HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2023 May 08.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2023 January ; 8(1): 3–5. doi:10.1016/j.bpsc.2022.11.001.

The Important Link Between Sleep and Brain Health in Autism

Dea Garic

Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Sleep has several therapeutic and restorative roles in brain health, facilitating memory consolidation, cognitive ability, synaptic plasticity, immune function, and metabolic clearance of inflammatory proteins that accumulate throughout the day (1,2). Sleep problems are more than 4 times more prevalent in individuals with autism spectrum disorder (ASD) compared with individuals without ASD (3) and can have adverse effects on brain development and quality of life of both the individual and their families (1). While numerous studies have shown that sleep problems in ASD emerge early in life and prevail well into adulthood, the early biological mechanisms involved remain unclear.

In the current issue of *Biological Psychiatry*, Linke *et al.* (4) provide important new insights into how auditory-thalamic functional connectivity (FC), sensory sensitivities, and sleep problems are interconnected in children with ASD. First, the authors reported greater levels of impairment in sensory sensitivity scores and higher rates of sleep problems among children ages 1.5 to 5 years who have ASD compared with a matched typically developing (TD) group. Further, greater sensory sensitivity was associated with more sleep problems in children with ASD, indicating that sensory overresponsivity could potentially play an important role in sleep behavior. While the relationship between sensory sensitivities and sleep problems has been previously reported in children with ASD (5), Linke *et al.* have expanded on this research by examining if atypical FC might be an underlying factor.

Connections between the thalamus and the auditory cortex develop early in life and have been linked to atypical sound processing in older children with ASD; therefore, the authors focused on examining whether auditory-thalamic FC might underlie the relationship observed between heightened sensory sensitivity and sleep problems. They found that children with ASD had greater auditory-thalamic FC during sleep compared with TD children, and that this overconnectivity was associated with longer sleep latency. Sleep latency, which is defined as the length of time needed to fall asleep, was the only aspect of sleep that was associated with overconnectivity, which might suggest a specific sleep-connectivity association, but future studies will help determine whether this relationship also exists for other sleep problems (e.g., sleep disturbances). Sleep latency is one of the most pronounced sleep problems experienced by children with ASD (6), and Linke *et al.*'s findings provide key insight into how atypical FC plays a driving role.

Address correspondence to Dea Garic, Ph.D., at dea_garic@med.unc.edu.

Another important contribution of the Linke *et al.* (4) study was their finding that the auditory cortex, but not the thalamus, had increased blood oxygen level–dependent (BOLD) signal amplitude during sleep in children with ASD compared with TD children. This was particularly striking because TD children and adults tend to show the opposite pattern, with increasing BOLD activity in the thalamus but decreasing BOLD activity in auditory regions during sleep (7). Moreover, in both children with and without ASD, Linke *et al.* found that signal amplitude in the thalamus was negatively associated with auditory cortex signal and auditory-thalamic FC. Therefore, the heightened BOLD signal in the auditory cortex observed in the ASD sample compared with TD children might be indicative of atypical thalamocortical gating of auditory sound processing during sleep. Collectively, children with ASD are more likely to experience sensory overresponsivity and delayed habituation to auditory stimuli, possibly as a result of atypical auditory-thalamic connectivity, which might therefore interfere with sleep.

In sum, the findings of this study extended previous observations of heightened sleep problems, sensory over-sensitivity, and atypical brain development in ASD, and perhaps more importantly this study could serve as an exemplary empirical framework to improve our understanding of the underpinnings of sleep problems. This was accomplished through an innovative study design involving collecting sleep measures, sensory measures, and successfully scanning toddlers and young children with ASD without the use of sedation, which allowed for examination of resting-state FC during natural sleep.

A distinctive strength of this study is the use of sleep stage control analyses. While electroencephalography is often used to determine sleep stage, simultaneous electroencephalography–magnetic resonance imaging (MRI) acquisition is extremely difficult to achieve in clinical pediatric populations; therefore, Linke *et al.* (4) conducted multiple analyses to ensure that group differences in sleep stage were not a confounding factor. Control analyses included comparing subject arrival time, how long the child had been asleep prior to FC MRI data collection, examining successive FC MRI acquisitions to confirm that there were no differences caused by transitioning between sleep stages, and comparing global signal amplitude between groups as a proxy for deep sleep. The control analyses described in this article serve as an exemplary procedure for reducing the potential of sleep stage differences influencing group differences in FC collected during sleep and should be considered in future studies.

Most studies to date have not included sleep measures in studies of brain development in ASD, and the study by Linke *et al.* (4) will hopefully promote further examination into this important field of work. Parent-report questionnaires offer an attainable starting point for adding sleep measures to ongoing studies, as they are low cost, take little time, and are easy to collect from parents. Moving forward, future studies could also 1) collect direct sleep measures, 2) explore complementary mechanisms involved in sleep problems (e.g., the glymphatic system), and 3) establish temporal specificity in associations between brain development and sleep.

As characterizing sleep problems in autism continues to garner increasing attention, it is important to note that parent-report questionnaires offer only limited insight into the

biological mechanisms involved. There are multiple aspects of vulnerability in sleep health; therefore, it will be important to use direct sleep measures to characterize sleep components, such as sleep stages, sleep fragmentations, and overall sleep efficiency. Using questions such as “trouble sleeping” or “resisting bedtime” can miss a large portion of sleep quality parameters–sleep might appear normal but be less restorative. For example, most restorative sleep occurs during slow-wave sleep, which questionnaires are unable to reliably measure (8). Questionnaires make it difficult to disentangle sleep components, and this is further complicated by individual differences in interpreting questions. In fact, the two parent-reports used in this present study—the Child Behavior Checklist and an adapted Brief Infant Sleep Questionnaire—did not provide findings congruent with each other even in the same sample, highlighting the need for direct sleep assessment for future investigation. Incorporating longitudinal polysomnography, actigraphy, and/or mattress sleep sensors would allow for a more comprehensive examination of sleep patterns throughout the night, as well as potentially expanding our understanding of causal relationships between brain-behavior associations.

Sleep has complex neural and metabolic functions to maintain homeostasis in the brain. For instance, a network of cerebrospinal fluid (CSF)–filled perivascular pathways, known as the glymphatic system (9,10), is vital for the distribution of growth factors and the clearance of metabolic byproducts (e.g., amyloid-β) that accrue during wake states. Glymphatic function is largely considered a feature of the sleeping brain, with the majority of CSF circulation occurring during sleep states (2,10). While examinations of glymphatic function have focused primarily on neurodegeneration, glymphatic function might also be a driving force in early brain development, particularly in neurodevelopmental disorders associated with an increased prevalence rate of sleep problems, such as ASD. Glymphatic function is a vital component of restorative sleep and might represent an additional piece of the puzzle along-side auditory-thalamic overconnectivity. Examining glymphatic biology by including measures from structural MRI (e.g., CSF and perivascular space volumes) could be coupled with functional MRI analyses like those in Linke *et al.* (4), with the potential to inform further comprehensive systematic explanations for sleep problems in ASD.

Lastly, the Linke *et al.* (4) study opens the door for considering the temporal specificity of associations between auditory-thalamic FC, sensory sensitivities, and sleep problems in future studies. For the present study, no significant age-related differences in auditory-thalamic FC were observed in this cross-sectional sample of 1.5- to 5-year-olds. A longitudinal examination of sleep and FC with larger samples could provide more insight into how auditory-thalamic FC unfolds across early development and can help untangle some temporal precedence in sleep and brain development. While thalamocortical connections play a vital role in regulating sleep, sleep problems might also further exacerbate atypical FC.

Overall, Linke *et al.* (4) have presented evidence that auditory-thalamic overconnectivity could be an underlying mechanism involved in the connection between sensory sensitivities and elevated sleep problems in children with ASD. These findings build upon and extend previous research by incorporating diagnostic assessments, two parent-report sleep questionnaires, sensory profile questionnaires, and FC analyses in very young children

with ASD and in matched control subjects. This study should serve as an exemplar for conducting natural sleep neuroimaging studies in conjunction with sleep measures. Hopefully, future studies will consider integrating direct sleep measures, exploring complementary mechanisms (i.e., the glymphatic system), and using longitudinal designs to expand our understanding of the complex dynamics between sleep and brain health in ASD. Linke *et al.* have set the framework for placing sleep characteristics into the context of an interconnected, biologically driven model, which is crucial for gaining a deeper insight into how and why sleep problems occur and is vital for developing more effective, targeted interventions for improving long-term outcomes.

Acknowledgments and Disclosures

DG is supported by Eunice Kennedy Shriver National Institute of Child Health and Human Development Grant No. K01HD109445.

The author reports no biomedical financial interests or potential conflicts of interest.

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