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REVIEW ARTICLE

DDL-920 mediated enhancement of γ-oscillations targeting γ-aminobutyric acid receptors: a novel therapeutic strategy to improve cognition in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the leading cause of dementia and poses significant health challenges globally. Characterised by cognitive decline and neurodegenerative pathology, including neurofibrillary tangles and amyloid plaques, AD currently lacks effective treatments that halt its progression. This article explores a novel therapeutic approach using DDL-920, a small molecule that enhances gamma oscillations by targeting -aminobutyric acid type A receptors (GABAARs), thereby improving cognitive function independent of amyloid and tau pathology. Preclinical studies demonstrate that DDL-920 enhances endogenous gamma oscillations, crucial for higher-order cognitive functions, in AD mouse models. Unlike traditional therapies focusing on amyloid clearance, DDL-920 shifts the focus to enhancing brain activity. While current treatments primarily manage symptoms, DDL-920's unique mechanism may offer a new avenue for cognitive improvement. However, the translation of its efficacy to human populations remains uncertain due to individual variability in brain rhythms and the complexity of neurodegeneration. Further research, including human trials, is essential to assess the long-term viability and scalability of DDL-920 as a therapeutic option for AD.

Key words: DDL-920; Gamma oscillations; Cognitive function; Alzheimer's disease; GABA receptors; Neurodegeneration

Abbreviations

Alzheimer's disease (AD); Sporadic Alzheimer's disease (SAD); Autosomal dominant Alzheimer's disease (ADAD); -aminobutyric acid type A receptors (GABAARs); Parvalbumin-expressing interneurons (PV+INs); Central nervous system (CNS); Behavioural and psychological symptoms of dementia (BPSD); Blood brain barrier (BBB); Subcutaneous (SQ); Transcranial magnetic stimulation (TMS); Transcranial direct current stimulation (tDCS)

Introduction

Alzheimer's disease (AD) is the leading cause of dementia and one of the most significant health challenges of the twenty-first century [1]. First recognised in 1907, AD has numerous potential causes; however, its precise aetiology remains unclear [2]. The disease is characterised by a progressive decline in cognitive function, including difficulties in learning new information, retrieving previously acquired knowledge, and the presence of other impairments such as dysexecutive syndrome (problems with planning, decision-making, and problem-solving), apraxia (difficulty performing learned movements despite having the physical ability), or aphasia (impairment in language comprehension or expression) [3]. AD exists in two forms: (1) sporadic Alzheimer's disease (SAD) and (2) autosomal dominant Alzheimer's disease (ADAD), a rare genetic variant affecting less than 1% of cases, typically before the age of 65 years. The likelihood of developing sporadic AD doubles approximately every five years in individuals over 65 years of age [4]. Two

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Key Points

- Modulating endogenous -oscillations with DDL-920 represents a paradigm shift in Alzheimer's disease therapeutics, targeting cognitive functions directly through brain rhythm enhancement rather than traditional amyloid or tau reduction strategies.
- Despite promising preclinical results, translating the efficacy of DDL-920 to human applications faces challenges due to interindividual variability in -oscillation patterns and the complexity of Alzheimer's disease pathology in advanced stages.

Table 1. Pharmacokinetic properties of DDL-920.

Route of Administration	Bioavailability	Brain Penetration	Duration of Effect	Safety Profile
Oral	High	Effective	4.5 hours	No significant short-term effects observed in animal models
Subcutaneous	Moderate	Effective	4.5 hours	Comparable to oral; additional studies needed

primary pathological features define AD: neurofibrillary tangles, caused by the accumulation of hyperphosphorylated tau proteins within neurones, and amyloid plaques, formed from amyloid- peptides that aggregate outside the nerve cells [5]. Tau and amyloid-, which are the central components of these lesions, remain the focus of extensive research.

DDL-920 and γ-oscillations

Cognitive decline remains a major challenge in AD [6]. Several clinical studies have examined ways to delay the onset of memory loss and cognitive impairment in individuals at risk of developing AD [7]. Since tau neurofibrillary tangles (abnormal protein accumulation in brain cells) are closely linked to cognitive decline and loss of synaptic connections, therapeutic trials are currently being conducted to develop tau-targeting immunotherapies and other treatments that modify tau pathology [8]. Previous research has shown that stimulating the brain with auditory, visual, or transcranial techniques (such as magnetic or electrical stimulation) can decrease the accumulation of amyloid plaques in the brain – a key feature of AD [9]. However, these techniques do not improve the cognitive skills. Recently, Wei et al. [10] attempted to fill this critical gap by focusing on modulating endogenous γ-oscillations, a key brain rhythm involved in cognition, particularly in memory and attention. γ-Oscillations (30-120 Hz) are crucial for linking neuronal circuits and coordinating the brain activity required for higher-order mental functions [11]. In AD, these oscillations are significantly reduced, contributing to early cognitive deficits [12]. This study introduced a small molecule, DDL-920, that enhances γ-oscillations by targeting GABA type A receptors (GABAARs) containing $\alpha1\beta2\delta$ subunits, which are responsible for the tonic inhibition of parvalbumin-expressing interneurons (PV+INs) [10]. By restoring the power of γ-oscillations, DDL-920 showed the potential to directly improve cognitive function in AD mouse models, even without addressing amyloid or tau pathology. In essence, this study shifts the focus from amyloid clearance to functional enhancement of brain activity, aiming to improve the brain's cognitive processes by modulating its natural rhythms.

Pharmacokinetics and delivery of DDL-920 in Alzheimer's disease

Current treatments for AD primarily aim to manage symptoms rather than provide a cure, focusing on slowing the progression of cognitive decline and addressing the behavioural and psychological symptoms of dementia (BPSD). Currently, four medications - donepezil, memantine, galantamine, and rivastigmine - are currently approved for use. These drugs can be classified into two categories: (1) cholinesterase inhibitors (donepezil, galantamine, rivastigmine), which help maintain communication between brain cells by preventing the breakdown of acetylcholine, a key neurotransmitter and (2) glutamate modulators (memantine), which regulate excessive glutamate activity to prevent further neuronal damage. They are administered either orally or via transdermal patches [13,14]. Although not curative, these medications are prescribed to slow the progression of the disease, stabilise, or temporarily improve cognitive function, and manage behavioural disturbances [15]. These drug therapies are likely to be more effective when administered during the early asymptomatic stages, prior to the onset of neurodegeneration. Unfortunately, the blood-brain barrier (BBB) poses a significant obstacle for drug delivery to the central nervous system (CNS), leading to the development of various strategies to overcome this challenge [16,17]. As a result, higher dosages may be required, which can increase the risk of unwanted side effects [18]. Based on the pharmacokinetic profile of DDL-920 (refer to Table 1), oral or subcutaneous (SQ) delivery appears to be the ideal route of drug administration. In the study [10], DDL-920 showed good bioavailability when administered orally, with sufficient concentrations detected in the brain to modulate γ-oscillations effectively. The pharmacodynamic effects (increased γ-oscillation power) lasted for approximately 4.5 hours in the AD mice, indicating that oral delivery can sustain the therapeutic effect for a reasonable duration. Moreover, DDL-920 was also tested via subcutaneous injection, and it reached effective concentrations in the brain.

Limitations of amyloid-targeting therapies and the novel mechanism of DDL-920

Two drugs, aducanumab and lecanemab, target amyloid- plaques in the brain [19] and are considered one of the primary pathological hallmarks of AD [20]. These drugs aim to reduce amyloid- deposition, but their effect on cognitive function remains modest, with limited clinical benefits observed in many patients [21]. Additionally, side effects such as brain swelling and microhaemorrhages have raised concerns regarding their safety and long-term use [22]. DDL-920 offers a novel mechanism for enhancing γ-oscillations through the modulation of PV+INs. By modulating GABAARs containing $\alpha1\beta2\delta$ subunits, DDL-920 has the potential to improve cognitive performance independent of the amyloid plaque load [10]. Therefore, DDL-920 could shift the therapeutic focus from reducing the amyloid burden to targeting functional brain activity critical for cognition. One of the key concerns regarding DDL-920 is that preclinical tests are still in the early stages and conducted exclusively on animal models. The study reported no significant short-term side effects in animal models, but the long-term viability of DDL-920 is unknown [10]. Chronic modulation of GABAARs might carry the risks of tolerance, compensatory changes, or downreg-

Table 2. Challenges in adapting DDL-920 from animal models to human studies

Challenge	Impact on Efficacy	Potential Solutions
Complexity of human oscillatory dynamics	Reduced predictability of response	Advanced modelling of human brain rhythms
Variability in γ-oscillation patterns	Some patients may see little benefit	Personalized dosing or tailored therapeutic protocols
Advanced disease pathology	Limited efficacy in late-stage AD	Early intervention and combination therapy

Table 2: This table examines the challenges in adapting DDL-920 from animal models to human studies, addressing the complexities of human neurophysiology and variability in treatment response.

ulation of receptors, which could reduce the drug's efficacy over time, requiring dose adjustments or limiting long-term benefits [23]. Moreover, the balance between enhancing γ-oscillations and avoiding potential hyperexcitability or abnormal brain rhythms is difficult to achieve. Overstimulation of γ-oscillations can lead to unintended consequences, such as seizures or other forms of neuronal hyperactivity [24]. To mitigate these risks, long-term studies assessing the stability of γ-oscillation enhancement, receptor regulation, and cognitive effects in both preclinical and human models are necessary. Future clinical trials should monitor for signs of tolerance, receptor adaptations, or paradoxical cognitive effects to determine whether DDL-920 remains effective and safe over extended treatment periods. Additionally, investigating intermittent dosing schedules or combination therapies may help prevent receptor desensitisation while maintaining therapeutic benefits.

One of the limitations of the current treatments is their administration in the later stages of AD. For instance, studies involving mice with genetic mutations associated with ADAD, which leads to rapid accumulation of amyloid plaques, have facilitated testing of anti-amyloid immunisation strategies aimed at eliminating these plaques [25]. However, in multiple human clinical trials employing this approach, while a reduction in amyloid load was observed, there was no significant clinical improvement or delay in disease progression [26]. Wei et al. tested DDL-920 in 3- to 4-month-old AD model mice, which represent an early to moderate stage of the disease [10]. The positive cognitive effects in this model suggest that the drug might be most effective if administered in earlier stages, when γ-oscillation deficits first emerge. However, at later stages, when neuronal circuits are severely damaged, the capacity of DDL-920 to restore cognitive function may be diminished. Therefore, it is difficult to predict whether the efficacy of DDL-920 would remain consistent in advanced stages of AD or in patients with complex comorbidities. In the later stages of AD, DDL-920 could still hold value as part of a multimodal treatment approach, possibly in combination with drugs targeting amyloid- or tau. Even if the drug cannot reverse the broader cognitive decline in more advanced AD, it could help improve quality of life by enhancing specific functions that are reliant on γ-oscillatory activity. Indeed, rapid and accurate diagnosis should consider target populations with specific risk factors, such as a family history of AD (including genetic factors like the $\epsilon 4$ allele) and isolated memory complaints [1]. Early intervention with DDL-920 may theoretically slow the progression of cognitive decline by sustaining γ-oscillatory activity and maintaining functional neural networks [27].

Challenges in translating preclinical findings to human applications of DDL-920

Preclinical testing of DDL-920 was conducted in mouse models of AD [10]. While these models replicate some of the hallmark features of AD, such as amyloid- deposition and cognitive decline, they are far simpler than human brains in terms of structure, neuronal connectivity, and neurophysiology [28]. The human brain possesses a significantly more intricate network of neurones and regional interactions that may affect how γ-oscillations are generated and maintained [29]. Because of these differences, the ability of DDL-920 to modulate γ-oscillations in animal models may not translate effectively into human brains (refer to Table 2). Animal models are typically younger and in less advanced stages of disease than most human patients [28]. Given the variability in the generation of γ-oscillations and the difference in cognitive processing demands between animals and humans, the effects observed in murine models may not scale effectively to humans without significant loss of efficacy. Moreover, in humans, γ-oscillations are involved in various cognitive functions, including attention, working memory, and sensory processing [30]. The strength, frequency, and regional synchronisation of these oscillations can vary widely among individuals, even in healthy populations. Factors such as age, disease stage, genetic background, and cognitive reserve can influence the generation and maintenance of γ-oscillations [31]. These oscillations are not uniformly generated, and the same task can require different oscillatory patterns depending on an individual's cognitive load or neural plasticity [24]. The pharmacological mechanism of DDL-920 targets γ-oscillations in a "state-dependent" manner, meaning that it enhances γ-oscillations during tasks that naturally require these rhythms. Because humans have unique patterns of brain activity, some patients may respond well to the drug, whereas others may see little benefit. Similarly, the variability in brain rhythms across individuals and the heterogeneous nature of cognitive demands in different environments suggest that scaling DDL-920 as a one-size-fits-all approach may not work. Its efficacy can be highly personalised, requiring individualised dosing or usage protocols, which complicates its scalability for broad clinical applications.

To address these concerns, future human trials must incorporate biomarkers, such as EEG-based γ-oscillation measurements, to identify patients most likely to benefit from DDL-920. Moreover, carefully controlled dose-response studies will be necessary to balance cognitive enhancement with safety concerns. Recognising these limitations early can help refine trial designs and optimise DDL-920's potential as a clinical therapy for AD.

Comparative efficacy of DDL-920 and non-invasive techniques for enhancing γ-oscillations

Current non-invasive methods for enhancing γ-oscillations in humans, such as transcranial magnetic stimulation (TMS) and sensory stimulation (for example, visual and auditory stimulation), aim to induce γ-oscillations through external stimulation [32–34]. While these methods are promising, they face challenges in terms of maintaining consistent effects, patient tolerability, and timing synchronisation with the natural rhythms of the brain [35]. TMS involves using magnetic pulses to stimulate specific brain regions involved in cognition. Studies suggest that γ-frequency TMS can enhance γ-oscillations and improve cognitive function in AD patients [32]. However, the effects are often temporary, requiring frequent sessions to sustain benefits [36]. Moreover, variability in individual brain structure and responsiveness to stimulation can lead to inconsistent results across patients. Accessibility is another limitation - TMS requires specialised equipment and clinical

Table 3. Influence of disease stage on therapeutic benefits and limitations of DDL-920

Disease Stage	Potential Benefits	Limitations	Additional Therapeutic Considerations
Early	Preserves γ-oscillation activity	Uncertain long-term safety	Screening high-risk populations
Moderate	Improves cognition in partially intact circuits	Reduced efficacy as neurodegeneration progresses	Combined with other therapeutic agents
Advanced	May enhance quality of life for specific tasks	Severely damaged networks limit effectiveness	Multimodal approach recommended

Table 3: This table outlines how the timing of DDL-920 administration may influence its therapeutic benefits and limitations across different stages of Alzheimer's disease.

supervision, making it less practical for routine use [37]. Sensory-based neuromodulation, such as light flickering at γ-frequencies (40 Hz) or auditory tone stimulation, has been shown to increase γ-oscillation activity and reduce amyloid plaque build-up in animal models [38]. Despite these promising results, some studies have indicated that these techniques do not significantly improve cognitive function. One study has demonstrated that 40 Hz optogenetic stimulation enhanced spatial memory , but significantly failed to alter plaque loads [39]. Unlike pharmacological interventions, sensory stimulation lacks precise control over γ-oscillation modulation, making it a less reliable therapeutic strategy [40].

In contrast to these neuromodulation techniques, DDL-920's pharmacological approach offers a significant advantage over external stimulation methods by enhancing endogenous γ-oscillations rather than by attempting to impose an artificial rhythm [10]. This could lead to more natural and sustained cognitive enhancement compared to the short-term effects of external methods. DDL-920 directly targets γ-oscillations by modulating specific GABA-A receptors, ensuring a more precise and controlled enhancement of brain rhythms compared to the indirect stimulation provided by TMS or sensory-based approaches. Moreover, preclinical studies in AD mouse models have shown that the effects of DDL-920 last longer, whereas external neuromodulation techniques often require repeated sessions to maintain benefits. Another key advantage is the potential for personalised treatment, as DDL-920's dosage can be adjusted based on an individual's response, offering a tailored approach to therapy. While DDL-920 presents an innovative alternative to external stimulation, its scalability might be limited by the same factors that challenge non-invasive techniques, namely, individual variability in brain rhythms and diminished capacity for oscillation generation in advanced neurodegenerative stages (refer to Table 3) [31]. Non-invasive methods, such as TMS and sensory stimulation, although currently less consistent, are becoming more accessible in clinical settings [41]. As these methods improve, they can offer more affordable and less complex alternatives to pharmacological interventions, particularly in resource-limited settings. Scaling a pharmacological therapy, such as DDL-920, for widespread clinical use would require cost-effective production and distribution. Additionally, regular administration for chronic diseases, such as AD, could lead to high costs for patients, especially if personalised or frequent adjustments are needed to optimise efficacy.

Conclusion

Current treatments for AD primarily target amyloid- plaques with limited success in improving cognitive outcomes, the novel approach of modulating γ-oscillations through DDL-920 represents a promising shift. By enhancing endogenous brain rhythms critical for cognition, DDL-920 offers potential cognitive improvements independent of amyloid or tau burden. However, despite promising preclinical evidence, these findings remain preliminary, and significant challenges must be addressed before DDL-920 can be considered a viable treatment option. Key concerns include the variability of γ-oscillatory activity in humans, potential long-term neuroadaptive changes, and the unknown safety profile of chronic modulation of GABAARs. Furthermore, the extent to which the effects of DDL-920 in animal models will translate to human patients remains uncertain.

Moving forward, rigorous clinical trials are essential to determine the safety, efficacy, and scalability of DDL-920 in AD patients. Future research should focus on identifying biomarkers for patient selection, optimising dosing strategies, and assessing long-term cognitive and neurophysiological outcomes. While DDL-920 represents a potential shift in AD treatment paradigms, its clinical utility remains speculative until validated in human studies.

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Ethics Approval and Consent to Participate

Not applicable

Authors' Contribution

Manuscript preparation (draft and final editing): AA, HH. All authors have read and approved the final manuscript.

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Declaration of Competing Interest

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Consent for Publication

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Availability of Data and Material

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