Sleep Disruption During Early Life as it Relates to the Development of Autism Spectrum Disorder

Author Name: Ebubechukwu G. Abolo

Abstract:

Sleep is a state of minimal consciousness, during which brain activity is altered. Though the role of sleep during development is not definitively established, sleep during early life is essential for proper cognitive development. Losing sleep early in life is associated with neurodevelopmental disorders, such as Autism Spectrum Disorder (ASD), where 80% of patients present with sleep disruptions, such as insomnia or multiple night awakenings. ASD is a disorder that encompasses numerous disorders marked by repetitive behaviors and social deficits. The purpose of this review is to discuss sleep across the lifespan and discuss the link between early-life sleep disruption and ASD. Additionally, this review summarizes the role of synaptic plasticity within the brain during sleep. Synaptic plasticity, put simply, is the brain's ability to mold itself in response to new information. Synaptic plasticity is different in the brain of persons with ASD and neurotypical persons. As synapses are a major target of sleep, the last section and conclusions discuss the potential therapeutic opportunities that targeting sleep, and indirectly synapses, could present for ASD patients.

Introduction:

Sleep is a set period when the mind is put at ease and the brain may return to a homeostatic balance. Sleep dominates early life, and continuously changes throughout one's lifetime (1). Though sleep has been linked to synaptic remodeling throughout life, the role of sleep in brain development is not yet clearly defined (2). The importance of sleep for the developing brain is suggested by sleep being a comorbidity in many neuropsychiatric developmental disorders including Autism Spectrum Disorder (ASD). This review will describe how the composition of sleep changes throughout development, the impact of early life sleep loss on adult behavior, and the relation between sleep, synapses, and development. Understanding how sleep and development affect synapse regulation may reveal key therapeutic opportunities for patients with autism.

Sleep Architecture in the Developing and Mature Brain:

The amount and composition of sleep differ throughout development. Sleep is composed of two stages, Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep. NREM sleep, also known as Slow Wave Sleep, is characterized by high amplitude and low-frequency brain waves. This is a result of the synchronized cortical neuronal firing in the brain. NREM is divided into three stages (N1, N2, N3) that are determined by electroencephalographic (EEG) recorded brain wave activity and indicate sleep depth with N3 being the deepest sleep stage (1). In contrast, REM sleep is characterized by lower amplitude activity because there is less neuronal synchrony, resembling the waking state. The ratio of REM to NREM is distinct during different developmental time points. Likewise, the ratio of REM and NREM-like states that occur in developing animals is also different from mature mammals. NREM and REM sleep are clearly defined in adults by EEG sleep readouts, however, these readouts are not present in human infants and developing mammals (1). It is unclear if the NREM and REM sleep that occurs in infants performs the same function as in adults..

Infants sleep nearly 18 hours a day with 50-80% of that being REM-like sleep (3). In comparison, adults sleep ~8 hours a day with only 2-3 hours of that being REM sleep (3). This drastic difference in sleep amount and architecture has led scientists to question what the role of sleep is during development and if it is different between children and adults. Indeed, many

studies have begun to link neuropsychiatric developmental disorders, such as Autism Spectrum Disorder (ASD), with early-life sleep disruptions (4-6).

Autism and Early Life Sleep:

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that encompasses a diverse array of disorders characterized by deficits in social behavior, such as verbal and nonverbal communication, and repetitive behaviors, which can be diagnosed by age 2 (1). Sleep disruption has arisen as another common symptom present in 80% of patients with ASD. Recent literature has also suggested that this sleep loss may not just be a symptom of ASD but also contribute to the onset and progression.

Using polysomnography, defined by the Mayo Clinic as a "test used to diagnose sleep disorders," scientists found that patients with ASD had markedly increased sleep disruptions than children without ASD (7). Nearly 80% of preschoolers with autism experience disrupted sleep (4). These sleep problems include insomnia, trouble falling asleep (it takes 11 minutes longer on average for people with autism), night terrors, trouble staying asleep, and sleep apnea. Children with autism experience nearly ⅓ less REM sleep than neurotypical children, leading to lifelong effects on behavior (4). In a study conducted by Ben-Gurion University of the Negev, electroencephalogram (EEG) recordings acquired through polysomnography evaluations of 29 children with ASD were compared with those of 23 neurotypical children (2). Children with ASD experienced significantly less slow wave activity (SWA) than their neurotypical counterparts (1). Poor sleep in children with ASD correlated with worse social skills, more severe repetitive behaviors, and increased difficulty making friends compared to other children, as well as lower scores on intelligence tests (4). However, it is unknown if loss of sleep during development can directly worsen these symptoms, though recent studies have begun to address this.

A 2015 study testing the effects of a longer nap time within 4 hours of learning for children 6 to 12 months of age found that frequent naps for infants and young children lead to the development of a better memory (3). The association between slow wave activity (SWA) and synapse maturation suggests that sleep actively contributes to brain development. Sleep is linked with language acquisition, auditory discrimination, visual learning, and motor development. Sleep deprivation during development is associated with long-lasting developmental consequences (1). SHANK3+/-, a prominent synapse protein, when mutated is known to cause ASD and ASD-like symptoms. Heterozygous SHANK3 mutated mice (SHANK3+/-), a common ASD model mouse, at baseline have no behavioral deficits. Following early life sleep disruption, the mice endured sex-specific shifts in behavior as a result of early life sleep disruption. Male SHANK3+/- mice had social deficits and impaired sensory gating, both common symptoms of patients with ASD, while female SHANK3+/- mice were more likely to take risks (6). This paper was one of the first to connect early-life sleep with long-lasting ASD-like adult phenotypes. This supports the hypothesis that sleep has a strong influence on development and may actively contribute to ASD symptoms. Additionally, these results show that sleep disruption has different long-lasting effects depending on age, sex, and genetic vulnerability. Though it is unclear what could be the mechanisms behind these long-lasting effects on behavior.

Synapses, Autism, and Sleep:

Sleep regulates synapses- the spaces between nerve cells- in the brain, such as the ones that play an important role in cognitive function. Learning requires the formation of new synapses and the removal of inappropriate synapses. The Synaptic Homeostasis Hypothesis (SHY) states that sleep decreases the number and size of synapses to offset the increase in synaptic activity while awake (1). Supporting this hypothesis is literature showing overall decreases in synapse density and strength following sleep (1). Though, other literature has indicated certain synapses increase in strength following sleep. It has been suggested that an increase in certain synaptic connections may be important for memory consolidation and retention. Nonetheless, the consensus is that sleep has a profound effect on synapses across the brain, though its effect may be region or synapse-specific (1). It is unknown if the same changes occur at the synapse in developing and mature animals. This is a major concern as ASD and other neurodevelopmental disorders are synaptopathies, diseases of the synapse. Brain maturation starts with massive synaptogenesis, primarily in the cortex, which is then refined by experience-dependent synaptic pruning and circuit formation, during the prenatal and early postnatal period (1). Children with autism have more synapses than neurotypical children, potentially due to a decrease of synaptic pruning during development, affecting brain function and behavior (2).

In a 2014 study, Guomei Tang Ph.D., assistant professor of neurology at CUMC, examined 13 brains from children with autism from ages 2-9 and 13 brains from children with autism ages 13-20 in comparison to 22 neurotypical children (2). The brain cells of children with autism were filled with old and damaged parts and were very deficient in a degradation pathway known as “autophagy,” a process cells use to degrade their own components (2). A potential mechanism for this synaptic pruning defect is linked to a protein called mTOR, which when overactive causes brain cells to lose their ability to conduct autophagy (2). However, the drug rapamycin, which, blocks synaptic potentiation stimulated by neurotrophic factors within the brain, has proven effective at ameliorating autistic-like behaviors in mice, even if administered after the appearance of behaviors through the restoration of normal synaptic pruning (2, 8).

Context and region-specific mechanisms during sleep could potentially increase or decrease the number of synapses present in the brain after development. REM sleep, in particular, may play an active role in the sculpting of synapses by removing spurious neuronal connectivity during the early postnatal period and regulating dendritic spines (1). Additionally, the Ontogenetic Hypothesis, which links REM sleep to the development of endogenous neural activity within the brain, explains the predominance of REM sleep during the postnatal period to convey the extensive production and remodeling of synapses during infancy (1). Synaptopathies which include abnormal synaptic morphology, number, function, excitatory/inhibitory balance, and expression of genes encoding synaptic proteins have been associated with ASD (1). Because of the efficiency of drugs like rapamycin at lessening the social abnormalities resulting from autism in mice through the mending of pathways for synaptic pruning, synapses could be a potential target to treat ASD and repair sleep health (2).

Future Directions and Conclusions:

In conclusion, sleep is heavily intertwined with synaptic plasticity affecting the length of REM sleep and NREM sleep, the latter being the most restorative part of sleep to the mind and body (1). Synapse regulation occurs during sleep, fine-tuning the connections that play an important role in different functions of the brain. Different symptoms of Autism Spectrum Disorder (ASD) can be worsened by sleep deprivation, exacerbating the condition for the 80% of

children with autism who experience disrupted sleep. Though its role is not yet clearly outlined, sleep is important to the nurturing of the brain during development, and its regulation of synapses is a potential link between early life sleep disruption and the behavioral abnormalities observed in Autism Spectrum Disorder (ASD). For these reasons, the synapse appears as a promising therapeutic target to treat or reduce the impact of Autism Spectrum Disorder (ASD).

References

[1] Barone, I., Hawks-Mayer, H., & Lipton, J. O. (2019). Mechanisms of sleep and circadian ontogeny through the lens of neurodevelopmental disorders. *Neurobiology of Learning and Memory*, *160*, 160–172. https://doi.org/10.1016/j.nlm.2019.01.011
https://pubmed.ncbi.nlm.nih.gov/30668981/
10.1016/j.nlm.2019.01.011
[2] Tang, G., Gudsnuk, K., Kuo, S., Cotrina, M. L., Rosoklija, G., Sosunov, A. A., Sonders, M. S., Kanter, E., Castagna, C., Yamamoto, A., Yue, Z., Arancio, O., Peterson, B. S., Champagne, F. A., Dwork, A. J., Goldman, J. E., & Sulzer, D. (2014). Loss of MTOR-Dependent macroautophagy causes autistic-like synaptic pruning deficits. *Neuron*, *83*(5), 1131–1143. https://doi.org/10.1016/j.neuron.2014.07.040
https://pubmed.ncbi.nlm.nih.gov/25155956/
10.1016/j.neuron.2014.07.040
[3] Alrousan, G., Hassan, A., Pillai, A. A., Atrooz, F., & Salim, S. (2022). Early life sleep deprivation and brain development: insights from human and animal studies. *Frontiers in Neuroscience*, *16*. https://doi.org/10.3389/fnins.2022.833786
https://www.frontiersin.org/articles/10.3389/fnins.2022.833786/full
10.3389/fnins.2022.833786
[4] Furfaro, H. (2023, March 10). Sleep problems in autism, explained. *Spectrum | Autism Research News*. https://www.spectrumnews.org/news/sleep-problems-autism-explained/
https://www.spectrumnews.org/news/sleep-problems-autism-explained/
[5] Jones, C. E., Opel, R. A., Kaiser, M. E., Chau, A. Q., Quintana, J., Nipper, M. A., Finn, D. A., Hammock, E. a. D., & Lim, M. M. (2019). Early-life sleep disruption increases parvalbumin in primary somatosensory cortex and impairs social bonding in prairie voles. *Science Advances*, *5*(1). https://doi.org/10.1126/sciadv.aav5188
https://pubmed.ncbi.nlm.nih.gov/30729165/
10.1126/sciadv.aav5188
[6] Lord, J., Gay, S. M., Harper, K. M., Nikolova, V. D., Smith, K. M., Moy, S. S., & Diering, G. H. (2022). Early life sleep disruption potentiates lasting sex-specific changes in behavior in genetically vulnerable Shank3 heterozygous autism model mice. *Molecular Autism*, *13*(1). https://doi.org/10.1186/s13229-022-00514-5
https://molecularautism.biomedcentral.com/articles/10.1186/s13229-022-00514-5
10.1186/s13229-022-00514-5
[7] *Polysomnography (sleep study) - Mayo Clinic*. (2023, February 17). https://www.mayoclinic.org/tests-procedures/polysomnography/about/pac-20394877
https://www.mayoclinic.org/tests-procedures/polysomnography/about/pac-20394877
[8] Tang, S., Reis, G. F., Kang, H. C., Gingras, A., Sonenberg, N., & Schuman, E. M. (2001). A rapamycin-sensitive signaling pathway contributes to long-term synaptic plasticity in the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(1), 467–472. https://doi.org/10.1073/pnas.012605299
https://pubmed.ncbi.nlm.nih.gov/11756682/
10.1073/pnas.012605299
[9] Arazi, A., Meiri, G., Danan, D., Michaelovski, A., Flusser, H., Menashe, I., Tarasiuk, A., & Dinstein, I. (2019). Reduced sleep pressure in young children with autism. *SLEEP*, *43*(6). https://doi.org/10.1093/sleep/zsz309

https://pubmed.ncbi.nlm.nih.gov/31848619/
10.1093/sleep/zsz309
[10] Ebstein, F., Küry, S., Papendorf, J. J., & Krüger, E. (2021). Neurodevelopmental Disorders (NDD) Caused by Genomic Alterations of the Ubiquitin-Proteasome System (UPS): the Possible Contribution of Immune Dysregulation to Disease Pathogenesis. *Frontiers in Molecular Neuroscience*, *14*. https://doi.org/10.3389/fnmol.2021.733012
https://pubmed.ncbi.nlm.nih.gov/34566579/
10.3389/fnmol.2021.733012
[11] Frank, M. G. (2020). The ontogenesis of Mammalian sleep: Form and function. *Current Sleep Medicine Reports*, *6*(4), 267–279. https://doi.org/10.1007/s40675-020-00190-y
https://pubmed.ncbi.nlm.nih.gov/33816063/
10.1007/s40675-020-00190-y