Sleep and Neurological Diseases and Disorders Across the Life Span

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ASD- Autism Spectrum Disorder
SCZ- Schizophrenia
AD- Alzheimer's Disease
REM- Rapid Eye Movement
NREM- Non- Rapid Eye Movement
SHY- Synaptic Homeostasis Hypothesis
SWA- Slow Wave Activity
GABA- Gamma-Aminobutyric Acid
NMDA- N-methyl-D-aspartateA

Abstract

Sleep is an essential pillar of health at every stage of life, and even a single night of poor sleep can produce measurable cognitive deficits. Chronic sleep disturbances are increasingly linked to neurological disorders, including Autism Spectrum Disorder (ASD), Schizophrenia (SCZ), and Alzheimer's Disease (AD), where underlying causes remain incompletely understood. Converging evidence indicates that sleep disruption, together with gene mutations affecting synaptic function, interferes with homeostatic processes that stabilize neural circuits. This review examines how alterations in sleep timing, duration, and architecture impair synaptic plasticity, particularly the balance between Hebbian and homeostatic mechanisms. Across ASD, SCZ, and AD, persistent and non-restorative sleep disturbances are associated with circadian dysregulation, reduced slow-wave activity and sleep spindles, and impaired synaptic downscaling. These disruptions contribute to disorder-specific outcomes, including behavioral dysregulation in ASD, psychosis, and cognitive impairment in SCZ, and neurodegeneration and β-amyloid accumulation in AD. Shared molecular pathways, including NMDA receptor dysfunction, GABAergic imbalance, and mutations in synaptic proteins such as SHANK3, further link sleep abnormalities to disease progression. The bidirectional relationship between sleep and pathology suggests that sleep disturbance both reflects and drives neurological dysfunction. Together, these findings highlight sleep as a central mechanism in synaptic stability and a promising target for therapeutic strategies across multiple neurological disorders.

Introduction

In this review, we discuss the overlap of Autism Spectrum Disorder (ASD), Schizophrenia (SCZ), and Alzheimer's Disease (AD), specifically the impact of sleep disruption on synaptic plasticity. We will first cover an overview of sleep and synaptic plasticity, and then an overview of each disease: its symptoms, diagnosis, genetic and environmental factors, relevant sleep information, and treatment options. Finally, we examine common mechanisms of the diseases and their impact on sleep and associated processes.

Autism Spectrum Disorder (ASD), Schizophrenia (SCZ), and Alzheimer's Disease (AD) are all neurological diseases that have little-known etiologies. However, all three are synaptopathies, or diseases of the synapse, and have chronic poor sleep as a symptom (Ishida et al. 2018). Understanding these disorders and how atypical sleep affects patients can provide valuable insight into diagnostic, prevention, and symptom alleviation.

Sleep is vital for several homeostatic processes and helps maintain physical and mental health. It is regulated by the circadian rhythm (Deboer 2018). Disruptions to its rhythm are seen as both markers and potential drivers of neurological and psychiatric disorders. (“What Is Synaptic Plasticity?” 2016). Sleep plays a major role in returning the synapse to homeostasis. There have been several links made between sleep duration or quality and the ability for synapses to downscale (Hanlon et al. 2011). Examining atypical sleep patterns, sleep disruptions, and their effects on synaptic plasticity can give insight into neurological diseases that are driven by synaptic processes.

Synaptic plasticity comprises both Hebbian mechanisms that encode experience and homeostatic mechanisms that stabilize network activity. Converging evidence indicates that sleep promotes synaptic normalization and memory consolidation, whereas sleep loss disrupts homeostatic scaling and biases circuits toward maladaptive potentiation. Thus, examining how sleep timing, duration, and continuity alter synaptic plasticity can clarify disease mechanisms underlying disorders with circuit instability.

We will discuss the impact of sleep disruption on neurological disorders, focusing on ASD, SCZ, AD. We describe evidence for a link between sleep and synaptic plasticity, which could elucidate the pathologies driving these conditions and provide new directions for therapeutic strategies.

Sleep and Synaptic Plasticity

Sleep: Structure, Stages, and Regulation

Sleep plays a crucial role in regulating homeostatic processes, one of which is homeostatic synaptic plasticity, a negative feedback mechanism that stabilizes neural networks.

During sleep, our bodies are unconscious and have reduced responsiveness to the outside world. There are two main types of sleep: rapid eye movement (REM), and non-rapid eye movement (NREM), with three different stages (N1, N2, N3), each with a unique function. We cycle through each stage in a 90-minute cycle about 5-6 times each night (Hirota and King 2023). The cycle starts with N1, characterized by light sleep, followed by N2 with deeper sleep, lower body temperature, and reduced heart rate. This stage is also characterized by two well-known brain wave patterns, sleep spindles and K complexes, as recorded on an EEG monitor. Sleep spindles are believed to play a role in synaptic plasticity. The last stage in NREM is N3, when sleep is the deepest. At this stage, the body repairs, rejuvenates, and replenishes itself. After N3, our bodies quickly pass again through N2 and finally reach the last stage of the

sleep cycle, REM sleep. During this phase, most dreaming occurs, and the eyes move rapidly. About 75% of our sleep is spent in the NREM phase, mostly in the N2 phase (Deboer 2018).

The circadian rhythm and homeostatic sleep are the two main processes that regulate our sleep patterns. While adapting to external signals, they work together to maintain a healthy balance between wakefulness and rest. The circadian rhythm aligns our internal clock to the day-night cycle, and homeostatic sleep increases the need for sleep the longer we stay awake. The circadian rhythm is controlled by two cues: light and internal rhythms. Homeostatic sleep controls two aspects of sleep: length and depth. It is regulated by sleep need and characterized by slow-wave activity on an EEG. The more sleep deprived we are, the more slow wave activity can be observed,

Mechanism of Synaptic Plasticity

There are two types of synaptic plasticity: Hebbian and Homeostatic. Hebbian plasticity strengthens or weakens synapses depending on their activity. It is an extremely fast process that uses positive feedback mechanisms to encode information. Homeostatic plasticity is a mechanism that returns neuronal activity toward a set point after a perturbation, preventing saturation or silencing of neuronal signals. It uses negative feedback mechanisms to preserve coding abilities.

One purpose of sleep is restoring synaptic homeostasis. A popular theory is the ‘Synaptic homeostasis hypothesis’ (SHY). Synaptic plasticity is the brain’s ability to change and adapt through experiences, with neural pathways strengthening as they are being used. While awake, these connections grow stronger and consume energy and space. To maintain balance, it is necessary to weaken connections periodically. This restorative process occurs during sleep. According to SHY, wakefulness leads to a net increase in synaptic strength, and sleep to a net decrease. This downscaling restores energy balance and prepares the brain to adapt efficiently again upon waking. In essence, sleep provides a vital reset, freeing the brain from external demands and maintaining overall neural stability (Tononi and Cirelli 2012).

The hypothesis heavily supports that slow wave activity (SWA) is a reflection of the average synaptic strength reached during the prior wake period, and that SWA mediates synaptic depression. Stronger synapses show larger and steeper SWA triggered by an increase in neuronal synchrony. The amplitude of SWA is related to the number of active neurons that are in an up or down state near synchrony, which is directly related to the strength and magnitude of synaptic connections.

Another theory that builds off of SHY is that changes in the slope of SWA reflect homeostatic changes, specifically the decrease of sleep pressure. ((Davis et al.; Hanlon et al.) This mechanism suggests that slow wave activity is not just related to synaptic depression, but is directly related to the functions of sleep.

Regardless of the mechanism, there is a strong link between synaptic depression and slow waves that helps regulate synaptic strength. According to SHY, sleep helps renormalize

synaptic strength, promoting downscaling of connections that strengthened during periods of wake (Tononi and Cirelli, “Sleep and Synaptic Homeostasis”).

Autism Spectrum Disorder and Sleep

Symptoms and Diagnosis

ASD is defined by social deficits and repetitive behaviors. In severe cases, there is a significant lack of communication, often expressed by nonverbal or very limited verbal communication. Since people with severe autism cannot be independent, some individuals have a substantial need for support in daily living. We will discuss diagnosis, relevant gene mutations, environmental factors, and what role sleep plays within ASD.

During the last couple of decades, the diagnostic process for ASD has been refined significantly. New symptoms and prognosis have made identifying and diagnosing those with ASD much easier. The first measurable behavior changes or social decline in children usually starts at age 2. Those with less severe symptoms may not be officially diagnosed until later in life. The diagnostic process is divided into two categories: social communication and restrictive or repetitive behavior. The severity of symptoms in each category will determine the level and type of care needed, case by case (Hirota and King).

Genetic Etiologies to ASD and Synaptic Dysfunction

Other than behavioral indicators to determine the presence of ASD, mutations related to synaptic dysfunction have been correlated to risks regarding both ASD and sleep disorders. About 50% of human patients with similar gene mutations have been found to have ASD, with a higher risk of experiencing insomnia-related traits(Ishida et al.).

For example, mutations in the SHANK3 gene are linked to the development of ASD. Shank proteins are found in the postsynaptic density region of the synapse. They provide scaffolding to help organize neurotransmitter receptors, which play an important role in synaptic by maintaining postsynaptic strength (“SFARI | A Bidirectional Switch Affecting Phosphorylation of Shank3 Influences Homeostatic Synaptic Plasticity”).

Mutations in Shank proteins have been linked to the development of several neurological diseases or disorders, including ASD and AD (Ishida et al.). Mice with a deletion in the SHANK3 gene displayed traits, such as repetitive behaviors and social interaction deficits. On top of that, they exhibited insomnia related traits, circadian abnormality, and decreased REM sleep. There is likely a relationship between a mutation in the SHANK3 gene, ASD related behaviors, sleep insomnia, and atypical synaptic plasticity function (Ishida et al.)

Another gene involved in synaptic function and associated with ASD is CNTNAP2. When mutated in a zebrafish model, the larvae displayed increased nighttime activity. However, when estrogen was injected into the mutated larvae, much of their hyperactivity decreased, which might be relevant for ASD diagnosis. There is a 1:4 ratio of females to males in people

diagnosed with ASD. Estrogen increases GABA and NMDA signalling. Since compromising these pathways can lead to synaptic dysfunction, estrogen may act as a stimulus to increase synaptic function, which can have protective effects against ASD symptoms and pathogenesis (Doldur-Balli et al.)

Environmental Risk Factor and Sleep Disturbance

Other than genetic mutations, there have been links between ASD and certain prenatal, neonatal, and postnatal environments, including a lack of maternal attention or care, and environmental pollutants. One such example is how most individuals with ASD also have sleep issues, especially insomnia. Other common disorders include parasomnia, daytime sleepiness, bedtime resistance, sleep disorder breathing, and more.

Sleep issues in people with ASD often include Insomnia, sleep onset latency, reduced sleep efficiency, and reduced total sleep time. Around 40% of autistic adults report some circadian rhythm disorders (Ballester et al.). These disorders arise due to clock and melatonin pathway gene variations, not routine light exposure patterns, or brain development abnormalities that result in a failure to understand or recognize social cues associated with sleep timing. Circadian rhythm sleep-wake disorders can be treated with external melatonin (Ballester et al.).

These sleep disturbances have a negative effect on quality of life. Synaptic homeostasis is the process by which the synaptic signaling strengths decrease and return to a sustainable state in terms of energy intake and strength. The main challenges for individuals who have ASD are social communication, interaction, repetitive behaviors, and unusual sensory processing. Without being able to downscale, the synaptic signaling pathways could worsen their conditions, further challenging their lives.

Treatment and Sleep Effects

Aripiprazole and risperidone are the only two approved drugs to treat ASD symptoms. They mainly affect behavioral symptoms like irritability and disruptiveness, but they are not preventative of sleep issues. However, Antipsychotics, such as risperidone, have also been shown to significantly improve sleep and reduce aggressive behaviors in both low and high doses (Ballester et al.).

Synaptic signaling provides insight into the pathogenesis of ASD. Specifically, the SHANK3 gene highlights the importance of synaptic downscaling. Combining how sleep impairs synaptic downscaling and the effects of SHANK3 mutations, regulating synaptic pathways is a vital function that helps with memory and cognitive function. Sleep can also act as a treatment for improving synaptic downscaling in ASD patients, improving adaptability and cognitive function.

Conclusion

As discussed above, the main driving factors include genetic and environmental factors. However, the etiology for 70% of ASD is still unknown (Hirota and King). What may address this

question is the interplay between a host of causal factors, such as genetic predispositions and environmental insults, such as sleep loss. Future research must address many factors at once to really conclude causation for ASD.

Schizophrenia and Sleep

SCZ affects 0.4% people worldwide and has detrimental impacts on life quality (Winship et al., “An Overview of Animal Models Related to Schizophrenia”). In this section, we will discuss what schizophrenia is, how it’s diagnosed, relevant genes and other possible causes, the impact that sleep and synapses have on SCZ, and treatment options.

Symptoms and Diagnosis

Schizophrenia symptoms are categorized as positive or negative symptoms. Positive symptoms are excessive or distorted forms of normal functioning. This includes delusions, hallucinations, disorganized speech and behavior, symptoms that deviate from an individual's perspective of reality. On the other hand, negative symptoms are the decrease or absence of normal functions. These include apathy, social isolation, and diminished affect. Finally, cognitive dysfunction refers to a difficulty in mentally processing that is helpful in adapting to the world around us. These processes include memory, paying attention, problem-solving, language, and reasoning. Taken together, individuals with schizophrenia have a hard time distinguishing perception from real reality.

Several genes have been found to increase the risk of developing SCZ. Diagnosing SCZ is challenging because there is no quantitative scale for SCZ, and behavioral diagnosis is often ambiguous. To be diagnosed, patients must meet 6 criterias. These include:

Criteria	Conditions
1.	1. Experiencing delusions, hallucinations, disorganized speech, or catatonic behavior during a one-month period. Two of these symptoms must be experienced and must be present for a significant amount of time.
2.	Normal level of functioning in work, personal life, or self-care is below the expected level of achievement prior to experiencing symptoms.
3.	Positive and negative symptoms persist for at least 6 months, meeting the first criterion.
4.	Schizoaffective disorder and depressive or bipolar disorder are ruled out due to no manic, major depressive, or mood episodes occurring during the duration of the symptoms.

5.	The symptoms are not a result of substance, drugs, medication, or another medical condition.
6.	If there is a history of ASD or communication disorders, a diagnosis of schizophrenia is only made if there are prominent hallucinations or delusions, in addition to other symptoms, prevailing for at least 1 month.

Symptoms do not typically start to appear until adolescence or early adulthood, appearing gradually over time. Schizophrenia presentation can often be mistaken for typical adolescent behavior. On top of that, schizophrenic behavior overlaps with other mental disorders, such as bipolar disorder, major depressive disorder, substance use disorders, and delirium or dementia. In order to diagnose schizophrenia, all other mental disorders must be ruled out (Rahman and Lauriello).

Genetic causes of schizophrenia: with a focus on synaptic-related genetic mutations

Although there is no known direct cause for schizophrenia, there are many risk factors that can influence the chance of developing this mental disorder. Overall, there is an increased risk among men to develop schizophrenia, with a 1.4:1 male: female ratio. Males are typically diagnosed earlier than females, but often have worse outcomes. Individuals with schizophrenia are much more vulnerable to becoming homeless due to their warped perspective of mortality. They also have a mortality rate of two to three times that of normal humans (Rahman and Lauriello).

There are few known genetic causes of schizophrenia, many involving genes related to proteins relevant for neural plasticity, synaptogenesis, and glutamatergic or dopaminergic function. For example, gene DISC1 is considered a high-risk gene for schizophrenia. DISC1 mutations in mouse models have shown a brain morphology of enlarged ventricles and reduced cortical thickness and behavioral abnormalities like hyperactivity and impaired volitional behavior, all consistent with schizophrenia.

22q11.2 deletion syndrome is a genetic disorder that occurs when part of chromosome 22 has been deleted. Chromosome 22. Unmutated, chromosome 22 is responsible for providing instructional proteins for our immune system, heart development, and neural function. However, when mutated, deficiencies include but are not limited to: immune deficiency, learning disabilities, and heart disease (McDonald-McGinn et al.). It is also associated with developing schizophrenia(Bassett and Chow). Around 1.1% of schizophrenic cases are caused by this syndrome. In mice with this deletion syndrome, there have been alterations in cortical and subcortical grey matter volumes, enlarged ventricles, and reduced spine size and dendritic complexity (Bassett and Chow).

Dysbindin is a synaptic protein that regulates many systems involved with synaptic transmission and is encoded in the DTNBP1 gene. DTNBP1 mutations impact NMDA receptor functionality and impair memory. Mice carrying DTNBP1 mutations have also shown

schizophrenia-like behavior, and dysbindin has been identified as a risk factor (Winship et al., "An Overview of Animal Models Related to Schizophrenia").

Reduction in the expression of Reelin, a protein involved in synaptic formation and plasticity, has also been reported in patients with schizophrenia. Reelin mutations have been reported to produce schizophrenia-like conditions in mice, including increased neuronal packing and reduced dendritic spine density in the hippocampus and frontal cortex. This can lead to deficits in memory, executive function, and social behavior. However, the behavior, social interactions, and cognitive deficits in the mice have been found to yield variable results.

Both glutamate and NMDR's are highly involved with parts of the synapse, allowing Ca2+ into postsynaptic dendrites. However, mutations in the genetic coding for these complexes are highly associated with schizophrenia. When mutated, the shape, structure, and thus function of both glutamate and NMDR receptors are not able to properly regulate the synapse, influencing synaptic signaling strength. This lack of regulation has links to both positive and negative symptoms of schizophrenia (Hall and Bray).

Genetic risk factors for schizophrenia impact both the formation of synaptic networks during brain development and their function in adulthood. The observation that several key genes linked to schizophrenia affect processes like synaptogenesis and neuronal connectivity is consistent with the neurodevelopmental theory, proposing that issues with establishing synaptic connections early in life can contribute to the onset of schizophrenia.

Environmental factors: with a focus on sleep disruption

Environmental factors like prenatal stress, nutritional issues, and substance use can worsen the risk of developing SCZ, especially in people with a genetic predisposition.

Sleep dysfunction is a common issue for people with schizophrenia, and it often correlates with psychotic experiences. Many SCZ patients also have insomnia, which worsens symptoms. However, the opposite was reported as well, that sleep issues worsen psychotic episodes. Some patients use extreme measures, like hypnotic or neuroleptic medication, to initiate sleep (Ferrarelli).

There are many correlations between sleep and psychotic episodes. Around 250,000 people reported that insomnia significantly increases the chance of experiencing a psychotic symptom. On top of that, studies have shown that nightmares were associated with paranoia and hallucinations. In a study with normal individuals, sleep deprivation was shown to induce psychotic episodes, including cognitive disorganization, anhedonia, and perceptual distortion. Even in those at risk of developing schizophrenic symptoms, shortening sleep correlated with higher paranoia, and less restful sleep predicted more hallucinations in healthy individuals. Sleep disturbances are not just a by-product of psychotic symptoms, but can also be a contributing factor to them (Benson; Ferrarelli).

Treatment Approaches and Sleep

Cognitive-Behavioral Therapy for Insomnia (CPT-I) can be used as a therapy to reduce insomnia. For patients with SCZ, there is evidence that this therapy reduces psychotic

symptoms and hallucinations. Studies also show that individuals with SCZ have deficits in oscillatory activities like sleep spindles and slow-wave activities. Non-invasive brain simulations (NIBS) techniques have been used to modulate sleep oscillatory activity, resulting in better sleep for those with psychotic episodes (Ferrarelli).

Schizophrenia has two main approaches for treatment: medical and physical. One of the main medical or drug-related treatments targets dopamine. An increase in dopamine synthesis can lead to psychosis, so many antipsychotics downregulate dopamine production or signaling pathways (Maurus et al.; Yang and Tsai). However, these antipsychotics don't eliminate dysfunctions. Gamma-Aminobutyric Acid (GABA) and glutamate are neurotransmitters that are associated with psychosis. Glutamate, for example, has the ability to bind to NMDRs to decrease negative symptoms and cognitive impairment. GABA is an inhibitory neurotransmitter in the central nervous system. It is vital to the brain's rhythm-generating networks, mechanisms for memory, perception, and consciousness. Abnormalities in GABA signaling may be causative for schizophrenia, and substances that mimic GABA have been linked to improving schizophrenic symptoms. Lessening of negative symptoms has further been attributed to gluten-free diets, more exercise, and treatments targeting hormones, estrogen receptors, and nicotinic and muscarinic cholinergic agents. Those with schizophrenia generally practice less physical activity than the general population (Maurus et al.). In general, exercise and physical activity have been shown to promote mental health. The increased impact of physical activity on mental and physical health has made it a therapeutic approach. Exercise has the potential to increase psychotic episodes, symptom severity, and overall quality of life (Maurus et al.; Yang and Tsai).

Alzheimer's Disease and Sleep

Clinical Features and Diagnosis of AD

AD is a severe dementia that causes memory loss, confusion, and cognitive decline. It is the most common type of dementia, affecting over 55 million worldwide. Currently, there are no cures available, and only a few treatments can slow its progression (Cummings et al.). The gold standard for diagnosis is the presence of β-amyloid plaques, intraneuronal neurofibrillary tangles, and amyloid angiopathy. The three conditions for AD to be diagnosed are:

1. The plaques should stain positively with β-amyloid antibodies and be negative for prion antibodies (which are diagnostic of prion diseases).
2. An increased number of plaques and tangles is found compared to those of similar age who do not have dementia.
3. Frequent accumulation of TDP-43 protein, aggregation of alpha-synuclein in the form of Lewy bodies in the amygdala
4.

Symptoms and Disease Progression

AD is characterized by a variety of symptoms that affect mental processing and memory. The most common symptom is memory loss. Most patients initially have short-term memory loss. As symptom severity increases, the patient's cognitive function decreases. Other symptoms include poor judgment, confusion, language disturbance, visual complaints, withdrawal, and hallucinations. In some cases, seizures, symptoms similar to Parkinson's disease, and increased muscle tone can occur. 95% of Alzheimer's patients start to show symptoms after the age of 65. The duration of the disease usually lasts 8-10 years, but more severe cases often shorten the duration. Death is mainly caused by general inanition, malnutrition, and pneumonia. Those with early onset AD (EOAD), defined by a start of disease before the age of 65, often have very aggressive symptoms (Bird).

75% of AD cases have no known etiology (Hodges et al.). Familial inherited AD can be caused by mutations in the amyloid precursor protein, yet these mutations only account for about 1% of AD cases. Similarly, the majority of Down Syndrome patients have AD pathology by the age of 40 and develop clinical symptoms by the age of 65 (DeTure and Dickson).

Treatment Approaches

There are currently only 5 treatment options to improve the cognitive symptoms of AD. These include 3 types of cholinesterase inhibitors (galantamine, rivastigmine, donepezil), one NMDA receptor antagonist, and a combination of a fixed dose of donepezil and memantine are approved. Galantamine increases cognitive performance, increasing the management of daily activities. Rivastigmine increases metabolism in the hippocampus, producing satisfactory cognitive outcomes. However, the drug can induce nausea, dizziness, and vomiting. Rivastigmine works by inhibiting AChE and butyrylcholinesterase in the cerebrospinal fluid of the brain. Donepezil is also an AChE inhibitor, increasing cognitive function and decreasing NPI and NPI-D scores. NPI (Neuropsychiatric Inventory) measures neuropsychiatric symptoms in individuals with dementia, while the NPI-Distress score (also known as NPI-D) quantifies the level of emotional and psychological distress experienced by the patient's caregiver due to those symptoms.

Lastly, memantine acts as an NMDA receptor antagonist by activation of NMDA ion channels in a preferential manner, ultimately resulting in an increase in normal neuronal activity. This drug results in an increase in cognitive and behavioral activities (Cummings et al.).

Sleep and Circadian Disruption in AD

As AD progresses, the circadian rhythm becomes more irregular and sleep disturbance becomes more regular. The neuropathic changes caused by AD are likely the reason for these changes. On the other hand, an increase in sleep disturbance and an unsynchronized circadian rhythm can also increase the risk factor for developing AD. The formation of memories is dependent on undisturbed sleep. Shorter sleep has been linked to impaired cognitive function. Those individuals with greater levels of sleep disturbance showed a more rapid rate of cognitive decline and a higher risk of developing AD (Irwin and Vitiello).

On top of that, sleep disturbance and excessive daytime sleepiness have been associated with an increase in β-amyloid deposition. Additionally, sleep disordered breathing also increased the risk of dementia and was associated with a higher incidence of all-cause dementia, Alzheimer's disease, and vascular dementia. Overall, sleep disturbances and insomnia can vastly increase the risk of developing AD (Irwin and Vitiello).

Inflammation linking Sleep and AD

When investigating potential mechanisms for the relationships between sleep disturbances and AD, inflammation emerges as a central mechanism connecting sleep disturbance and AD progression, with sleep quality closely tied to inflammatory activity. Improved sleep corresponds with reduced inflammation, whereas disrupted sleep contributes to its elevation. This heightened inflammatory response appears early in the development of Alzheimer's disease and intersects with lifestyle factors such as obesity and physical inactivity, which further amplify inflammatory processes. These same processes influence key pathways involved in AD progression, including the accumulation of β-amyloid peptide. In humans, sleep facilitates the reduction of β-amyloid concentrations, while sleep disturbance triggers stress responses that stimulate immune activity and elevate inflammation (Irwin and Vitiello).

Emerging Therapies

Because of AD's complexity, many treatments have failed. There has been a recognition in recent years of the use of combination therapy to target symptoms. These combinations target behavioral and cognitive symptoms and are flexible in addressing drug targeting, delivery, or timing. Some examples include the use of multifunctional molecules, such as rasagiline, a MAOB inhibitor. This has effects on the amyloid processing (Cummings et al.).

Gene therapy has also been a strategy that has been extensively studied. Treatment would generally involve mutating the gene that expresses a therapeutic enzyme or growth factor. Targeted genes include APP, PSEN1, and PSEN2, APOE: all genes that have proven to increase the risk of AD (Cummings et al.).

ASD, SCZ, AD, and Sleep Overlap

Shared Role of Synaptic Dysfunction

In all 3 neurological diseases or disorders, synaptic dysfunction plays a large role in the development and progression. Furthermore, sleep disturbances have a similar impact on behavior and progression of each disease. In ASD, sleep disturbance amplifies core symptoms, worsening emotional and physical regulation. In SCZ, sleep disturbance provokes key symptoms of psychosis and cognitive impairment. Lastly, sleep disturbance accelerates neurodegeneration and memory loss in AD. Although these effects of sleep disturbances are varied, each has negative effects. This is partially due to the effect that sleep disruption has on

synaptic homeostatic abilities.(Tononi and Cirelli, “Time to Be SHY?”) In ASD, lack of adequate REM disrupts synaptic downscaling and can worsen sensory and behavioral rigidity.

NMDA Receptor Dysfunction across Disorders

In SCZ, sleep loss leads to hyperdopaminergic states and psychosis-like symptoms.

AD, SCZ, and ASD all involve synaptic interactions related to the NMDA receptor. In Alzheimer's, one treatment option is an NMDA antagonist.(Cummings et al.) In SCZ, when dysbindin, a gene that codes for synaptic transmission, is mutated, working memory is impaired.(Winship et al., “An Overview of Animal Models Related to Schizophrenia”) In ASD, when NMDA receptors are impaired can lead to ASD symptoms. (Doldur-Balli et al.) The NMDA receptor plays a crucial role in the presynaptic glutamate release and the postsynaptic homeostatic synaptic plasticity. This strengthening and weakening of the pathways is crucial for learning and memory. When the receptor is mutated or compromised, it can lead to significant defects in the synaptic pathways, leading to certain neurological disorders such as ASD, AD, and SCZ.

SHANK3 and Synaptic Scaffolding Proteins

The Shank gene is a prominent gene in synaptic plasticity. Shank proteins act as scaffolding proteins, organizing neurotransmitter receptors, cytoskeleton proteins, protein ion channels, and enzymes. Overall, this forms a large signaling device crucial to synaptic postsynaptic density regions. Mutations of the SHANK3 gene have been associated with both ASD, AD, and SCZ. (“SFARI | A Bidirectional Switch Affecting Phosphorylation of Shank3 Influences Homeostatic Synaptic Plasticity”)

GABAergic Dysfunction and Neural Excitability

GABA plays a central role in homeostatic synapses. GABA regulates neural excitability by inhibiting overactive circuits. It also plays a central role in sleep structure by promoting slow-wave and REM sleep and in synaptic homeostasis, which restores circuit stability during sleep. When GABA signaling is disrupted, the brain experiences hyperexcitability. In AD, reduced GABAergic signaling contributes to sensory hypersensitivity, anxiety, and repetitive behaviors, all core ASD traits. Sleep studies also show that reduced GABA and melatonin dysregulation may jointly disturb REM sleep and circadian rhythm. However, estrogen can enhance GABAergic signaling, possibly explaining the lower prevalence of ASD in females. (Doldur-Balli et al.). In SCZ, GABA dysfunction in SCZ primarily affects prefrontal cortical interneurons, especially parvalbumin (PV)-positive interneurons, which synchronize neural oscillations. Studies also show reduced GAD67 (an enzyme that synthesizes GABA) expression in PV neurons, and reduced GABA transporter levels, which can cause abnormal neural rhythms, disrupting working memory, attention, and sensory gating. This loss of inhibitory control results in increased dopaminergic and glutamatergic activity, contributing to hallucinations and

delusions, key symptoms of SCZ. (Winship et al., “An Overview of Animal Models Related to Schizophrenia”)

Sleep spindles and slow-wave sleep, which rely on GABAergic thalamocortical synchronization, are reduced in SCZ and AD— directly linking GABA dysfunction to sleep disruption. Reduced Sleep spindles and SWA are also linked to synaptic homeostatic processes. GABA deficits are largely developmental, disrupting circuit formation and synchronization, which is why there is more overlap in ASD and SCZ than AD. (Davis et al.)

Disruption of Synaptic Homeostasis by Sleep Loss

A major overlap lies in how sleep disturbances affect synaptic plasticity. Normally, sleep supports synaptic downscaling. (Tononi and Cirelli 2012). In all three disorders, disrupted sleep interferes with this process, leading to excessive synaptic strength or instability.

All three disorders show persistent and non-restorative sleep disturbances rather than occasional sleep issues. In ASD, insomnia, long sleep onset latency, and reduced total sleep time are common symptoms (Ballester et al. 2020). In schizophrenia, insomnia, fragmented sleep, and nightmares often occur (Ferrarelli 2021). In Alzheimer's disease, frequent awakenings, circadian fragmentation, and daytime sleepiness often occur. (Irwin and Vitiello 2019). Although expressed differently, each disorder involves disruption of the circadian timing system.

There is a Bidirectional Relationship between sleep and symptoms in each disorder. Sleep and sleep disturbances are both a result of underlying pathology and also a driver of symptom severity and progression. For example, poor sleep worsens behavioral symptoms in ASD (Ballester et al. 2020). In Schizophrenia, sleep loss can induce or intensify psychosis (Benson 2006). Sleep disruption accelerates cognitive decline and β-amyloid accumulation in Alzheimer's disease (Irwin and Vitiello 2019).

Conclusion

Sleep is a fundamental regulator of neural homeostasis, with a central role in maintaining synaptic plasticity and overall brain function. This review highlights how disruptions in sleep—particularly in timing, duration, and architecture—interfere with homeostatic synaptic processes, contributing to neurological dysfunction. Sleep supports synaptic downscaling and memory consolidation, while sleep loss biases neural circuits toward maladaptive potentiation. Because synaptic plasticity relies on a balance between Hebbian and homeostatic mechanisms, disturbances in sleep can destabilize neural networks and impair cognitive and behavioral function.

Autism Spectrum Disorder (ASD), Schizophrenia (SCZ), and Alzheimer’s Disease (AD) share underlying features as synaptopathies, with genetic and environmental factors converging on disrupted synaptic signaling. Across all three conditions, sleep disturbances are highly prevalent and closely tied to symptom severity. In ASD, sleep disruption exacerbates behavioral

rigidity and sensory dysfunction; in SCZ, it contributes to psychosis and cognitive impairment; and in AD, it accelerates neurodegeneration and memory decline. These effects are mediated through overlapping biological pathways, including NMDA receptor dysfunction, GABAergic imbalance, and mutations in synaptic scaffolding proteins such as SHANK3, all of which impair synaptic regulation and network stability.

A key unifying theme is the bidirectional relationship between sleep and disease progression. Persistent, non-restorative sleep disturbances—such as insomnia, circadian dysregulation, and impaired sleep architecture—both result from and contribute to pathological processes. Disruption of slow-wave activity and sleep spindles further impairs synaptic homeostasis, reinforcing neural instability. In AD, sleep disturbance is additionally linked to inflammation and β-amyloid accumulation, while in SCZ and ASD, altered neurotransmitter systems and developmental circuit abnormalities play a larger role. Together, these findings position sleep as a critical mechanism underlying disease progression and a potential target for therapeutic intervention across multiple neurological disorders.

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