CROSS TALK

Why it’s difficult to study sleep in autism

BY **CLAIRE CAMERON**

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Sleep problems are unusually common in people on the spectrum, and yet the topic is poorly understood. In this Cross Talk, five scientists discuss the biggest hurdles they face in understanding the relationship between autism and sleep.

For some, the issues are largely technical: The gold-standard sleep test is time-consuming and costly to administer. For others, it’s a lack of funding, ill-defined terms or fragmentation of the field. Despite the challenges, these scientists agree on the importance of the work, and that progress in this field requires collaboration, investment and large datasets.

Ruth O'Hara

Associate Professor,Stanford University

Complex technology can bog down research into sleep issues in people on the spectrum.

Assessing sleep in autism can be technically tricky

The evidence to date points to profound differences between the sleep of individuals with autism and that of typical people or those with developmental delay. But our ability to identify and treat sleep problems is hampered by expensive and complex technology. This technology is particularly difficult to use with individuals who, by virtue of their condition, are wary of new people, devices or circumstances.
We use a method called polysomnography to assess brain function during sleep. In this technique, participants have to sleep wearing an electroencephalography (EEG) cap that has multiple wires emerging from it, as well as a sensor over their mouth and nose. At the moment, polysomnography

produces the most comprehensive assessment of sleep of any method, providing information on the stages of sleep as well as the presence of sleep disorders. There's a range of sleep features that may be impaired in autism, from reduced rapid eye movement (dream) sleep to increased levels of sleep-disordered breathing. We need to define which of these problems a child has. This information can inform treatment.

Yet children with autism require quite a long time to get accustomed to the polysomnography. Sometimes in our work, two or three researchers spend many hours over the course of a month with the children, helping them get used to the device. They talk to them and to their parents about how the apparatus works. They let the children try the device on their dolls or watch the sleep study being implemented on their siblings. This takes a lot of time and resources, which can restrict our ability to do this kind of study in sufficiently large numbers of individuals to characterize sleep in autism.

New technologies may help us. For example, we are looking into a stand-alone device that sits beside the bed and uses an acoustic system to study sleep parameters. The device picks up the sound of a person's heartbeat to measure her heart rate and monitors her sleep patterns from the sound of her breathing. We are comparing the data we get from this device with those from polysomnography to see whether we can use it to assess sleep dysregulation and sleep architecture in a large number of individuals with autism.

One issue that technology cannot solve, however, is bias. If I advertise for a sleep study in autism, the people who show up at my door are those who have profound sleep problems. We don't see people with milder problems and so may not be able to ferret out the diversity of sleep problems in autism.

Beth Malow

Professor of neurology and pediatrics,Vanderbilt University

Sleep problems may underlie some core features of autism.

The importance of sleep in autism is underappreciated

Sleep in autism may be under-researched because lack of sleep seems like a peripheral problem to many autism researchers. Comorbidities in autism — **epilepsy**, sleep, gastrointestinal issues and so on — haven't received the same attention from the scientific community as the core features

of autism. That may be changing — and should.

Sleep problems have a large impact on a person's quality of life. From our work, we see that not sleeping well clearly affects daytime functioning. In a study published this year, we reported that **when children sleep more**, they are more attentive. They also are less aggressive, calmer, have less severe autism features and respond better to therapies. By treating sleep problems, clinicians can improve some of the core features of autism.

These effects also can be an important — but unappreciated — **confound in autism research**. Say you are studying a new treatment for language delay. If half the kids getting the therapy sleep well, but the other half don't, the ones who benefit from the treatment may be the ones who are sleeping better. A good night's sleep may help them pay attention to the therapist.

I would like to see sleep become more mainstream in autism research. I would even like sleep to be considered a core feature of autism as it is in other developmental conditions. Once sleep problems are recognized as a fundamental issue in autism, they are likely to receive funding for research. Then the best people in the field will want to study sleep.

As with other autism research, understanding sleep in autism requires collecting data from a large, varied population. Instead of just recruiting participants from large academic medical centers, we should seek people out in community settings. Doing so will provide the data we need to have confidence in our results.

Ashura Buckley

Pediatric neurologist,National Institute of Mental Health

Fragmentation in the field hampers progress on sleep and autism.

Solutions for sleep in autism require a common approach

The bidirectional relationship between sleep and behavior is well known. And clinicians, researchers and parents all recognize that sleep is essential to healthy development. Yet the complex interactions that govern sleep, along with the different frameworks used to talk about it, have combined to stall progress in understanding these essential relationships.

To overcome this impasse, I recommend a swift and decisive move toward convergence science. In this model, experts from multiple disciplines not only share knowledge, but actually meld their fields to produce new disciplines that are greater than the sum of their parts.

There has been little consistency across disciplines regarding how we approach the metrics of

sleep. Establishing a common approach to the acquisition of sleep data — including EEG and behavioral measures — will help us begin to accurately track the maturation of the sleeping brain. It will also enable us to identify patterns associated with typical and atypical trajectories. In order to do that, we must foster a multidisciplinary field covering both sleep and neurodevelopment.

Traditional clinical categories such as insomnia or circadian rhythm disorder allow us to determine the best treatments for a disrupted sleep-wake cycle. These categories do not, however, reflect the complex shifting of **neurotransmitters** and electrophysiological potentials that occur each night and over critical periods in development. These shifts underlie both typical sleep behavior and sleep disorders.

If we accept that sleep is a process — an active and essential participant in the building and maintenance of brain circuits — we can begin to ask how that process serves brain development. In the first few years of life, the circuits that underlie language, memory, motor skills and emotional and sensory associations are all forming. It is for this period that we have the least amount of objective data. We need to know much more about the work the sleeping brain is doing during this time. We also need to understand how these newly built circuits function in children who develop typically, as well as in those diagnosed with neurodevelopmental conditions.

Using the sleep EEG to detect changes in brain rhythms over time allows us to measure and quantify how these circuits mature in relation to development and behavior. The electrical signals produced during sleep provide a unique and early window into circuit development long before the associated behaviors appear.

Sorting out which signals are **biomarkers** for sleep disorders as opposed to markers of aberrant neurodevelopment in general is a complex undertaking. This is where the sophisticated measurement of the sleep process becomes important, and team science becomes indispensable. Earlier this year, the National Institute of Mental Health hosted a workshop dedicated to establishing a consortium on sleep and neurodevelopment research. The group includes neurologists, child psychiatrists, and sleep and pulmonary medicine specialists. It also includes geneticists, psychologists, neuroscientists, computational experts and bioengineers. It has become clear that no single discipline, working in isolation, can put the sleep and neurodevelopment pieces together.

This article was not written as part of Ashura Buckley's official duties as a government employee. The views expressed in this editorial do not necessarily represent the views of the U.S. government.

Philippe Mourrain

Associate professor of psychiatry and behavioral sciences,Stanford University

Animal models could reveal the circuits that control sleep, deep

under the brain's surface.

To understand sleep in people with autism, we need fish

Sleep problems are extremely common among individuals with autism, and it is likely that they contribute to other features of the condition. However, we don't know yet to what extent sleep disruption leads to the cognitive aspects of autism.

One problem is our limited understanding of the function of sleep in cognition. EEG provides only superficial measures of brain activity, and yet circuits critical for sleep are located deep in the brain. In my lab, we are studying the function of sleep and these neural networks using mouse and zebrafish. Zebrafish embryos are completely transparent, so you can look deep inside their brains, which share core commonalities with ours.

We can use whole-brain imaging and fluorescent proteins to record the activity of each neuron in the fish brain. This allows us to characterize the effects of sleep on the entire brain, not just at its surface. We can then identify networks of neurons critical for sleep.

In mice and zebrafish, we can then use techniques such as optogenetics and pharmacological tools such as hypnotics to manipulate specific networks. These methods may help us manipulate sleep and arousal states that are crucial for optimal memory and cognition. Once we know the role of each network in maintaining normal sleep architecture, we can look for disruptions in mouse models of autism.

We hope our findings will one day allow researchers to target certain neural networks in people with autism to improve sleep, and that this, in turn, will ease other features of the condition. The challenge is getting the funds to do these important experiments.

The current funding climate pushes researchers to work on animals that are more closely related to people than zebrafish are. Yet zebrafish embryos are the only see-through vertebrate model that allows us to explore the entirety of a brain similar to ours, and to discover the intimate cellular and neuronal mechanisms that underlie complex behaviors.

Amanda Richdale

Associate professor of psychology,La Trobe University

The field needs better definitions of sleep quality and more longitudinal studies.

Sleep problems in autism remain ill-defined and overlooked

Individuals with autism tend to have poorer sleep quality and more insomnia throughout their lives than do people in the general population. Taking a long time to go to sleep, waking up early in the morning and staying awake for a long time at night are some of the common problems among people with autism.

We do not understand what causes these often severe and intractable sleep difficulties in autism, and they may not respond to our treatments. We also don't fully understand the associations between sleep and daytime behavior, anxiety, attention, core autism features and gastrointestinal issues.

There are several reasons for this lack of information. First, clinicians often don't ask families about their child's sleep quality, so these problems may not even come up. Even when they do, it is often hard to define them. It is typically up to parents to describe them, and what one family considers problematic, another may tolerate. What's more, research shows that parents' knowledge about sleep and sleep problems across childhood is generally poor. And clinicians do not typically address sleep when prescribing treatments for autism.

At the same time, experts debate the definitions of common sleep-quality indicators, such as sleep duration and sleep continuity. These indicators change with age and can differ from one individual to the next. And among people with autism, there may be subgroups of sleep problems. Subjective sleep quality may also differ from objective sleep measurement. In 2015 and 2017, the National Sleep Foundation published guidelines for **sleep duration** and draft guidelines for **sleep-quality indicators** across the lifespan.

Understanding sleep problems in autism also has not been a priority area for research or research funders, and does not feature highly at either autism or sleep research meetings. As a result, we lack studies of individuals at different ages and over time, as well as research on therapies.

Autism researchers should recognize the potential importance of sleep for other conditions associated with autism. Insomnia, for example, may underlie a range of mental health conditions, including anxiety and depression, which are also common in individuals on the spectrum.

Changing scientists' attitudes toward and approach to sleep problems in autism is a critical step toward a better understanding of the condition's core features and comorbid conditions.