

University of Wisconsin Center for Sleep Medicine and Sleep Research

The University of Wisconsin Center for Sleep Medicine and Sleep Research was established in 2008 to create a nationally preeminent academic sleep center, consistent with the recommendations of the 2006 Institute of Medicine report on sleep loss and sleep disorders. The establishment of the Sleep Center included the construction of a 17-bed clinical and research sleep laboratory and adjacent clinic, with state-of-the-art features, including the world's first high density (256 channel) EEG (hdEEG) recording capability, available in every bedroom. These unique resources provide for the development of integrative approaches to address critical scientific questions and craft clinical and public health policy regarding the prevention and treatment of sleep apnea.

The University of Wisconsin has a long history of excellence in sleep research and clinical sleep medicine, with a unique group of faculty across multiple departments and schools that are internationally-recognized for their expertise in epidemiology, neurophysiology, molecular biology, genetics, and sleep disorders, as well as their leadership roles in sleep research and sleep medicine. There are at least 20 faculty involved in sleep research and/or clinical sleep medicine across the departments of Comparative Biosciences, Medicine, Neurology, Nursing, Orthopedics and Rehabilitation Medicine, Pediatrics, Pharmacy, Population Health, and Psychiatry. Some highlights of the history of sleep research at UW are detailed below.

The study of sleep apnea has been a key area of research at the University of Wisconsin for over 20 years; population studies performed here have established the high prevalence of sleep and have begun to identify its correlates and outcomes, including hypertension, cardiovascular and cerebrovascular disease, impaired cognitive function, hypersomnolence, decrements in daytime functioning, premature all-cause and cardiovascular mortality, and increased mortality from cancer. In 1987, Professor Terry Young, with the help of basic, clinical, and biostatistical researchers on campus, constructed what is now considered a landmark study: the Wisconsin Sleep Cohort Study (WSCS). Based on a sample of over 1,500 state employees, the WSCS is now in its 20th year of continuous NIH funding, and continues to collect longitudinal data, including overnight polysomnography, on both normal and abnormal sleep, change over time, and many other parameters every 4 years on this dedicated sample of the Dane County population. This highly successful study first reported the high prevalence of sleep apnea in both men and—even more shockingly—in women (as sleep apnea was thought to be a rare disease of men, and almost nonexistent in women). These findings, published in the *NEJM*, have been cited over 2000 times, and were responsible for initiating increased research and clinical efforts worldwide. Data from the sleep cohort have resulted in over 100 reports in peer reviewed journals including *JAMA*, *Ann Int Med*, *NEJM*, *Arch Intern Med*, *Am J Respir Crit Care Med*, *Sleep*, *Brain*, *Lancet*. Prospective analyses, using the longitudinal data, show a role for sleep apnea in incident hypertension, incident stroke, incident depression and cancer mortality.

One of the currently NIH-funded ancillary studies of the WSCS is led by Professor F. Javier Nieto, Chair of the Department of Population Health Sciences, and explores the relationships among sleep disordered breathing, vascular dysfunction and the metabolic syndrome. Professor Nieto was the principal investigator for a field center of two large community-based epidemiologic studies, the Atherosclerosis Risk in Communities (ARIC) Study and the Sleep Heart Health Study (SHHS). Dr. Nieto participated as a member of the IOM panel that reviewed the current state of the field of sleep medicine and resulted in the 2006 IOM report "Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem." He currently serves on the NIH Sleep Disorders Research Advisory Board.

UW has also developed outstanding research programs related to the genetics, molecular biology and neurobiology of sleep. Professor Ruth Benca moved to UW in 1993 to pursue a dual clinical and research career. She has established a number of animal models relevant for studying sleep in mood disorders, including migratory birds as a model for sleep changes in mood disorders (published in *PLoS Biology*) and is considered an expert on sleep abnormalities in psychiatric disorders. She has held a variety of national leadership positions in sleep research and sleep medicine, including serving on the Board of Directors of the American Academy of Sleep Medicine (AASM), as President of the Sleep Research Society (SRS), and as President of the Associated Professional Sleep Societies (APSS). She was recently elected to the steering committee of the emerging CTSA Sleep Research Network and is co-investigator in a multi-site project to develop data-sharing software for clinical sleep research studies. She serves as Director of the Center for Sleep Medicine and Sleep Research as well as the medical director for the clinical sleep center at the University of Wisconsin.

In 2001, Professors Chiara Cirelli and Giulio Tononi were recruited to UW and have brought in a diverse and complementary set of techniques including sleep genomics and proteomics, large-scale computer models of sleep and wakefulness, the first setup for all-night, hdEEG recordings of sleep and the first apparatus for performing simultaneous transcranial magnetic stimulation and hdEEG. Together, Drs. Tononi, Cirelli and Benca were successful in securing over \$10 million in DARPA funding for a grant to study techniques to prevent sleep deprivation relevant for humans using a variety of animal models. Drs. Tononi and Cirelli have identified molecular markers of the states of sleep and waking (published in *Neuron*) and have dissected sleep genetically in *Drosophila* (published in *Science* and *Nature*). Their findings have implications for the functions of sleep as well as for understanding the adverse consequences of sleep deprivation on cognition, emotion, and health, and pave the way for genomics and proteomics studies in humans. Drs. Tononi and Cirelli have developed a new hypothesis about the functions of sleep—the *synaptic homeostasis hypothesis*—that forms the basis of a Conte Center (in collaboration with Dr. Benca and Dr. Martin Raichle from Washington University) that was funded by NIH. According to the hypothesis, plastic processes during wakefulness result in a net increase in synaptic strength in many brain circuits; during sleep, synaptic strength is globally downscaled to a baseline level that is energetically sustainable and beneficial for memory and performance. Sleep is thus the price we have to pay for plasticity, and one of its important functions would be the homeostatic regulation of the total synaptic weight impinging on neurons. In 2005, Dr. Tononi received an NIH Pioneer Award in recognition of his work on the investigation of sleep mechanism and function; he is the only sleep researcher and one of only two psychiatrists to receive this award.

In recognition of the excellence and breadth of sleep research and clinical expertise at the UW, the Center for Sleep Medicine and Sleep Research was established in 2008, making it one of the first independent academic sleep centers in the US, rather than a division of an existing department. Missions of the Center include the following:

1. Facilitate and enhance basic and clinical sleep research within the UW campus.
2. Develop new technology for the study of sleep and sleep disorders through the translation of new neurophysiologic recording techniques, such as high resolution EEG, transcranial magnetic stimulation and/or brain imaging, and noninvasive cardiovascular and respiratory monitoring.
3. Coordinate educational efforts in basic sleep science and sleep medicine, including outreach to healthcare providers throughout the region.

4. Address areas of public policy relevant to sleep and sleep disorders, such as prevention of sleep deprivation.
5. Provide community education and outreach related to sleep and health.
6. Provide outstanding clinical care to patients with sleep disorders including outpatient services and diagnostic laboratory testing.

Dr. Ruth Benca was appointed Center Director and reports directly to the Dean of the UW School of Medicine and Public Health, Dr. Robert Golden. There are also an Administrative Director, a Clinical Manager, an Information Technology specialist and an administrative assistant assigned to the Center. The Center receives regular input from an Advisory Board consisting of chairs and section heads from relevant departments and other key faculty and staff from the UW-Madison, who meet to review progress of the Center on a yearly basis and make recommendations for operations and long-term planning. Membership in the Center is open to all clinical and research faculty and academic staff throughout the UW Campus involved in clinical and/or research programs related to sleep.

The Sleep Center includes a multi-disciplinary clinical program, with over 4500 clinic visits and over 3000 sleep laboratory studies per year. To facilitate translational research, a key feature of the clinical program is that all patients fill out a series of standardized and validated questionnaires that include ratings and screening instruments for insomnia, sleep apnea, narcolepsy, parasomnias, circadian rhythms, anxiety, depression, quality of life, and health information. All patients are also asked to sign an IRB-approved consent form if they are willing to be included in a research contact database and/or if they would allow their de-identified data to be used for research purposes.

The most novel feature of the Center is the incorporation of state-of-the-art physiological recording techniques in the laboratory that will soon be the standard of care for all patients. Every bedroom is electromagnetically shielded and capable of recording up to 256 channels of EEG (high density or hdEEG) for the entire night, making the Center the world's largest hdEEG recording facility of any kind.

The UW Sleep Center is thus poised not only to answer some of the most fundamental questions regarding how sleep benefits the brain and the body but also to improve the diagnosis and treatment of the full range of sleep disorders. Some of the major missions of the center are to strengthen interdisciplinary translational research and develop new technologies for the study of sleep and sleep disorders, including hdEEG, transcranial magnetic stimulation, brain imaging, and noninvasive cardiovascular and respiratory monitoring. Few sleep programs in the country have the necessary organizational structure and are as well prepared as UW to bring cutting edge research capabilities to bear on research in sleep and sleep disorders.