The Correlation between Neurodegenerative Diseases and Sleep and the Application of Deep Brain Stimulation Therapy

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Abstract. Neurodegenerative diseases are increasingly prevalent among older adults and are often accompanied by significant sleep disturbances, which not only reduce quality of life but may also contribute to disease progression. While conventional treatments remain limited in effectiveness, deep brain stimulation (DBS)—a neuromodulatory technique originally developed for movement disorders—has emerged as a potential therapy for alleviating both motor and non-motor symptoms, including sleep dysfunction. This paper reviews current applications of DBS in neurodegenerative diseases with a focus on sleep outcomes. The analysis examines clinical studies and experimental evidence examining multiple stimulation targets. In AD, stimulation of the nucleus basalis of Meynert (NBM), fornix, and ventral capsule/ventral striatum (VC/VS) has been associated with improved subjective sleep quality and slowed cognitive decline, though results remain inconsistent. In PD, subthalamic nucleus (STN) stimulation has been shown to improve total sleep time, REM and slow-wave sleep, and reduce insomnia and restless leg syndrome, whereas globus pallidus internus (GPi) and ventral intermediate nucleus (VIM) targets show less clear sleep benefits. For HD, preliminary data suggests that GPi stimulation may improve motor symptoms, though effects on sleep are largely unknown. Overall, DBS demonstrates promise as a novel approach for mitigating sleep disturbances in neurodegenerative disorders. However, current evidence is limited by small sample sizes, heterogeneity of study designs, and insufficient long-term data. Larger, controlled trials are needed to clarify its efficacy, mechanisms, and optimal targets.

Keywords: Deep brain stimulation, neurodegenerative disease, sleep disorders.

1. Introduction

Neurodegenerative diseases, such as Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD), are becoming increasingly prevalent among older adults [1]. They are characterized by progressive neuronal loss, and the accumulation of toxic proteins. In addition to their hallmark motor and cognitive symptoms, these disorders frequently cause significant sleep disturbances, including disruption of circadian rhythms due to degeneration of neurons in suprachiasmatic nucleus, restless leg syndrome (RLS), and sleep apnea [2]. Sleep dysfunction is very common across all the neurodegenerative disorders, occurring in 40% to 90% of patients, which not only diminishes quality of life but may also accelerate disease progression. [2, 3].

Although current treatments for insomnia, such as cognitive behavioral therapy for insomnia (CBT-I), can be effective in the general population, many patients with neurodegenerative diseases do not respond adequately, resulting in limited therapeutic options [4]. So, it's necessary to explore and develop novel approaches that address sleep dysfunction in these patients.

Deep brain stimulation (DBS), a neuromodulatory technique primarily applied to treat movement disorders, has shown potential in improving sleep quality. It is a medical procedure in which electrodes are implanted in specific brain regions. These electrodes deliver electrical impulses that modulate brain activity, helping to manage certain disorders. The stimulation can also influence brain cells and neurotransmitters involved in the development of these conditions [5].

For example, bilateral stimulation of the fornix and nucleus basalis of Meynert in AD patients significantly improved subjective sleep quality [6]. Likewise, subthalamic nucleus (STN) stimulation in PD patients has been found to increase total sleep time, enhance rapid eye movement (REM) and slow-wave sleep, reduce both PSQI and Epworth Sleepiness Scale (ESS) scores, and alleviate restless leg syndrome (RLS) symptoms [7].

While some reviews exist for specific diseases like PD, a comprehensive synthesis across neurodegenerative diseases, including mechanisms and broader applications, is lacking.

Therefore, this paper aims to evaluate the therapeutic potential and the application status of DBS in mitigating sleep disturbances associated with neurodegenerative diseases, with a focus on its clinical efficacy and possible mechanisms of action.

2. Alzheimer's disease (AD)

AD is a common neurodegenerative disease and is the most common form of dementia, featuring initial memory loss and cognitive impairment, affecting behavior, visuospatial orientation and speech ability [8]. The rate of AD diagnosis changes with the age with 0.4 % in people with the age 65 to 74, 3.2 % for 75 to 84, and 7.6 % for 85 and above [8]. AD is associated with sleep deprivation bidirectionally. Sleep disturbances have a prevalence of 50% in AD patients [9].

In AD, REM sleep is quantitatively reduced compared to normal aging, with shorter episode duration but preserved episode number and latency. EEG during REM shows slowing (increase in delta and theta, decrease in alpha and beta), especially in parietotemporal and frontal regions, likely linked to degeneration of cholinergic brainstem and forebrain structures. REM sleep behavior disorder (RBD) is rare in AD; when present, it often indicates mixed or borderline pathology [10].

Also, patients show significantly reduced SWS, and increased wakefulness is observed in AD patients in a study published in 1982, which indicates a lower sleep efficiency [11].

Obstructive sleep apnea (OSA) occurs when you stop breathing during sleep because of a blockage in your windpipe. AD patients have a 5-fold increase in risk of getting OSA [12].

Excessive daytime sleepiness (EDS) occurs when you repeatedly fall asleep during the day. Epidemiological surveys indicate that the prevalence of EDS in this population is about 50% [13].

These disorders not only contribute to disease progression (including cognitive decline) but also place a significant burden on caregivers.

2.1. Pathophysiological mechanism

The pathological hallmarks include accumulation of amyloid β-peptide, which is produced by β-amyloid precursor protein (APP), a transmembrane protein, and tau protein. β-amyloid accumulation significantly contributes to oxidative stress, neuroinflammation, and mitochondrial dysfunction. Tau protein is of paramount importance to the production of tubulin and microtubule stabilization, which is integral for normal functioning of the neuron. Hyperphosphorylation of the tau protein can induce a conformational change that forms oligomers from monomers, resulting in the formation of neurofibrillary tangles. Both exacerbate the condition [8].

A primary driver of sleep problems in AD is the progressive neuronal and synaptic damage caused by the deposition of Aβ and tau neurofibrillary tangles in brain regions that are fundamental to sleep regulation, such as basal forebrain, hypothalamus, pons and medulla oblongata. This leads to the disruption of sleep architecture and fragmentation of sleep, significantly contributing to the progress of disease [14].

A study in transgenic mice has demonstrated that amyloid deposition in the brain—and, in certain cases, tau aggregation—can significantly disrupt normal sleep architecture and circadian rhythm, with such disturbances often arising even before detectable amyloid plaque formation. Reported abnormalities include reduced day–night oscillations in brain lactate, phase delays in circadian rhythm, altered nocturnal activity patterns, and decreased amounts of non-REM sleep [15].

Moreover, both Aβ and tau appear to play essential roles in sleep regulation by influencing the expression levels of orexin A and adenosine A1R in mice, two molecules that are critical for maintaining proper sleep–wake balance. Consistently, AD mouse models exhibit reduced non-rapid eye movement (NREM) sleep along with increased wakefulness [16].

Also, impairment of NREM fast spindle expression in the frontal cortex is associated with increased microglial activity and synaptic loss. Reduced spindle activity correlates with poorer

consolidation of episodic memory during sleep since it is essential for synaptic plasticity and memory retention, further contributing to cognitive decline and accelerating AD's progression [17].

2.2. Treatment and application of DBS in AD

Approved AD treatments include cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and the NMDA antagonist memantine. Adjuncts include huperzine and vitamin D [8]. Recently, FDA-approved DMTs such as aducanumab and lecanemab target amyloid-β, with additional amyloid-, tau-, and neuroprotective agents in trials [18].

Currently, three brain regions have been explored as DBS targets to improve memory and cognition in AD: the nucleus basalis of Meynert (NBM), the fornix, and the ventral capsule/ventral striatum (VC/VS) [19].

NBM is selected as a target, as severe damage to the basal forebrain cholinergic system, especially the nucleus basalis of Meynert (NBM), reduces cholinergic input to the cortex and is speculated to be involved in the progression of Alzheimer's disease. This loss impairs information flow to the cortex. It may help to stabilize the activity in memory-associated circuits and induce neurotrophic factor production, improving the cognitive function. In a 2024 study, NBM-DBS can significantly improve subjective sleep quality (PSQI). A phase I RCT reported that one year of stimulation in six patients led to a modest 3-point worsening in ADAS-cog (suggesting relatively slow progression) and almost stable MMSE scores, with effects described as superior to anticholinergic therapy. However, studies for DBS in NBM yielded inconsistent results. A follow-up analysis in 10 patients showed non-significant improvement in ADAS-mem, stabilized MMSE and but ADAS-cog continued to decline, consistent with cortical thinning in fronto-parieto-temporal regions [19-21].

The fornix, a key cholinergic pathway to the hippocampus, is linked to memory impairment and AD progression. Fornix-DBS may stabilize the Papez circuit and The Default Mode Network (DMN), increase hippocampal volume and glucose metabolism, and slow atrophy, though findings are inconsistent, too. Small studies in mild AD showed mixed cognitive outcomes, with some benefits in metabolism and limited cognitive improvement. Larger trials found no overall clinical benefit, though older patients (>65) may respond better. In severe AD, limited early improvements have been observed. During sleep, fornix DBS can help to consolidate memory. Other effects of fornix DBS are still unknown [19].

Furthermore, VC/VS-DBS is also a potential target because it connects to frontal networks that regulate executive functions—such as initiative, problem-solving, and decision-making—that are often severely impaired in AD. Moreover, since VC/VS neurons degenerate later than temporal regions, they may represent a more favorable site for modulation with DBS. In a phase I open-label study involving three patients followed for over 18 months, stimulation at the VC/VS slowed cognitive decline without notable side effects. However, more data is needed to judge its therapeutic value [19].

3. Parkinson's disease (PD)

PD is a chronic and progressive neurodegenerative disease featuring both motor—such as muscle rigidity, speech and gait alterations and tremors--and non-motor disabilities. It is the second most common neurodegenerative disease [2]. It mostly occurs in elderly people and can impact 1-2% of the population aged higher than 65. The onset of Parkinson's disease is classified into three categories: young onset, with an average age of 57; intermediate onset, averaging 65; and late onset, averaging 73 years [8].

Sleep disturbances are seen in up to 80% of individuals with PD. after 5 years of diagnosis. Common disturbances include insomnia (especially sleep-maintenance type), affecting around 44% of patients and excessive daytime sleepiness, which may involve sudden "sleep attacks" [22].

Also, rapid eye movement (REM) sleep behavior disorder (RBD)—featuring dream enactment movements such as shouting or punching—can appear years before motor symptoms, making it a key

early marker of PD. Overall, polysomnography research find RBD affects 25–50% of PD patients, with about 20% of them before the onset of parkinsonism [22].

Moreover, Obstructive sleep apnea (OSA) appears in many patients as well. It can cause repeated breathing pauses, leading to desaturations of oxyhemoglobin and fragmentations of sleep [22].

Furthermore, restless legs syndrome (RLS) also occurs very often. It produces an urge to move the legs at night, but it's not unique to PD [22].

3.1. Pathophysiological mechanism

In PD, the pathological hallmark is the accumulation of Lewy bodies containing aggregated α-synuclein, a 140-amino-acid lipid-binding protein encoded by the SNCA gene on chromosome 4. Normally, α-synuclein exists as a soluble, tetrameric α-helix that binds negatively charged membrane phospholipids, but under pathological conditions it misfolds into β-sheet structures, forming insoluble fibrils. Furthermore, aging, pacemaking neuronal activity, elevated cytosolic Ca^{2+} contribute to oxidative stress in mitochondria, leading to neurodegeneration. Oligomers likely drive PD onset, while fibrillary α-synuclein aggregates promote its spread by prion-like seeding and cell-to-cell transmission [8].

Insomnia in PD is multifactorial, arising from motor symptoms (bradykinesia, dyskinesia, tremor, dystonia), comorbidities (RLS, cramps, nocturia, psychiatric or cognitive issues), the neurodegenerative process itself, and dopaminergic medications. Excessive daytime sleepiness (EDS) in PD is multifactorial, too. It may result from dysfunction of dopaminergic and non-dopaminergic sleep–wake networks, with a narcoleptic-like phenotype suggested by sleep attacks, REM intrusions, and partial hypocretin cell loss, though cataplexy is absent and CSF hypocretin remains normal. The role of hypocretin cell loss is unclear. Dopaminergic drugs, especially agonists, can induce EDS and sleep attacks, with higher levodopa equivalent doses linked to greater risk. Other treatments for non-motor symptoms (antidepressants, hypnotics, clonazepam, antipsychotics) may also contribute.

In addition, patients show reduced circadian amplitude of melatonin secretion. PD patients with excessive daytime sleepiness showed even lower level of melatonin. These findings suggest that circadian dysfunction may contribute to insomnia and excessive daytime sleepiness seen in PD [23].

RBD is attributed to lesions within brainstem regions that normally mediate REM sleep muscle atonia. The unusually rapid and precise movements seen in RBD episodes are thought to arise from motor cortical activity transmitted via the pyramidal tract. Because brainstem damage disrupts the pontomedullary pathways for REM atonia, these cortical commands reach spinal motor neurons unchecked [22].

In patients with PD, OSA is more likely caused by ageing rather than PD itself since their apnoea-hypopnea index is not much higher than healthy, age-matched people.

RLS is linked to insufficient iron intake and dysfunction in dopamine, adenosine, and glutamate systems within CNS, with strong genetic contributions. RLS shares dopamine dysfunction with PD and responds to dopaminergic drugs, but idiopathic RLS does not predispose to PD. RLS occurs more often in PD patients (10–55%) than the general population, sometimes reflecting other PD symptoms or long-term dopaminergic treatment [22].

These sleep disorders reduce quality of life, contribute to fatigue, cognitive decline, and may accelerate disease progression. Diagnosis uses questionnaires, diaries, actigraphy, and polysomnography. Management is individualized, combining sleep hygiene, cognitive behavioral therapy, medication adjustments, and targeted treatments such as positive airway pressure therapy for OSA or clonazepam/melatonin for RBD [22].

3.2. Treatment and DBS

Despite diverse therapies, no cure exists. PD treatments include levodopa, dopamine agonists, and MAO-B inhibitors, with trials targeting α-synuclein oligomers. Severe cases may use deep brain stimulation, surgery, or aromatic l-amino acid decarboxylase (AADC) gene therapy [8].

For PD, the primary DBS targets are the subthalamic nucleus (STN), globus pallidus internus (GPi), and ventral intermediate nucleus of the thalamus (VIM) [24].

STN is generally considered the preferred DBS target, as it can alleviate tremors, rigidity, akinesia, and dyskinesias, while also enabling a significant reduction in anti-Parkinsonian medication for many patients. The EARLYSTIM trial demonstrated that STN-DBS performed earlier in PD (mean 7 years post-diagnosis) provided greater improvements in quality of life and motor symptoms than best medical therapy, with additional benefits for certain nonmotor symptoms such as sleep, pain, and anxiety. Due to its improvement of parkinsonism, both patients' subjective (insomnia, EDS) and objective sleep quality measures (total sleep time and wake time during sleep) improved [22,24]. Despite this, it has no significant effect on OSA and RBD [22].

GPi stimulation addresses all major PD symptoms—akinesia, rigidity, and dyskinesias—and allows patients to maintain or even increase their levodopa dosage without the risk of dopa-induced dyskinesias [24]. Although the basal ganglia are known to contain pathways that regulate sleep–wake behaviors through the cortico-striato-pallidal loop, research on their influence on sleep quality remains limited [25]. GPi DBS can increase baseline UPDRS motor off-medication scores by 27-54%, akin to 30-67% of STN DBS, as reported by data from randomized clinical trials [26].

VIM stimulation, particularly when applied bilaterally, is highly effective for controlling tremors. Vim-DBS provided sustained tremor control at 1 year and at a mean follow-up of 6.6 years after surgery [24]. It is also hypothesized that Vim is involved in networks of thalamus that sleep disorders may be attributed to [25].

4. Huntington's disease (HD)

Huntington's disease (HD) is a monogenic, fully penetrant neurodegenerative disorder inherited in an autosomal dominant pattern. It is characterized by progressive motor dysfunction (Dystonia, chorea, loss of coordination, behavioral difficulties), cognitive decline, and psychiatric symptoms such as depression or psychosis [8].

HD typically manifests in adulthood, with an average onset at age 40 and death occurring 15–20 years later, although 4–10% of cases are juvenile, defined as symptom onset before age 20. The incidence of HD is 5–10 per 100,000 individuals but rates vary across populations. In North America, people of African descent show slightly higher rates than Caucasians, while much lower rates are reported in South Africa and Zimbabwe, likely due to limited healthcare. Asian populations exhibit the lowest prevalence [8].

Sleep disturbance is very common in HD patients, with a prevalence rate of 87.8%, including longer sleep latency, lower sleep efficiency, more nocturnal awakenings, shortened and delayed REM sleep, and increased periodic leg movements [27, 28]. Also, one study shows that Huntington's disease mouse models can develop severe disruptions in circadian rhythms, sleep, heart rate, and body temperature [28].Moreover, HD patients show behavioral disorders such as RBD (lack of skeletal muscle atonia). Skeletal muscle atonia is a hallmark of REM sleep; when absent, it can cause sudden movements such as hitting, kicking, or tossing, often accompanied by vivid dreams with threatening content [29].

These sleep disorders may trigger sudden episodes of excessive daytime sleepiness (EDS) in inappropriate situations, such as while riding a bicycle, posing a risk of serious injury [29].

4.1. Pathophysiological mechanism

HD is caused by CAG repeat expansion in the polyglutamine region of the huntingtin gene. This mutation leads to protein misfolding, toxic aggregation, and impaired gene expression, resulting in progressive motor dysfunction, psychiatric symptoms, and cognitive decline [8].

The disruptions in circadian rhythm and sleep may stem from reduced amplitude and rhythm electrical activity in the brain's central clock (SCN) and progressive neuronal loss caused by accumulation of toxic proteins in sleep-regulating areas in the brainstem [30].

Moreover, melatonin is important for sleep onset, reduced signaling may contribute to lower sleep quality and efficiency in these patients. Early-stage HD patients show a delayed melatonin rise resembling delayed sleep phase syndrome (DSPS) like circadian rhythm disorder, with melatonin levels declining as disease worsens. It may also result from disruptions in the SCN's molecular oscillation, caused either by the local toxic effects of mutant huntingtin or by dysfunction in brain circuits projecting to the SCN [28].

For RBD seen in HD patients, it may be attributed to the accumulation of toxic huntingtin in regions regulating REM sleep atonia, such as the dorsolateral pons, locus coeruleus, medullary reticular formation, pedunculopontine tegmental nucleus, and hypothalamus, leading to their dysfunction and causing RBD [29].

In addition, sleep disturbances in HD—such as difficulty falling asleep, short sleep duration, and frequent awakenings—are often linked to psychiatric disorders like depression, mania, and anxiety. Depression occurs in about 30% of patients, frequently emerging before motor symptoms and associated with increased suicide risk, particularly in the preclinical and early stages of the disease. Evidence suggests depression in HD is largely endogenous, stemming from medial caudate damage and reduced glucose metabolism in the prefrontal and orbitofrontal cortex, with hypothalamic dysfunction also implicated. Nonetheless, psychosocial stressors, including coping with progressive disability and even receiving genetic testing results, contribute significantly to depression and anxiety, sometimes triggering suicidal behavior even in non-carriers [29].

4.2. Treatment and DBS

There is currently no therapy that slows or halts the progression of HD, and available treatments are limited to symptomatic management. Tetrabenazine, approved by the FDA, has been shown to reduce chorea, while deutetrabenazine, a deuterated analogue of tetrabenazine with improved pharmacokinetics, has also received approval. In addition, several other agents are being evaluated in clinical trials, though their efficacy remains to be established [8].

GPi is the only target that has been critically assessed for DBS in HD patients. GPi-DBS can improve the Unified Huntington's Disease Rating Scale (UHDRS) total score by 5.4–34.5% and the motor score by 3.8% to 97.8%, as evaluated by a literature review incorporated 20 eligible studies. When doing bilaterally, it can reduce the Chorea subscore by 21.4% to 73.6%. Little data is available for its effect on sleep [31].

5. Conclusion

DBS represents a promising therapeutic tool for alleviating sleep disturbances associated with neurodegenerative diseases such as AD, PD and HD. Current evidence suggests that DBS can improve subjective and objective sleep quality in selected cases—such as subthalamic nucleus stimulation in PD and nucleus basalis of Meynert or fornix stimulation in AD—by modulating sleep–wake regulating circuits and neurotransmitter systems.

Notwithstanding these encouraging findings, important limitations must be acknowledged. Results are still inconsistent across groups, and data for HD is very scarce, with virtually no studies delving into DBS effects on sleep in this population. Most available studies are small-scale, lack standardized outcome measures, and often focus on motor or cognitive endpoints rather than sleep as a primary target. Heterogeneity in stimulation sites, parameters, and patient characteristics further complicates interpretation. In addition, the long-term safety and efficacy of DBS on sleep remain underexplored, and mechanisms underlying observed improvements are not fully understood.

Future research should address these gaps through large-scale, multicenter randomized controlled trials with sleep outcomes as primary endpoints. Standardized polysomnographic and circadian rhythm assessments are needed to validate subjective reports. Moreover, comparative studies across targets (e.g., STN, GPi, NBM, fornix) will clarify which structures provide optimal benefit for specific sleep disorders. Preclinical work should also investigate the mechanistic pathways linking

neurodegeneration, circadian dysfunction, and DBS-induced network modulation. Ultimately, integrating DBS with pharmacological, behavioral, and neurotechnological strategies may lead to more comprehensive management of sleep dysfunction in neurodegenerative diseases.

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