# Newsletter

Stanford MEDICINE | Center for Sleep in Autism Spectrum Disorder
*Department of Psychiatry & Behavioral Sciences*


**Joachim Hallmayer**
Center PI

Dear friends and colleagues,

At the start of this new year, we wish you the best for all your endeavors in 2024. This is our first newsletter from the Center for Sleep in Autism Spectrum Disorder. We intend to have a newsletter every six months. The Center for Sleep in Autism is one of the ten Autism Centers of Excellence funded by the National Institutes of Health. The mission of the Center is to examine to what extent dysregulation of sleep is central to the development of characteristics of autism. There is a growing consensus that the neurobiology of autism may, at least in part, be attributed to synaptic dysfunction. Synapses are the foundation of neuronal plasticity. It has been long recognized that sleep is central to brain plasticity. Animal data demonstrate that sleep is essential for the maturation of fundamental brain structures and functions.

Epidemiological findings indicate that children with early sleep disturbance suffer later from cognitive, attentional, and psychosocial problems. Sleep is a significant concern for caregivers of autistic children and adolescents. Common symptoms are late sleep onset, frequent nighttime awakening and insomnia leading to NREM/SWS fragmentation and abnormal sleep quantity. Despite its central role in brain development and function, these sleep impairments are considered secondary in autism, frequently considered a concomitant co-occurring condition. The main goal of our Center for Sleep in Autism will be to determine if sleep disturbances reflect convergent pathways that can act as causal for, and/or co-aggravating factors of, core behavioral and cognitive differences in autism.

# Project overview: The Impact of Sleep Dysregulation on Autism

**Ruth O'Hara**
PI for Project 1

**Makoto Kawai**
Co-PI for Project 1

In recent scientific findings, it has been revealed that sleep disruptions affect 80% of children with Autism Spectrum Disorder (ASD). These disturbances in sleep patterns are not only challenging for the children themselves but also present significant burdens for their parents and caregivers. Moreover, insufficient subjective sleep quality has been linked to the exacerbation of core ASD symptoms, including repetitive behaviors and difficulties in social interaction and communication.

In the pursuit of a deeper understanding of the relationship between sleep and ASD, a groundbreaking research initiative has been launched. The primary objective of this study is to investigate whether dysregulated sleep plays a central role in both the development and manifestation of ASD symptoms. To achieve this, researchers will conduct comprehensive assessments comparing children with ASD to typically developing controls, all aged between 4 and 17 years old.

***The research will employ cutting-edge techniques to analyze various aspects of sleep, including sleep fragmentation measured through actigraphy, sleep architecture assessed via polysomnography (PSG), and daytime brain activity during a resting state, monitored through awake EEG (electroencephalogram).*** By examining these parameters, researchers aim to uncover potential correlations between sleep patterns and the severity of ASD symptoms.

However, conducting conventional sleep studies, such as PSG, poses substantial challenges when dealing with children with ASD. To overcome this hurdle, researchers will implement a systemic desensitization procedure. This innovative approach seeks to minimize sensory sensitivities, making the sleep study experience more tolerable and less distressing for the young participants.

The core hypothesis driving this research is both intriguing and promising: if the study can demonstrate that sleep fragmentation plays a significant role in the development of certain ASD traits and that improving sleep quality can alleviate these traits, it may establish a causal link between sleep and ASD.

# Project overview: Pharmacological Probing of Sleep Physiology on Autism

**Antonio Hardan**
PI for Project 2

In the current project, we propose to modulate the neurotransmitter systems implicated in the sleep-wake balance and examine their impact on sleep physiology in autistic children and adolescents. ***The goal is to promote better sleep by either targeting wakefulness by using receptors antagonists such as diphenhydramine (anti-histaminergic) and suvorexant (DORA) or promoting sleepiness by using a receptor agonist, zolpidem (nonbenzodiazepine receptor agonist).***

We aim at investigating the target engagement of three sleep-inducing agents with different mechanisms on gold standard PSG, actigraphy, and circadian rhythm in children and adolescents with autism between the ages of 8 and 17 years. The rationale behind the use of diphenhydramine, zolpidem, and suvorexant is related to their distinct pharmacological profiles and their differential effect on the primary neurotransmitters involved in sleep. Diphenhydramine has significant antihistaminic activities and concurrent sedative properties. Zolpidem is a nonbenzodiazepine receptor agonist and is a hypnotic targeting sleep-onset or sleep maintenance. Suvorexant is a DORA and is prescribed to target insomnia characterized by difficulty with sleep onset and/or sleep maintenance. Our pharmacological probing study of sleep architecture will allow us to examine, for the first time, whether we can effectively modulate altered sleep parameters in autistic children and adolescents and examine their impact on sleep quality and clinical features.

# Project overview: Whole Brain and Body Characterization of Sleep Disturbances and Interventions in Fmr1, Shank3 and Cntnap2 Knockout Zebrafish

**Philippe Mourrain**
PI for Project 3

Sleep is critical for proper synaptic connections and brain development. Our group previously established that sleep disruptions in zebrafish, like in other species, prevent normal structural synapse plasticity. Conversely, proper sleep and melatonin hypnotic/circadian treatment can improve these synaptic defects. ***While human (Projects 1 & 2) approaches permit exquisite studies of social interactions, repetitive behaviors, and associated cortical synaptic defects, zebrafish is a transparent vertebrate popular in developmental biology allowing whole brain and body investigation.***

Importantly, genes associated with autism like Fmr1, Shank3, and Cntnap2 are pan-neuronal, and their loss likely impacts the entire central nervous system during sleep. Using fluorescence-based polysomnography (fPSG) to capture whole-brain and whole-body imaging with single cell resolution during sleep, we have shown that zebrafish have sleep brain dynamics analogous to mammals. Similarities include a state we coined slow bursting sleep (SBS) which shares many commonalities with Non-REM slow wave sleep (SWS). Our preliminary data indicates that SBS is fragmented in developing Fmr1 zebrafish mutants. Further, studies from other groups have shown that based on actimetry, sleep/wake pattern is also disrupted in zebrafish cntnapt2ab and shank3ab mutants. However, their brain activity during sleep has not yet been investigated.

In this project we will apply fPSG to these three genotypes (fmr1, shank3ab, and cntnap2ab mutants) and controls to fully characterize their sleep neural and muscular dynamics during development. Next, we will apply the same pharmacological interventions (H1R antihistamine, GABAA agonist, and hypocretin/orexin receptors antagonist) used in human (Project 2), to improve sleep onset latency and sleep/SBS consolidation in these autism risk gene mutants. Then, we will investigate the respective beneficial effects of these NREM/SWS/SBS-sleep interventions on structural synapse density using longitudinal imaging of telencephalic, hypothalamic and spinal cord circuits expressing synaptic proteins fused to fluorescent markers such as PSD95-eGFP, Synaptophysin-eGFP or Gephyrin-eGFP. The transparency of the zebrafish model will reveal how sleep dynamics are disrupted throughout the entire brain and how sleep interventions can also be beneficial for synaptic normalization throughout the CNS, further establishing the causal/aggravating role of disrupted sleep in the development of autistic traits.

# Community-Based Participatory Research: Sleep and Neurodiversity Outreach for Research and Education- SNORE


## Lawrence Fung

Director for Dissemination and Outreach Core


***Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involved all partners in the research process and recognizes the unique strengths that each brings.*** CBPR begins with a research topic of importance to the community and has the aim of combining knowledge with action and achieving social change.

The Center for Sleep in Autism will form a Community-Academic Partnership (CAP) to:

1. Co-design methods of dissemination of known research related to sleep in individuals on the autism spectrum.
2. Co-design methods of dissemination of new research findings from the CSASD.
3. Co-determine the outreach strategies to all community stakeholder groups.

The CAP will create sleep toolkits for physicians, parents/care providers, and autistic adults.

The membership of the CAP includes parents, autistic adults, two physicians, one psychologist, one social worker, one job coach, one occupational therapist, one educational specialist, one disability services professional, and CSASD investigators.

**SNORE Members**

Alberto Navarro

Anh Dao

Anlor Davin

Beth Hankoff

Candace Adeszko

Char Houben

Cristina Chadalavada

Dana Won, MD

Gregory Garoppolo

Heather Satterwhite

Juliette Gudknecht

Kate Nowell-Smith

Kristina Okun

Maxfield Michael Sparrow Jones

Patrick Ryan

Sarah Doyle

Uli K. Chettipally

# Data Management and Analytic Core

## Booil Jo

The Data Management and Anaytic Core is led by Dr. Booil Jo. ***The data management and analysis core (DMAC) will manage our multi-domain, cross-species, comparative data sets; maintain and track the quality and eventual sources of heterogeneity, correct calibration and quality control of the data and control for the multiplicity of choices in the normalization and metrics.*** The proposed Autism Center of Excellence (ACE) employs a multi-modal program which encompasses four synergistic projects aimed at characterizing the role of sleep fragmentation and sleep physiology on the core symptoms, repetitive behaviors and cognitive function of children and adolescents with ASD and also in mouse and zebrafish models of ASD. We will collect clinical, behavioral, and objective measures of Sleep EEG, daytime awake, resting EEG, and actigraphy in children with ASD and controls. We will manipulate sleep architecture in children with ASD pharmacologically. In parallel the same set of measures and pharmacological manipulation will be studied in zebrafish and mouse models of ASD. The management and analysis of such large, multi-domain, comparative data sets include careful maintenance and tracking of the quality and eventual sources of heterogeneity, correct calibration and quality control of the data and control for the multiplicity of choices in the normalization and metrics. In line with the overall mission and specific aims of our ACE, the DMAC will work closely with other cores and the project investigators to integrate and manage data across all ACE Projects and to provide state-of-the-art and cutting-edge statistical analyses using reproducible approaches.

# Recruitment and Assessment Core

## Jennifer Phillips

## Joachim Hallmayer

Led by Drs. Phillips and Hallmayer, the Assessment Core will oversee the enrollment and characterization of 180 ASD patients and 100 controls for participation in the center from this cohort. ***The Assessment Core will be responsible for enrolling participants, reviewing and/or conducting diagnostic, clinical, cognitive and behavioral assessments, scheduling participants, data scoring, entry and tracking, quality control procedures, and data transfer procedures to the Data Management and Analytic Core.***

# Faculty

**Joachim Hallmayer**
Center PI, Director for Administrative Core

**Ruth O'Hara**
PI for Project 1, Co-director for Administrative Core

**Makoto Kawai**
Co-Pi for Project 1

**Antonio Hardan**
PI for Project 2

**Philippe Mourrain**
PI for Project 3

**Lawrence Fung**
Director for Dissemination & Outreach Core

**Jennifer Phillips**
Director for Assessment Core

**Booil Jo**
Director for Data Management Core

**Mirko Uljarevic**
Clinical Assistant Professor

**John Hegarty**
Clinical Assistant Professor

**Gordon Wang**
Clinical Assistant Professor

**Research Scientists & Clinicians**

Rochelle Coulson

James Jaggard

**Junior Investigators & Postdocs**

Christina Chick

Pahnwat Taweesedt

Toru Ishii

Kathleen Watson

**Trainees**

Shou En Chen

Gabby Finkelstein

Tia Lee

Anna Leith

Adriana Lopez

Julia Mancini

Zariah Mekile

Cassidy Miller

Keri Ngo

Grace Peterson

Natalie Saba

Andrew Song

Lydia Yaiser

**Staff**

Laura Alexandre

Isabelle Cotto

Erica Detemmerman

Eliana Gropman

Bohye Kim

Zetan Li

Robin Libove

Joseph McGrath

Maria Millan

Amy Nguyen

Natalie Rovero

Cristiana Vattuone

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# Do you have a child with autism? Want to learn about their sleep?

Stanford researchers are currently recruiting children with autism spectrum disorder (ASD) to participate in an observational sleep study*

## Who is eligible?

- English or Spanish speaking
- 4-17 years old
- ASD diagnosis

## What is involved?

- In-person parent and child interviews, cognitive assessments, parent questionnaires, and assessments of sleep

*After completing the study, children 8 years and older may be invited to join **sleep treatment trials** following initial participation if they are eligible

## Study Compensation

- $50 dollars per in-person visit and $100 for two-night, in-home sleep assessment

Interested in participating or want to learn more?
Sign up here: **https://redcap.link/ACESleep**
Contact us at **ACESleepStudy@stanford.edu** or **(650) 498-7215**

For general information regarding questions, concerns, or complaints about research, research related injury, or the rights of research participants, please call (650) 723-5244 or toll-free 1-866-680-2906

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# Want to contribute to the advancement of sleep medicine?

Stanford researchers are currently recruiting healthy children to participate in an observational sleep study and we could use your help!

## Who is eligible?

- English or Spanish speaking
- 4-17 years old
- No history of medical, genetic, psychiatric or developmental disorders

## What is involved?

- In-person parent and child interviews, cognitive assessments, parent questionnaires, and assessments of sleep

## Study Compensation

- $50 dollars per in-person visit and $100 for two-night, in-home sleep assessment

Interested in participating or want to learn more?
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