013). It is possible to mitigate microglial activation and cytokines production with the use of anti-inflammatory agents, which would help to reestablish the microenvironment in which neurons can repair and be plastic. On the same note, cellular energy availability can be enhanced by interventions that aid the work of mitochondria and lower the amount of oxidative stress, which is critical to maintaining the neuroplastic process (Van Hasselt & Iyengar, 2019).

BDNF and nerve growth factor are neurotrophic factors that are central to priming of neurons, which are involved in survival, synaptic development and neurogenesis. The ability of the brain to respond to environmental changes can be greatly promoted by strategies that increase these either by pharmacological agents, nutritional supplementation or gene-based strategies. Besides biochemical interventions, non-invasive neuromodulation methods like transcranial magnetic stimulation and transcranial direct current stimulation have demonstrated potential to enhance cortical excitability and network connectivity (Skaper, 2017). These methods when administered before rehabilitation can enhance physical and cognitive training responsiveness of the brain.

Priming as part of multimodal bio-rehabilitative is the change of reactive to proactive modes of therapy. Instead of attempting to rehabilitate using a degraded neural environment, clinicians have the ability to first maximize the biological conditions of plasticity, thus enhancing the of successful outcomes. This practice is consistent with the tenets of systems medicine that focus on the effects of targeting interconnected pathways, and no single targets. Through a combination of pharmacological priming with structured exercise, cognitive training and nutritional support, synergistic effects can be attained in the overall therapeutic efficacy (Cramer et al., 2011).

This review addresses the changing paradigm of multimodal bio-rehabilitative approaches in the Alzheimer disease, the paradox of inefficacy of exercise in later stages of the disease, and the importance of neural priming. We point out the advantages of neuroplasticity and the effectiveness of further behavioural and rehabilitative interventions through pharmacological and biological preconditioning strategies (Onose et al., 2021).

Table 1: Overview of multimodal bio-rehabilitative strategies and priming approaches in Alzheimer's disease.

Component	**Mechanism of Action**	**Key Interventions**	**Target Pathways**	**Clinical Benefits**	**Limitations**	**References**
Pharmacological Priming	Enhances neurotransmission and stabilizes synaptic activity	Cholinesterase inhibitors, NMDA receptor modulators	Cholinergic and glutamatergic systems	Improved responsiveness to rehabilitation	Side effects, limited long-term efficacy	(Murali Doraiswamy, 2002)
Anti-inflammatory Modulation	Reduces neuroinflammation and cytokine burden	NSAIDs, cytokine inhibitors	Microglial activation, IL-1β, TNF-α	Restores neuroplastic environment	Variable efficacy	(Ajmone-Cat et al., 2010)
Neurotrophic Enhancement	Promotes neurogenesis and synaptic growth	BDNF enhancers, growth factor therapies	Synaptic plasticity pathways	Improved learning and memory	Delivery and stability issues	(Lee & Son, 2009)
Mitochondrial Support	Enhances cellular energy production	Coenzyme Q10, metabolic modulators	ATP synthesis, oxidative stress	Increased neuronal resilience	Limited clinical validation	(Madireddy & Madireddy, 2023)
Physical Exercise	Stimulates neuroplasticity and flow	Aerobic and resistance training	BDNF signalling, vascular function	Cognitive and motor improvements	Reduced efficacy in advanced AD	(Du et al., 2021)
Cognitive Training	Strengthens neural circuits	Memory tasks, digital therapies	Cortical connectivity	Improved executive function	Requires patient compliance	(Robledo-Castro et al., 2023)
Neuromodulation	Enhances cortical excitability	TMS, tDCS	Network synchronization	Improved cognition	Cost and accessibility	(To et al., 2018)
Nutritional Therapy	Supports brain metabolism and reduces inflammation	Omega-3 fatty acids, ketogenic diet	Metabolic and inflammatory pathways	Neuroprotection	Adherence challenges	(Pietrzak et al., 2022)
AI-driven Personalization	Optimizes therapy selection	Multi-omics and predictive modelling	Systems biology networks	Precision treatment	Data complexity	(Ali, 2023)
Behavioural Support	Enhances engagement and adherence	Caregiver training,	Psychological pathways	Improved outcomes	Resource-intensive	(RJ et al., 2025)

		behavioural therapy				

2.The Molecular Gatekeeper—The IDOL-LRP1 Pathway

2.1. IDOL as an E3 Ubiquitin Ligase: How IDOL can Degradate Receptors

IDOL (also called MYLIP, Myosin Regulatory Light Chain Interacting Protein) is an E3 ubiquitin ligase that is crucial in the regulation of lipid metabolism and receptor homeostasis in the peripheral tissues and in the central nervous system. Liver X receptors (LXRs) transcriptionally regulate IDOL and are activated by high levels of intracellular cholesterol. When activated, IDOL facilitates the ubiquitination of certain cell surface receptors, but most prominently the members of the low-density lipoprotein receptor (LDLR) family, and their lysosomal degradation (Laskar & Laskar).

The molecular pathway includes the recognition of conserved intracellular motifs of the cytoplasmic tails of the LDLR and LDL receptor-related protein 1 (LRP1) by IDOL. IDOL binds directly to these receptors by the physical action of its FERM (band 4.1, ezrin, radixin, moesin) domain, which promotes the exchange of ubiquitin moieties of E2 conjugating enzymes on to lysine residues on the receptor proteins. This ubiquitination identifies the endocytosis and degradation receptors of the receptors and in effect lowers the surface expression of the receptors (Zhang et al., 2012).

This regulatory axis has far-reaching consequences in the context of the Alzheimer disease. LRP1, in its turn, is a multifunctional receptor that plays a role in lipid transport, endocytosis, and amyloid-beta (A) clearance. The IDOL indirectly affects the capability of the brain to eliminate neurotoxic peptides by enhancing the degradation of LRP1. In this way, IDOL is a molecular gatekeeper which regulates the presence of receptors required to ensure neuronal and vascular homeostasis (Figure 1).

Critically, it has been found that dysregulation of the LXR–IDOL pathway occurs in pathological conditions such as neuroinflammation and metabolic stress. High levels of expression of IDOL may enhance the area of receptor loss that, in turn, weakens neuronal performance and leads to the development of the disease. This has made IDOL a potential therapeutic target with its inhibition potentially recovering levels of the receptors and enhancing cellular resilience (Toader et al., 2024).

2.1. LRP1 and the Peripheral Sink Effect an Amyloid-Beta Clearance Dynamics

One of the main pathological processes of the Alzheimer disease is the accumulation of amyloid-beta, which occurs due to an imbalance between its synthesis and clearance. The LRP1-mediated blood-brain barrier (BBB) transport is one of the most important among various routes involved in A beta clearance. LRP1 is abundantly expressed on the abluminal side of brain endothelial cells, and it helps the brain to transport ABB out of the interstitial fluid into the systemic circulation (Ramanathan et al., 2015).

The principle of the peripheral sink effect is that decreasing the amount of circulating A2 can stimulate its exit into the brain, thus reducing the amyloid burden in the brain. LRP1 is a key factor in this process as it can bind A across BBB to Apolipoprotein E (ApoE) carrier proteins and therefore transcytosis can occur. After getting into the periphery, A2 is further broken down by hepatic and renal systems (Ramanathan et al., 2015).

But this clearance pathway is perturbed by the degradation of LRP1 via IDOL. A decrease in the surface expression of LRP1 at the BBB decreases A β efflux, resulting in its build-up in the brain parenchyma and the formation of plaques. This does not only worsen neurotoxicity, but also facilitates a cascade of downstream, such as oxidative stress, synaptic dysfunction and neuroinflammation (Yang et al., 2025).

IDOL inhibition of LRP1 is an amyloid clearance. The maintenance of LRP1 allows restoring the effect of efficient A -hydro ferry across the BBB, thus improving the peripheral sink effect. Experimental research has shown that upregulation of LRP1 is associated with lesser amyloid load and enhanced cognitive performance in animals. In addition, LRP1 is also implicated with other clearance pathways, such as enzymatic degradation pathways with neprilysin and insulin-degrading enzyme, which its position as a core regulator of amyloid homeostasis (Erickson, 2012).

It is also interesting that a reduction in LRP1 expression is linked with aging and to which further exacerbates the impacts of IDOL activity. Thus, therapeutic interventions targeting the control of the IDOL-LRP1 axis can offer two-fold advantages since they can not only restore the receptors but also eliminate the age-related impairments in amyloid clearance (Sharma, 2025).

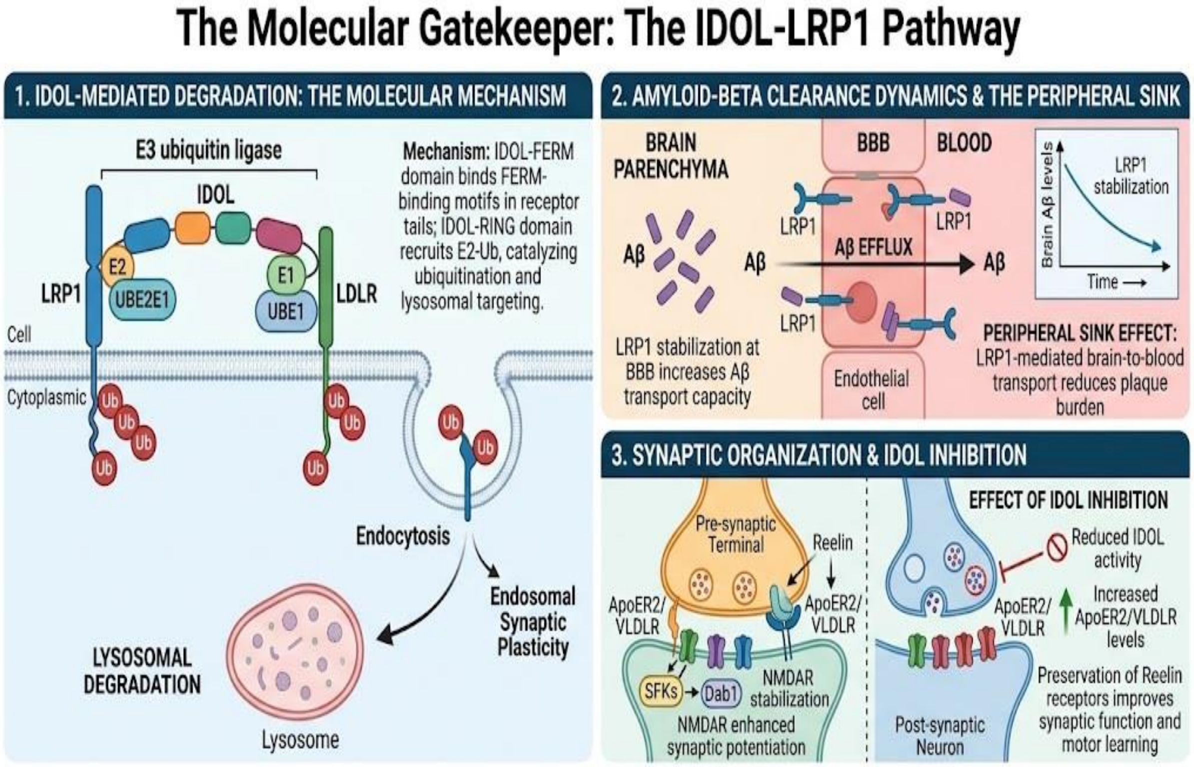

Figure 1: The Molecular Gatekeeper—The IDOL-LRP1 Pathway

2.3. Synaptic Organization: The Inhibition and Preservation of Reelin Receptors by IDOL

In addition to its involvement in lipid metabolism and amyloid clearance, the IDOL pathway has important consequences on the organization and plasticity of the synapses. Reelin is a glycoprotein that binds to the members of the LDLR family such as ApoE receptor 2 (ApoER2) and very-low-density lipoprotein receptor (VLDLR) and controls neuronal migration, dendritic spine growth, and synaptic strength. Reelin signalling plays a critical role in supporting synaptic architecture and various processes including learning and memory (Herz & Chen, 2006).

As with LDLR and LRP1, IDOL targets ApoER2 and VLDLR to be ubiquitinated and degraded. Increased IDOL activity, in turn, results in a drop in Reelin receptor availability that disrupts downstream signalling pathways that play a vital role in supporting synaptic activity. These involve perturbation of Dab1 (Disabled-1) phosphorylation cascade, regulating cytoskeletal dynamic and synaptic plasticity (Hong et al., 2010).

Reelin signalling is of utmost importance in Alzheimer disease in which synapse loss is a significant correlate of cognitive impairment. The results indicate that ApoER2 and VLDLR levels can be stabilized by preventing IDOL, thus preserving Reelin-mediated signalling pathways. This has been linked to a better synaptic integrity, a better long-term potentiation (LTP) and a better in learning and memory tasks in experimental models (Lane-Donovan & Herz, 2017).

Additionally, Reelin signalling has been demonstrated to prevent of the harmful outcomes of amyloid-beta such as tau hyperphosphorylation and synaptic toxicity. IDOL inhibition can offer a protective mechanism beyond structural maintenance into functional resilience by maintenance of Reelin receptors. This is especially applicable to the scenario of motor learning and coordination; wherein cerebellar and cortical loops are largely dependent on Reelin-dependent (Singh et al., 2024).

The second critical factor is the interaction between lipid metabolism and synaptic functions. The main lipid carrier in the brain ApoE combines with ApoER2 and VLDLR to control the cholesterol that is delivered to neurons. Cholesterol plays a crucial role in synapses and membrane stability, and dysregulation may lead to neurotransmission problems. This can be achieved by inhibiting the degradation of these receptors by the action of IDOL and thereby maintain a healthy lipid and healthy synapses (Lane-Donovan & Herz, 2017).

3.Fueling the Plasticity—Metabolic Flux & GLP-1 Agonism

3.1. Cerebral Hypometabolism: Type 3 Diabetes of the Alzheimer Disease

One of the most constant and initial pathological characteristics of Alzheimer disease is cerebral hypometabolism. Neuroimaging, especially fluorodeoxyglucose positron emission tomography, demonstrates that there is a significant decrease in glucose uptake and metabolism in the central areas of the brain such as hippocampus, temporal and motor cortices. Since glucose is the main energy source of neurons, the deficit in glucose metabolism causes the lack of activities of synapses, transmission of signals, and general neuronal activity (Daulatzai, 2017).

This form of metabolic dysfunction has resulted in the conceptualization of Alzheimer disease as "Type 3 Diabetes of the brain that is a state of insulin resistance in the brain. There is a lowered insulin signalling response on neurons which is necessary to control glucose transport and cellular metabolism. Consequently, there is a reduction in the expression of glucose transporters, which restricts the supply of glucose in the cell and thus, energy production is impaired. Insulin signalling is also vital to synaptic plasticity, learning and memory therefore its impairment is an aspect that leads to cognitive and motor impairment (Benarroch, 2014).

Cerebral hypometabolism in the motor cortex is a major challenge to successful rehabilitation. Activity-dependent remodelling of synapses is a process involved in motor learning and functional recovery, and thus it demands a lot of energy. The lack of energy will lead to neurons being unable to support the biochemical mechanisms behind synaptic strengthening and network reorganization. This causes discrepancy between energy requirements of rehabilitation and the metabolic capacity of the brain, and results in inconsistent therapy (Li & Sheng, 2022).

This is aggravated by mitochondrial dysfunction. Mitochondria in Alzheimer disease are less efficient in oxidative phosphorylation, with the result that there is a decrease in adenosine triphosphate production, and an increase in the production of reactive oxygen species. Such alterations not only reduce the energy supply, but also cause oxidative damage, which further deteriorates neuronal performance. Also, mitochondrial dynamics, modified fission and fusion processes, are part of the factors that lead to cellular instability and decreased resilience (Sheeran & Pepe, 2006).

In this condition the metabolic coupling between astrocytes and neurons also is influenced. In normal conditions, the astrocytes aid in the neuronal functioning by supplying lactate as an alternative energy source during the times of increased demand. But, when glucose metabolism is impaired, the process is destabilized, and the brain capacity to sustain energy demand in the process of rehabilitation is further diminished. All these elements make cerebral hypometabolism a serious impediment to neuroplasticity and functional recovery in Alzheimer disease (Bonvento & Bolanos, 2021).

3.2.GLP-1 Receptor Agonists as Biocatalysts: Increasing Energy and Mitochondrial activity

The glucagon-like peptide-1 receptor agonists are becoming promising therapeutic agents to treat the metabolic dysfunction in Alzheimer disease. Initially created to be used in the management of type 2 diabetes mellitus, these drugs, such as liraglutide, semaglutide, and exenatide, have shown considerable neuroprotective and metabolic results. They can cross the blood-brain barrier and hence have a direct action with cells of the central nervous system, such as neurons and glial cells. The GLP-1 receptors are ubiquitous in the brain, and they play a role in controlling cellular metabolism, survival and plasticity. The stimulation of these receptors leads to intracellular signalling pathways that include cyclic adenosine monophosphate, protein kinase A and phosphoinositide 3-kinase/protein kinase B. These pathways contribute to the increase in glucose uptake, enhance insulin sensitivity, and neuronal survival (Dong et al., 2022).

Among the most significant implications of GLP-1 receptor agonists, the improvement of the mitochondrial functions and energy generation should be mentioned. These agents stimulate major regulators of mitochondrial biogenesis, such as, AMP-activated protein kinase and peroxisome proliferator-activated receptor gamma coactivator-1 alpha. This causes the increase of mitochondrial number and efficiency of oxidative phosphorylation causing elevated adenosine triphosphate levels. GLP-1 agonists directly treat the metabolic impairments that are presented by Alzheimer disease by restoring the generation of cellular energy (Reznick & Shulman, 2006).

Besides increasing energy metabolism, GLP-1 receptor agonists also decrease oxidative stress through augmenting antioxidant defences and lowering the generation of reactive oxygen species. They are also involved in stabilizing mitochondrial membranes, calcium homeostasis, which is crucial in keeping neurons excited and avoiding cell death. All these effects result in a more desirable intracellular environment to enable neuronal functioning and plasticity (Houldsworth, 2024).

The anti-inflammatory effects are also observed with the activation of GLP-1 receptors. It suppresses the activation of microglial and the discharge of pro-inflammatory cytokines, improving the chronic neuroinflammatory situation in Alzheimer disease. This decreased inflammation also helps in metabolic recovery and an increase in the response to the rehabilitative interventions of the brain. Via clinical and preclinical research, GLP-1 receptor agonists have demonstrated the capability to enhance cognitive function, decrease amyloid pathology, and enhance synaptic integrity (Wang et al., 2015).

3.3. Pharmacological Synergy: Metabolic Flux: The Energy of Synaptogenesis

The creation of new synaptic connections (synaptogenesis) is a very energy-intensive process and needs a large volume of adenosine triphosphate. The brain tries to restructure its neural networks in the process of rehabilitation, particularly in motor and cognitive training, using activity-based plasticity. This would entail cytoskeletal remodelling, protein synthesis, vesicle transport and membrane expansion and require large amounts of metabolic resources (Arora, 2025).

The rate of processing energy substrates through the metabolic pathways to produce energy and vital biomolecules is known as metabolic flux. Increasing metabolic flux also makes sure that neurons receive an unlimited and adequate source of energy to aid in the formation of synapses and network adjustment. In Alzheimer disease, plasticity is restricted by impaired metabolic flux and thereby decreases the effectiveness of rehabilitation (Błaszczyk, 2025).

GLP-1 receptor agonists stimulate the metabolic flux through augmentation of glucose uptake and mitochondrial efficiency. This two-fold effect will make sure that the production of energy is equal to the enhanced demand created when rehabilitative activities are taking place. Due to this, the neurons will be in a better position to maintain the mechanisms needed to strengthen synapses and reorganize the networks.

Pharmacological synergy- This is the concept that is created when metabolic enhancement is used along with behavioural interventions. Physiological activity and mental training raise the activity of the neurons and energy. With this demand backed by enhanced availability of energy, then there are high chances of successful synaptic remodelling occurring. Conversely, in its absence, the same interventions might not yield significant results because of inadequate metabolic support (Clemente-Suárez et al., 2025).

Increased metabolic flux also aids in the making of vital biomolecules needed to develop synapses, such as neurotransmitters, structural proteins and membrane lipids. It also mediates the activation of plasticity-related signalling pathways like the mechanistic target of rapamycin and cyclic adenosine monophosphate response element-binding protein pathways. These pathways control expression of genes related to learning, memory and growth of the neurons (Caroni et al., 2012).

4.The "Biomarker-Primed" Clinical Protocol

The idea of a biomarker-primed clinical protocol is a significant development in the treatment of neurodegenerative diseases, especially Alzheimer, to match the treatment strategies with the biological preparedness of the patient. This approach does not follow a standard form of rehabilitation but instead, through the use of molecular indicators, the brain is most likely to respond to the intervention, which is why this approach will maximize the efficacy of any therapeutic intervention. In the first step, the biological optimization is a preparatory step in which key biomarkers like phosphorylated tau (p-Tau 217) and amyloid-beta ratios (A2/40) are measured to determine a readiness score. The level of underlying pathology, vulnerability of synapses, and competency of metabolism, which are reflected in this score, can be used by the clinicians to design interventions. Higher p-Tau 217 correlates well with tau pathology, neurodegeneration, whereas changes in A2 ratios of A242/40 are indicative of amyloid load and impaired clearance mechanisms (Table2). Combined, these biomarkers offer a quantitative model of assessing the presence of a neural environment allowing plasticity (Dal Bello-Haas, 2002). In this lead-in period, the pharmacological approach based on the inflammatory, metabolic, and receptor stabilization is introduced to enhance the internal environment of the brain. This can consist of mitochondrial functional improvement interventions, neurotrophic factor availability, and receptor system stabilization of neurotransmitter signalling. The aim is to decrease the pathological load and at the same time increase the biological substrate necessary to rehabilitate (Lukyanova & Kirova, 2015).

When the readiness score shows an ideal window, the protocol changes to the functional motor rehabilitation stage whereby behavioural and physical interventions are implemented in a very organized and focused way. High-Intensity Interval Training (HIIT) is a key factor in this stage because of the powerful impact on neuroplasticity and metabolic activation. HIIT is exercise where brief periods of intense exercise are separated by intervals of rest, and which stimulates the release of brain-derived neurotrophic factor (BDNF), a mediator of synaptic growth and plasticity. HIIT is even more effective, when used in combination with pre-pharmacological priming, which increases the sensitivity of BDNF to the receptor, to induce synaptic remodelling and functional recovery. The greater need caused by HIIT is facilitated by enhanced metabolic flux, making neurons able to maintain the processes of cytoskeletal reorganization, neurotransmitter production, and expansion of the membrane, required. This symbiosis of metabolic preparedness and physical activity allows an environment where neural networks can be restructured more effectively (Jiménez-Maldonado et al., 2018).

Simultaneously, Robot-Assisted Gait Training (RAGT) is a technologically advanced platform of strengthening motor pathways and enhancing coordination. RAGT systems provide repetitive, accurate and adaptive movement patterns to promote motor learning and the integration of neural pathways. The efficiency of this method is also increased by stabilization of receptor systems like LRP1 and Reelin receptors which are key in synaptic organization and neuronal communication. The brain will be in a better position to combine sensory and motor information during training by maintaining these receptor pathways during previous priming interventions. This results in better gait, balance and motor functionality. Also, RAGT enables a regular intensity and progression of which can be challenging to attain using traditional forms of rehabilitation, especially in cognitively impaired patients (Alrasheed et al., 2024).

The last step of the protocol is cantered on the maintenance, which is critical in maintaining the gains realized in the rehabilitation process and avoiding relapse. The problem of washout (initial improvement over time) is one of the most significant problems of neurorehabilitation because of the progressive character of the disease, as well as the discontinuation of intensive interventions. To deal with this, the maintenance stage focuses on the of metabolic maintenance and moderate exercise to maintain synaptic stability and network integrity. Ongoing administration of metabolic stimulants, including those that aid mitochondrial activity and glucose metabolism, can sustain sufficient energy need in neuronal functions. Meanwhile, frequent low- to moderate-intensity physical activity, as well as cognitive involvement, keeps neural networks active and flexible. Biomarker monitoring can also be carried on throughout this stage to identify the initial signs of deterioration and intervene with a necessary adjustment of intervention (Moss & Cook, 2012).

This is a biomarker-directed process that will be a transition to precision rehabilitation, wherein interventions are brought dynamically into harmony with the biological condition of the patient. Through the combination of molecular diagnostics and specific therapeutic approaches, the treatment results can be made more effective and lasting. The protocol does not only tackle the underlying pathology but also takes advantage of the plasticity of the brain in a controlled and optimized way. Consequently, it can provide an overall approach to enhancing both cognitive and motor ability in neurodegenerative patients (Martino et al., 2011).

Table 2: Biomarker-Primed Clinical Protocol in Neurorehabilitation

Phase	Stage Name	Primary Objective	Key Biomarkers / Inputs	Core Interventions	Molecular & Cellular Mechanisms	Neural Systems Targeted	Functional Outcomes	Clinical Monitoring Tools	Translational Significance	References
Phase A	Biological Optimization (Lead-In)	Establish neural readiness for rehabilitation	p-Tau 217, Aβ42/40 ratio, neurofilament light chain, inflammatory cytokines	Anti-inflammatory therapy, metabolic enhancers, receptor stabilization agents	Reduction of tau phosphorylation, improved amyloid clearance, stabilization of membrane recepto	Hippocampus, cortical association areas, BBB endothelial interface	Improved synaptic baseline stability, reduced neurotoxicity, enhanced plasticity potential	CSF biomarker profiling, blood plasma assays, PET imaging	Creates biologically permissive environment for neuroplasticity	(Virk, 2022)

					rs, mitochondrial efficiency enhancement					
Phase A	Readiness Scoring System	Quantify rehabilitation eligibility	Composite biomarker index (tau burden, amyloid ratio, metabolic status)	AI-driven biomarker integration models	Multivariate normalization of disease load and metabolic capacity	Whole-brain network assessment	Personalized therapy timing and stratification	Machine learning predictive models	Enables precision rehabilitation initiation	(Saliev, 2025)
Phase A	Metabolic Preconditioning	Restore energy homeostasis	Glucose uptake rate, insulin signalling markers, ATP levels	GLP-1 receptor agonists, insulin sensitizers	Activation of AMPK, PGC-1α pathways, improved mitochondrial biogenesis	Cortical motor networks, basal ganglia	Enhanced neuronal energy availability	FDG-PET imaging, mitochondrial assays	Removes metabolic bottleneck for plasticity	(Chen et al., 2025)
Phase A	Receptor Stabilization Module	Preserve synaptic receptor integrity	LRP1, LDLR, ApoER2 expression levels	IDOL inhibition strategies, lipid regulation therapy	Reduced ubiquitination of LDLR family receptors, increased receptor	BBB transport systems, synaptic membranes	Improved amyloid clearance, synaptic signalling preservation	Molecular receptor imaging, proteomic profiling	Enhances clearance and synaptic signalling capacity	(Yu et al., 2021)

					recycling					
Phase B	Functional Activation (HIIT Phase)	Induce neuroplasticity via high energy demand	BDNF levels, lactate concentration, cortisol response	High-Intensity Interval Training (HIIT), resistance training	Increased BDNF secretion, synaptic potentiation, calcium-dependent signalling activation	Motor cortex, cerebellum, hippocampal circuits	Improved memory, motor strength, executive function	VO_2 max testing, wearable biosensors, cognitive scales	Converts metabolic readiness into functional gains	(Di Liegro et al., 2019)
Phase B	Synaptic Remodelling Phase	Strengthen neural connectivity	Synaptic density markers, PSD-95, synaptophysin	Combined exercise + cognitive training	Activity-dependent synaptogenesis, dendritic spine growth	Cortico-hippocampal networks	Enhanced learning capacity, improved recall	EEG connectivity mapping, fMRI	Reinforces long-term circuit restructuring	(Barrantes, 2024)
Phase B	Robot-Assisted Gait Training (RAGT)	Restore motor coordination and gait stability	LRP1-Reelin axis markers, motor evoked potentials	Robotic exoskeleton gait training	Reelin-Dab1 signalling preservation, motor pathway reinforcement	Spinal locomotor circuits, motor cortex, cerebellum	Improved gait symmetry, balance, reduced fall risk	Motion capture systems, gait kinematics	Enhances precision motor rehabilitation	(Shishi et al., 2024)
Phase B	Neurovascular Coupling Enhancement	Improve blood flow and oxygen delivery	Cerebral blood flow velocity, endothelial nitric	Aerobic exercise, vascular modulation drugs	Improved endothelial function, increased	Cortical and subcortical vascular networks	Enhanced endurance, reduced fatigue	Doppler ultrasound, MRI perfusion imaging	Supports sustained neuroplastic activity	(Zhong et al., 2025)

			oxide levels		perfusion					
Phase B	Neurotrophic Sensitization	Amplify response to growth factors	BDNF receptor sensitivity, TrkB activation levels	Pharmacological priming + exercise synergy	Upregulation of TrkB signalling, CREB activation	Hippocampus, prefrontal cortex	Improved learning and memory consolidation	Molecular receptor assays	Maximizes rehabilitation efficiency	(Li et al., 2025)
Phase B	Cognitive-Motor Integration	Synchronize motor and cognitive systems	EEG coherence, task-based activation patterns	Dual-task training, virtual reality therapy	Network reorganization across cognitive-motor loops	Fronto-parietal networks	Improved multitasking, coordination	EEG, VR performance metrics	Enhances real-world functional adaptation	(Bonanno et al., 2025)
Phase C	Maintenance Phase (Stability Phase)	Sustain functional gains	Synaptic stability markers, metabolic rate, inflammatory indices	Moderate exercise, dietary regulation, metabolic support	Maintenance of mitochondrial efficiency, suppression of chronic inflammation	Global brain networks	Long-term cognitive stability	Periodic biomarker reassessment	Prevents relapse and functional decline	(Kong et al., 2025)
Phase C	Metabolic Flux Preservation	Prevent energy decline post-rehabilitation	Glucose metabolism rate, ATP turnover	Continued GLP-1 agonist therapy, nutritional optimization	Sustained AMPK activation, mitochondrial maintenance	Cortical and subcortical circuits	Maintained cognitive and motor performance	Metabolic imaging, blood assays	Ensures durability of therapeutic gains	(Pingue et al., 2025)
Phase C	Anti-Inflammatory Maintenance	Control chronic neuroinflammation	IL-6, TNF-α, microglial activat	Low-dose anti-inflammatory	Microglial quiescence, cytokine	Limbic system, cortical immu	Reduced neurodegeneration rate	Cytokine profiling	Slows disease progression	(Zhang et al., 2026)

			ion markers	strategies	suppression	ne interfaces				
Phase C	Synaptic Preservation Strategy	Maintain connectivity integrity	Synaptic density, dendritic spine stability	Cognitive engagement, stimulation therapy	Prevention of synaptic pruning and loss	Cortical association networks	Sustained cognitive function	Neuroimaging, cognitive batteries	Maintains functional architecture	(Barrantes, 2024)
Phase C	Lifestyle Reinforcement Module	Long-term behavioural stabilization	Physical activity indices, sleep quality metrics	Structured lifestyle programs	Circadian regulation, stress reduction	Whole-brain regulation systems	Improved daily functioning	Wearable tracking devices	Enhances long-term adherence	(Gerhardsson et al., 2022)
Phase C	Washout Prevention Strategy	Prevent loss of rehabilitation gains	Functional decline markers, activity levels	Booster rehabilitation sessions	Reinforcement of synaptic plasticity cycles	Motor and cognitive networks	Sustained independence	Longitudinal functional assessment	Ensures continuity of benefit	(Paterno, 2026)
Phase C	AI-Guided Adaptive Monitoring	Dynamic adjustment of therapy	Multimodal data integration (biomarkers, imaging, behaviour)	Machine learning-guided treatment modification	Predictive modelling of decline and response	Whole-brain connectome	Personalized long-term optimization	Digital health platforms	Enables precision long-term care	(Onciul et al., 2025)

5.Clinical Implementation: Strategic Protocols for Functional Motor Restoration

5.1. The Chronobiological Approach

After biological priming has been done successfully, the time of rehabilitation turns out to be a crucial factor in a therapeutic outcome. The chronobiological approach aims at timing the highest intensity motor training sessions with those intervals when physiological readiness is at its highest levels, especially at times when the GLP-1 plasma levels and metabolic rate are high. This timing match makes sure that the neurons are optimally energized and receptor sensitive in the time of training. Clinicians can optimize the synaptic responsiveness and efficiency of neuroplastic processes by exploiting circadian rhythms and pharmacokinetic of metabolite agents. The use of these peak windows during training enhances energy use, helps to maintain neuronal firing, and improve chances of lasting functional gains (TAKI & AKDAĞ).

5.2. Precision Neuromotor Training

After the neural base is stabilized, rehabilitation techniques are presented which are precision based and are introduced to actively stimulate and strengthen motor circuits. Robot-Assisted Gait Training (RAGT) offers a pattern of movement which is structured, repetitive and adaptive and reinforces motor learning and pathway integration. This is complemented with exergaming platforms, which combines physical activity with a cognitive challenge to activate more than one neural net at a time. These therapeutic mechanisms have a specific effect on synaptophysin-linked synaptic vesicle activity, and LRP1-linked signalling pathways, which are important in efficient neurotransmission and circuit stability (Figure2). Precision neuromotor training fosters neural coordination, balance, and motor planning, and long-term neural adaptation by increasing variability, and progressing with difficulty (Esquenazi & Packel, 2012).

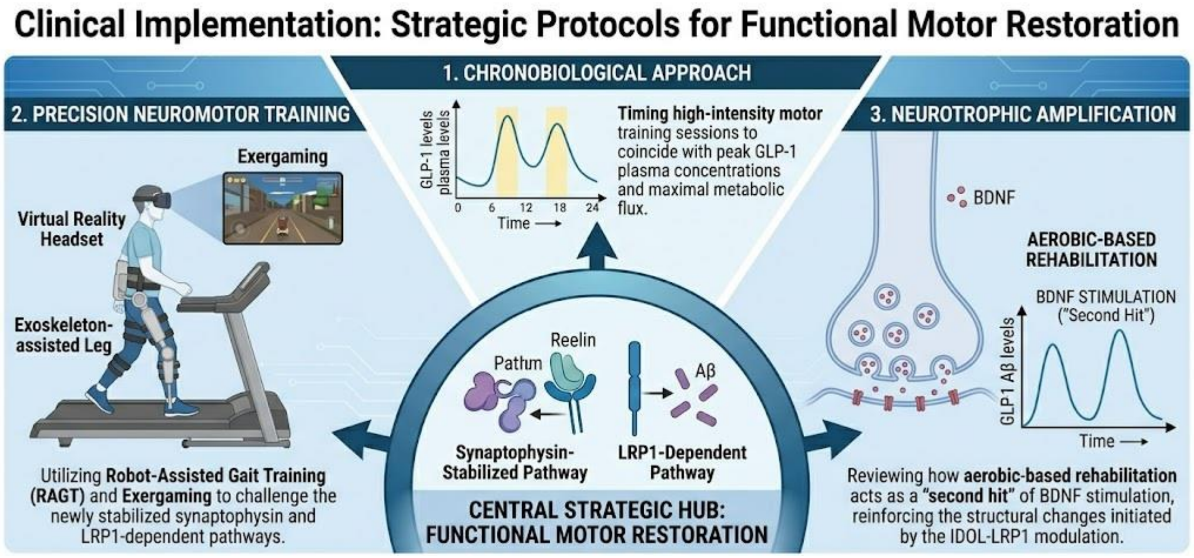

Figure 2: Clinical Implementation: Strategic Protocols for Functional Motor Restoration

5.3. Neurotrophic Amplification

Rehabilitation based on aerobic exercises is an effective enhancer of neuroplasticity since it is a secondary stimulus to release brain-derived neurotrophic factor. This second-hit effect is a continuation of earlier pharmacological priming which has an additional effect of increasing synaptic growth and stabilization. Enhanced BDNF levels aid the formation of dendritic spines, reinforcement of synapses and long-term potentiation. Aerobic exercise when coupled with metabolically optimized conditions, provides a synergistic environment to hasten functional recovery and consolidate motor learning (Ambrogio, 2024).

6.The Future of Neuro restoration: Bio-Digital Integration and Adaptive Rehabilitation

6.1. Wearable Biomarker Feedback Loops

There is a redefinition of the monitoring of the rehabilitation results in real time due to bio-digital technologies integration. Wearable sensors that can monitor gait symmetry, stride length and walking velocity can give unremitting and non-invasive data that can be used to measure motor performance. These digital measures are functional proxies of underlying biological functions, including amyloid clearance, synaptic efficiency and metabolic state. The association of movement patterns with a physiological data will allow clinicians to make inferences about whether neuroplastic processes are successfully invoked. This feedback loop makes it possible to make necessary changes in the therapy instantly, so that rehabilitation is not out of step with the changing biological status of the patient. Such systems allow predictive models to be created over time and predict when the decline or improvement will occur, thus turning rehabilitation into a proactive and responsive process (Palumbo et al., 2021).

6.2. The “Rehabilitation Prescription”

One significant change in clinical practice is to make rehabilitation a movable, data-based prescription and not a set of instructions. The intensity, duration and modality of therapy in this model is modified on a daily basis depending on the score of proteomic and metabolic readiness of the patient. These are the scores based on combination of biomarker profiles such as indicators of inflammation, energy metabolism and synaptic activity. Interventions can be modified to the current state of the patient biologically; thus, clinicians can prevent overtraining at optimal times and overloading patients during vulnerable times. This accuracy model guarantees every rehabilitation session is performed at the optimal intensity to optimize the results and reduce fatigue and risk (Lanotte et al., 2023).

6.3. Sustainability of Gains

The motor skills that are retained over the long term is one of the key indicators of the success of rehabilitation. There is some evidence that indicates that patients who experience biologically primed rehabilitation have a higher functional improvement that is more durable than their counterparts who receive normal care. The long-term metabolic support and continuous adaptive training can maintain synaptic integrity and avoid regression. This will not only increase the recovery in the short term but also the long-term independence and quality of life (Musicco et al., 2003).

7.Conclusion

To sum up, the new paradigm of biomarker-primed, multimodal neurorehabilitation is a groundbreaking development in the process of Alzheimer disease and other neurodegenerative disorders treatment. This method combines molecular priming, metabolic optimization and precision-guided rehabilitation to stimulate neuroplasticity and functional recovery by going beyond isolated therapeutic strategies. At the centre of this structure is the acknowledgement that successful rehabilitation requires neural substrate biological preparedness, which can be adjusted by applying specific interventions: stabilization of the IDOL-LRP1 pathway and enhancement of the metabolic condition under the influence of the GLP-1. Real-time monitoring and individualized changes in the treatment can also be facilitated by the introduction of sophisticated technologies, such as wearable sensors and adaptive feedback systems. Notably, this approach does not just enhance short-term rehabilitation but also sustainability of motor and cognitive improvements in the long term. With the development of the sphere, the overlap of bio-digital tools, systems biology, and personalized medicine is likely to streamline these protocols, make them more accessible and efficient. Finally, the integrative solution has a great potential of redefining neuro restoration and enhancing quality of life in patients with neurodegenerative diseases.

References

Ajmone-Cat, M. A., Bernardo, A., Greco, A., & Minghetti, L. (2010). Non-steroidal anti-inflammatory drugs and brain inflammation: effects on microglial functions. *Pharmaceuticals*, 3(6), 1949-1965.

Ali, H. (2023). Artificial intelligence in multi-omics data integration: Advancing precision medicine, biomarker discovery and genomic-driven disease interventions. *Int J Sci Res Arch*, 8(1), 1012-1030.

Alrasheed, R. A. R., Alanazi, S. F. S., Almutairi, R. O., Alshibani, R. M., Daghriri, R. I. A., Alshammari, M. M., Alotaibi, A. A. M., Alharbi, S. A., Alanazi, T. R., & Alharbi, Y. M. B. (2024). Brain Stroke: Physical Therapy and Rehabilitation Techniques-An Updated Review. *Egyptian Journal of Chemistry*, 67(13), 2245-2257.

Ambrogio, I. O. G.-S. (2024). Congress Chairs. *Clinical and Experimental Rheumatology*, *42*, 1285-1310.

Arora, R. (2025). *An integrated multi-omics approach to improve our understanding of ageing and neurodegeneration*

Barrantes, F. J. (2024). Cognitive synaptopathy: synaptic and dendritic spine dysfunction in age-related cognitive disorders. *Frontiers in aging neuroscience*, *16*, 1476909.

Benarroch, E. E. (2014). Brain glucose transporters: implications for neurologic disease. *Neurology*, *82*(15), 1374-1379.

Błaszczyk, J. W. (2025). Biomolecular Basis of Life. *Metabolites*, *15*(6), 404.

Bonanno, M., De Pasquale, P., Fonti, B., Gjonaj, E., De Salvo, S., Quartarone, A., & Calabrò, R. S. (2025). Neural control meets biomechanics in the motor assessment of neurological disorders: a narrative review. *Frontiers in Neural Circuits*, *19*, 1608328.

Bonvento, G., & Bolanos, J. P. (2021). Astrocyte-neuron metabolic cooperation shapes brain activity. *Cell metabolism*, *33*(8), 1546-1564.

Caroni, P., Donato, F., & Muller, D. (2012). Structural plasticity upon learning: regulation and functions. *Nature reviews neuroscience*, *13*(7), 478-490.

Chen, J., Liu, B., Yao, X., Yang, X., Sun, J., Yi, J., Xue, F., Zhang, J., Shen, Y., & Chen, B. (2025). AMPK/SIRT1/PGC-1α Signaling Pathway: Molecular Mechanisms and Targeted Strategies From Energy Homeostasis Regulation to Disease Therapy. *CNS Neuroscience & Therapeutics*, *31*(11), e70657.

Clemente-Suárez, V. J., Martín-Rodríguez, A., Curiel-Regueros, A., Rubio-Zarapuz, A., & Tornero-Aguilera, J. F. (2025). Neuro-nutrition and exercise synergy: exploring the bioengineering of cognitive enhancement and mental health optimization. *Bioengineering*, *12*(2), 208.

Clemente-Suárez, V. J., Martín-Rodríguez, A., Redondo-Flórez, L., López-Mora, C., Yáñez-Sepúlveda, R., & Tornero-Aguilera, J. F. (2023). New insights and potential therapeutic interventions in metabolic diseases. *International journal of molecular sciences*, *24*(13), 10672.

Cramer, S. C., Sur, M., Dobkin, B. H., O'Brien, C., Sanger, T. D., Trojanowski, J. Q., Rumsey, J. M., Hicks, R., Cameron, J., & Chen, D. (2011). Harnessing neuroplasticity for clinical applications. *Brain*, *134*(6), 1591-1609.

Crisci, I. (2021). A study on the cellular and molecular mechanisms underlying adult hippocampal neurogenic niche response to neuroinflammation.

Dal Bello-Haas, V. (2002). A framework for rehabilitation of neurodegenerative diseases: planning care and maximizing quality of life. *Journal of Neurologic Physical Therapy*, *26*(3), 115-129.

Daulatzai, M. A. (2017). Cerebral hypoperfusion and glucose hypometabolism: Key pathophysiological modulators promote neurodegeneration, cognitive impairment, and Alzheimer's disease. *Journal of neuroscience research*, *95*(4), 943-972.

Della Guardia, L. (2024). Exercise and non-pharmacological interventions to improve metabolic health and well-being in chronic conditions.

Di Liegro, C. M., Schiera, G., Proia, P., & Di Liegro, I. (2019). Physical activity and brain health. *Genes*, *10*(9), 720.

Dong, M., Wen, S., & Zhou, L. (2022). The relationship between the blood-brain-barrier and the central effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 2583-2597.

Du, X., Chen, W., Zhan, N., Bian, X., & Yu, W. (2021). The effects of low-intensity resistance training with or without blood flow restriction on serum BDNF, VEGF and perception in patients with post-stroke depression. *Neuroendocrinology Letters*, *42*(4), 229-235.

Erickson, M. A. (2012). *Inflammatory regulation of amyloid beta transport across the blood-brain barrier: Implications for Alzheimer's disease* Saint Louis University].

Esquenazi, A., & Packel, A. (2012). Robotic-assisted gait training and restoration. *American journal of physical medicine & rehabilitation*, *91*(11), S217-S231.

Gerhardsson, K. M., Iwarsson, S., & Schmidt, S. (2022). Light, activity and sleep in my daily life:: Design of an online intervention targeting changes to routines and the home.

Herz, J., & Chen, Y. (2006). Reelin, lipoprotein receptors and synaptic plasticity. *Nature reviews neuroscience*, *7*(11), 850-859.

Hong, C., Duit, S., Jalonen, P., Out, R., Scheer, L., Sorrentino, V., Boyadjian, R., Rodenburg, K. W., Foley, E., & Korhonen, L. (2010). The E3 ubiquitin ligase IDOL induces the degradation of the low density lipoprotein receptor family members VLDLR and ApoER2. *Journal of Biological Chemistry*, *285*(26), 19720-19726.

Houldsworth, A. (2024). Role of oxidative stress in neurodegenerative disorders: a review of reactive oxygen species and prevention by antioxidants. *Brain Communications*, *6*(1), fcad356.

Jiménez-Maldonado, A., Rentería, I., García-Suárez, P. C., Moncada-Jiménez, J., & Freire-Royes, L. F. (2018). The impact of high-intensity interval training on brain derived neurotrophic factor in brain: a mini-review. *Frontiers in neuroscience*, *12*, 839.

Kong, J., Xie, Y., Fan, R., Wang, Q., Luo, Y., & Dong, P. (2025). Exercise orchestrates systemic metabolic and neuroimmune homeostasis via the brain–muscle–liver axis to slow down aging and neurodegeneration: a narrative review. *European Journal of Medical Research*, *30*(1), 475.

Lane-Donovan, C., & Herz, J. (2017). The ApoE receptors Vldlr and Apoer2 in central nervous system function and disease: Thematic Review Series: ApoE and Lipid Homeostasis in Alzheimer's Disease. *Journal of lipid research*, *58*(6), 1036-1043.

Lanotte, F., O'Brien, M. K., & Jayaraman, A. (2023). AI in rehabilitation medicine: opportunities and challenges. *Annals of Rehabilitation Medicine*, *47*(6), 444-458.

Laskar, M. G., & Laskar, A. MYLIP/IDOL in regulation to cholesterol metabolism.

Lee, E.-G., & Son, H. (2009). Adult hippocampal neurogenesis and related neurotrophic factors. *BMB reports*, *42*(5), 239-244.

Li, J., Sun, L., Fang, F., & Morshedi, M. (2025). Enhancing neuroprotection through exercise: the synergistic effects of bioactive plant compounds via the CREB-BDNF signaling pathway. *Journal of Neuroimmune Pharmacology*, *20*(1), 69.

Li, S., & Sheng, Z.-H. (2022). Energy matters: presynaptic metabolism and the maintenance of synaptic transmission. *Nature reviews neuroscience*, *23*(1), 4-22.

Lukyanova, L. D., & Kirova, Y. I. (2015). Mitochondria-controlled signaling mechanisms of brain protection in hypoxia. *Frontiers in neuroscience*, *9*, 320.

Madireddy, S., & Madireddy, S. (2023). Therapeutic strategies to ameliorate neuronal damage in epilepsy by regulating oxidative stress, mitochondrial dysfunction, and neuroinflammation. *Brain sciences*, *13*(5), 784.

Martino, G., Pluchino, S., Bonfanti, L., & Schwartz, M. (2011). Brain regeneration in physiology and pathology: the immune signature driving therapeutic plasticity of neural stem cells. *Physiological reviews*, *91*(4), 1281-1304.

Moss, R., & Cook, C. C. (2012). Maintenance and relapse prevention. *Foundations of Addictions Counseling, 2nd Edition, Pearson Education, Upper Saddle River*, 260-277.

Murali Doraiswamy, P. (2002). Non-cholinergic strategies for treating and preventing Alzheimer's disease. *CNS drugs*, *16*(12), 811-824.

Musicco, M., Emberti, L., Nappi, G., Caltagirone, C., & Patients, I. M. S. o. O. o. R. o. N. (2003). Early and long-term outcome of rehabilitation in stroke patients: the role of patient characteristics, time of initiation, and duration of interventions. *Archives of physical medicine and rehabilitation*, *84*(4), 551-558.

Onciul, R., Tataru, C.-I., Dumitru, A. V., Crivoi, C., Serban, M., Covache-Busuioc, R.-A., Radoi, M. P., & Toader, C. (2025). Artificial intelligence and neuroscience: Transformative synergies in brain research and clinical applications. *Journal of Clinical Medicine*, *14*(2), 550.

Onose, G., Anghelescu, A., Blendea, C. D., Ciobanu, V., Daia, C. O., Firan, F. C., Munteanu, C., Oprea, M., Spinu, A., & Popescu, C. (2021). Non-invasive, non-pharmacological/bio-technological interventions towards neurorestoration upshot after ischemic stroke, in adults—Systematic, synthetic, literature review. *Frontiers in Bioscience-Landmark*, *26*(11), 1204-1239.

Palumbo, A., Vizza, P., Calabrese, B., & Ielpo, N. (2021). Biopotential signal monitoring systems in rehabilitation: A review. *Sensors*, *21*(21), 7172.

Paterno, A. (2026). Rewiring movement in Parkinson's disease: exercise, neuromodulation, and motor control-bridging neuroplasticity, gait biomechanics, and fatigue management for advanced rehabilitation.

Pietrzak, D., Kasperek, K., Rękawek, P., & Piątkowska-Chmiel, I. (2022). The therapeutic role of ketogenic diet in neurological disorders. *Nutrients*, *14*(9), 1952.

Pingue, V., Bossert, I., D'Ambrosio, D., Nardone, A., Trifirò, G., Canessa, N., & Franciotta, D. (2025). Brain glucose metabolism in patients with traumatic brain injury undergoing rehabilitation: a longitudinal 18F-FDG PET study. *Frontiers in neurology*, *16*, 1556427.

Rajan, R. K. (2025). A comprehensive review on adaptive plasticity and recovery mechanisms post-acquired brain injury. *Neuroprotection*, *3*(3), 226-252.

Ramanathan, A., Nelson, A. R., Sagare, A. P., & Zlokovic, B. V. (2015). Impaired vascular-mediated clearance of brain amyloid beta in Alzheimer's disease: the role, regulation and restoration of LRP1. *Frontiers in aging neuroscience*, *7*, 136.

Reznick, R. M., & Shulman, G. I. (2006). The role of AMP-activated protein kinase in mitochondrial biogenesis. *The Journal of physiology*, *574*(1), 33-39.

RJ, V., Mathias, E. G., Bhavana, R. S., Patil, S. P., & Kamath, R. (2025). Barriers and Facilitators of Implementing Cognitive Behavioral Therapy: A Systematic Review Based on the Consolidated Framework for Implementation. *Scientifica*, *2025*(1), 2693791.

Robledo-Castro, C., Castillo-Ossa, L. F., & Corchado, J. M. (2023). Artificial cognitive systems applied in executive function stimulation and rehabilitation programs: a systematic review. *Arabian journal for science and engineering*, *48*(2), 2399-2427.

Saliev, T. (2025). Brain aging: Unlocking personalized strategies for cognitive resilience. *Brain Network Disorders*, *1*(04), 217-229.

Salomone, S., Caraci, F., Leggio, G. M., Fedotova, J., & Drago, F. (2012). New pharmacological strategies for treatment of Alzheimer's disease: focus on disease modifying drugs. *British journal of clinical pharmacology*, *73*(4), 504-517.

Samanta, S., Ramesh, M., & Govindaraju, T. (2022). Alzheimer's is a Multifactorial Disease.

Sharma, V. K. (2025). Exploring LRP-1 in the liver-brain axis: implications for Alzheimer's disease. *Molecular Biology Reports*, *52*(1), 873.

Sheeran, F. L., & Pepe, S. (2006). Energy deficiency in the failing heart: linking increased reactive oxygen species and disruption of oxidative phosphorylation rate. *Biochimica et Biophysica Acta (BBA)-Bioenergetics*, *1757*(5-6), 543-552.

Shishi, C., Zhang, W., Dingyu, W., & Zhaoming, C. (2024). How robot-assisted gait training affects gait ability, balance and kinematic parameters after stroke: a systematic review and meta-analysis. *EuropEan Journal of physical and rEhabilitation MEdicinE*, 60(3), 400.

Singh, M. K., Shin, Y., Ju, S., Han, S., Kim, S. S., & Kang, I. (2024). Comprehensive overview of Alzheimer's disease: etiological insights and degradation strategies. *International journal of molecular sciences*, *25*(13), 6901.

Skaper, S. D. (2017). Neurotrophic factors: an overview. *Neurotrophic factors: methods and protocols*, 1-17.

Stoykov, M. E., & Madhavan, S. (2015). Motor priming in neurorehabilitation. *Journal of Neurologic Physical Therapy*, *39*(1), 33-42.

TAKI, F. N., & AKDAĞ, K. Ç. Circadian Rhythms and Chronotherapy: Integrating Molecular and Physiological Mechanisms into Physiotherapy and Rehabilitation Sciences. *Şerife DEMİR, F. Nur TAKI, Yusuf UZUN*, 139.

To, W. T., De Ridder, D., Hart Jr, J., & Vanneste, S. (2018). Changing brain networks through non-invasive neuromodulation. *Frontiers in human neuroscience*, *12*, 128.

Toader, C., Tataru, C. P., Munteanu, O., Serban, M., Covache-Busuioc, R.-A., Ciurea, A. V., & Enyedi, M. (2024). Decoding neurodegeneration: a review of molecular mechanisms and therapeutic advances in Alzheimer's, Parkinson's, and ALS. *International journal of molecular sciences*, *25*(23), 12613.

Van Hasselt, J. C., & Iyengar, R. (2019). Systems pharmacology: defining the interactions of drug combinations. *Annual review of pharmacology and toxicology*, *59*(1), 21-40.

Virk, G. K. (2022). *Blood based biomarkers for the identification of Alzheimer's disease using proteomics approaches* University of New South Wales (Australia)].

Wang, W.-Y., Tan, M.-S., Yu, J.-T., & Tan, L. (2015). Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Annals of translational medicine*, *3*(10), 136.

Yang, W., Wei, Z., & Wang, T. (2025). Unraveling the Role of LRP1 in Alzheimer's Disease: A Focus on Aβ Clearance and the Liver-Brain Axis. *Journal of Molecular Neuroscience*, *75*(2), 43.

Yap, T. A., Omlin, A., & De Bono, J. S. (2013). Development of therapeutic combinations targeting major cancer signaling pathways. *Journal of clinical oncology*, *31*(12), 1592-1605.

Yu, Q., Zheng, H., & Zhang, Y. (2021). Inducible degrader of LDLR: A potential novel therapeutic target and emerging treatment for hyperlipidemia. *Vascular Pharmacology*, *140*, 106878.

Zhang, F., Yang, W., Sun, R., Duan, X., Yang, Y., Wang, A., & Tian, Y. (2026). Cytokine–microglia interactions in neuroinflammation: Mechanisms, disease dynamics, and therapeutic strategies. *Antioxidants & Redox Signaling*, *44*(7-9), 311-331.

Zhang, L., Reue, K., Fong, L. G., Young, S. G., & Tontonoz, P. (2012). Feedback regulation of cholesterol uptake by the LXR–IDOL–LDLR axis. *Arteriosclerosis, thrombosis, and vascular biology*, *32*(11), 2541-2546.

Zhong, J., Li, G., Lv, Z., Chen, J., Wang, C., Shao, A., Gong, Z., Wang, J., Liu, S., & Luo, J. (2025). Neuromodulation of cerebral blood flow: A physiological mechanism and methodological review of neurovascular coupling. *Bioengineering*, *12*(5), 442.