NRC newsletter

http://med.uth.edu/nrc | News & Featured Research of the Neuroscience Research Center | volume 22, number 1, Winter 2016

# Daily Rhythms in Neural Circuits

*By Christophe P. Ribelayga, Ph.D.*

***Ribelayga***

*Abstract: A fundamental goal of neuroscience is to understand the ways in which interconnected neurons shape perception and behavior. Neural circuits are remarkably plastic because they are continually shaped by interaction with the environment. Work in my laboratory is focused on the plasticity of neural circuits in the retina in response to the day/night cycle.*

An essential function of the central nervous system (CNS) is to generate optimal physiological and behavioral responses to environmental cues. Rapid changes in the environment, such as during the course of the day, require rapid modification of the properties of the underlying neural circuits. Unraveling the mechanisms that control this daily plasticity demands an understanding of the relationships between the physical details of synaptic connectivity and single-unit dynamics, as well as the systems-level properties, such as sensory responses or motor outputs. Understanding the daily plasticity of neural circuits also requires identifying the mechanisms and signaling pathways involved in its control.

A remarkable feature of the daily rhythms in physiology and behavior is that they are not simply a response to the 24 hour changes in the physical environment, but they also reflect the activity of an internal time-keeping system built on circadian clocks. The primary hallmark of circadian clocks is that they continue to run in constant environmental conditions (e.g., total darkness) with periods of approximately 24 hours--hence the term *circadian*, from *circa* about and *dies* day. Circadian clocks are further characterized by their ability to synchronize to environmental rhythms through external cues, such as the light/dark

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# Studying Stress in Health and Disease

*By Nicholas J. Justice, Ph.D.*

***Justice***

*Abstract: My lab in the Center for Metabolic and Degenerative Diseases at the UTHealth Institute of Molecular Medicine is focused on how stress impacts disease. We use new molecular and genetic tools to map neural circuits that respond to stress and to understand stress-related neuropsychiatric symptoms in Alzheimer's Disease (AD). We have also initiated projects in the clinic looking for biomarkers that predict the development of post-traumatic stress disorder (PTSD) after trauma. Our research goals are to better understand what happens to the body in response to stress, how stress exacerbates ongoing disease, and how stress circuits can be inhibited to slow disease progression and improve health.*

## Introduction

We have all experienced stress and know what if feels like to be stressed, but how does this impact the way your body functions? From the pioneering work of Hans Selye, the grandfather of stress research, it is known that the body mounts a generalized stress response to a wide array of threats, or perceived threats, to homeostasis. These threats include potential challenges to the status of ones livelihood, such as financial stress, interpersonal stress, or dangerous situations such as near-miss car accidents. This same stress response is mounted to physiologic stressors that threaten homeostasis within the body, such as infection and hemorrhage. In response to stress, the brain releases the neuropeptide corticotropin releas-

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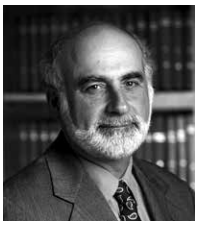
UTHealth | Neuroscience Research Center
The University of Texas Health Science Center at Houston

# Director's Column

*From the Director, John H. Byrne, Ph.D.*



The start of the new academic year was welcomed with great news from the University of Texas System Neuroscience and Neurotechnology Research Institute. In order to advance neuroscience research at its 15 institutions, UT System has awarded 45 seed grants, each worth $100,000, as part of a larger goal to facilitate progress towards the national BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative. Of these 45 grants, 10 of them were awarded to neuroscientists at the UTHealth Neuroscience Research Center. As with the local UTHealth BRAIN Initiative seed grants that I reported in our Summer 2015 issue of the NRC Newsletter, these UT System seed grants are designed to allow researchers to form collaborations and generate preliminary data to be highly competitive when applying for external funding from the NIH BRAIN Initiative and other extramural programs. Examples of some of the collaborative projects are:

Dr. Raymond Cho, Department of Psychiatry and Behavioral Sciences, for the project titled, "Direct probes and genetic underpinnings of neural oscillations," in which he will collaborate with Dr. Consuelo Walss-Bass in his department;

Dr. Yong Li, Department of Pediatric Surgery, for the project titled, "Novel neuromuscular junction model to study mechanisms of muscle atrophy." He has formed a strong inter-institutional collaborative team with Dr. Ping Wu, Department of Neuroscience and Cell Biology at the University of Texas Medical Branch;

Dr. David Marshak, Department of Neurobiology and Anatomy, for the project titled, "Analysis of neural circuits by electron tomography," in which he will work with Ms. Andrea Bordt, a Research Associate at UTHealth, and Dr. Michael Sherman, Department of Biochemistry and Molecular Biology at the University of Texas Medical Branch;

Dr. Christophe Ribelayga, Department of Ophthalmology and Visual Science, for the project titled, "Circadian plasticity of a network of electrically coupled neurons," in collaboration with Dr. Jiaqian Wu, Department of Neurosurgery, and Dr. Philippe Masson, Department of Mechanical Engineering at the University of Houston;

Dr. Claudio Soto, Department of Neurology, for two projects "Chimeric mice harboring human nerve cells as a model of Alzheimer's disease," in collaboration with Dr. Brian Davis, Center for Stem Cell & Regenerative Medicine, and, "Traumatic brain injury promotes Alzheimer's disease through seed formation," in collaboration with Dr. Pramod Dash, Department of Neurobiology and Anatomy;

Dr. Qingchun Tong, Center for Metabolic and Degenerative Disease, for the project titled, "To deconstruct a hypothalamic neurocircuit for feeding and grooming;"

Dr. M. Neal Waxham, Department of Neurobiology and Anatomy, for the project titled, "Design principles of synapses: An integrated view of proteins and membranes," in collaboration with co-investigator Dr. Ilya Levental, Department of Integrative Biology and Pharmacology.

Dr. Consuelo Walss-Bass, Department of Psychiatry and Behavioral Sciences, for the project titled, "Generation of human-derived neurons for the study of psychiatric disorders," in collaboration with Dr. Ying Liu, Center for Stem Cell and Regenerative Medicine, Dr. Michael Beckstead, Department of Physiology at the University of Texas Health Science Center at San Antonio (UTHSCSA), and James Lechleiter, Department of Cellular and Structural Biology at UTHSCSA. Dr. Walss-Bass has also received the honor of presenting her planned research to the UT Board of Regents in November; and

In collaboration with investigators, Dr. Shin Nagayama, Department of Neurobiology and Anatomy, and Dr. Behnaam Aazhang, Department of Electrical and Computer Engineering at Rice University, I received funding for the

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project titled, "Developing integrated methods for analyzing brain circuits."

A list of all recipients across UT System is posted to the UT System Neuroscience website (https://www.utsystem.edu/sites/neuroscience/ut-brain-seed-grant-awards). In addition, the UT System Neuroscience and Neurotechnology Research Institute plans to award another round of seed grants in 2016, thus continuing the shared goal of rapidly advancing the understanding of the brain.

As with every new academic year, the NRC has begun preparing for an exciting year full of educational events at every level. This year's topic for the Neurobiology of Disease Course, "Stress and the Brain," has left standing room only at almost every lecture. Drs. Joy Schmitz and Scott Lane from the UTHealth Department of Psychiatry and Behavioral Sciences have generated a great line-up of speakers covering topics that include the molecular effects of the stress response, perinatal stress on development, and the role of stress as it relates to brain-gut interactions and psychological disorders. The course schedule can be found on our website.

This fall, the NRC is also coordinated the 22nd annual Neuroscience Poster Session, which was held on Saturday, December 5th at the Cooley University Life Center in Houston. Graduate and medical students, postdoctoral fellows, residents, and faculty, from UTHealth, Baylor College of Medicine and Rice University presented their most recent neuroscience discoveries. This annual lively and educational morning is a great way to network with other neuroscientists in the Texas Medical Center. More information is available on our website.

We are currently working on plans for our two Brain Awareness events this spring: our Public Forum on "Stem Cell Therapy for Neurological Diseases" and Brain Night for Kids. Both of these events engage the local community and draw attention to the importance of neuroscience research and education. In addition, we are thrilled to host Dr. Kathleen Brady from the Medical University of South Carolina as our annual Distinguished Lecture in the Neurosciences on March 31, 2016. Please stay in touch through our website and social media pages.

***On October 14, 2015, Susan Lindquist, Ph.D., visited the McGovern Medical School to deliver the annual Ernst Knobil Distinguished Lecture. Dr. Lindquist is an investigator at the Howard Hughes Medical Institute and a professor of biology at The Whitehead Institute at the Massachusetts Institute of Technology. She is pictured here with (from left to right) Drs. Kevin Morano, Barbara Stoll, Julie Knobil and John Byrne.***

***Photo taken by Dwight C. Andrews.***

# news&information

## Grants & Awards

**Andrew Bean, Ph.D.,** Professor of Neurobiology and Anatomy, **Pedro Mancias, M.D.,** Associate Professor of Pediatrics, **Christine Markham, Ph.D.,** Associate Professor of Health Promotion and Behavioral Sciences at the UTHealth School of Public Health, and **Han Zhang, M.D.,** Associate Professor of Neurobiology and Anatomy, were among six UTHealth faculty to be recognized for teaching excellence by The University of Texas System Board of Regents.

**Raymond Cho, M.D., M.Sc.,** Associate Professor of Psychiatry and Behavioral Sciences, received the NARSAD Independent Investigator Award to investigate transcranial direct current stimulation (tDCS) as a novel therapeutic for cognition in psychotic disorders.

**Gerard Francisco, M.D.,** Chair of Physical Medicine and Rehabilitation, received the American Academy of Physical Medicine and Rehabilitation's Distinguished Member Award at their annual meeting in October. This honor recognizes members who have provided invaluable service to the specialty of physical medicine and rehabilitation.

Graduate students were recognized for their outstanding research and academic achievements through the Dean's Research Scholarship Awards. Recipients included: Drew Dolino, from the laboratory of **Vasanthi Jayaraman, M.D., Ph.D.,** Professor of Biochemistry and Molecular Biology; Cihan Mehmet Kadipasaoglu, from the laboratory of **Nitin Tandon, M.D.,** Professor of Neurosurgery; William O'Brien, from the laboratory of **Cheng Chi Lee, Ph.D.,** Professor of Biochemistry and Molecular Biology; and Kaiqi Sun, from the laboratory of **Yang Xia, M.D., Ph.D.,** Professor of Biochemistry and Molecular Biology.

Two students working in the laboratory of **Cameron Jeter, Ph.D.,** Assistant Professor of Diagnostic and Biomedical Sciences at the UTHealth School of Dentistry, recently received awards: 1) Sarah Arafat received the Jonathan Ship Award from the American Association of Dental Research which honors the best student poster in geriatric dental research; 2) Andre Loumeau received the Best Paper Award from the American Geriatrics Society for the best oral presentation in the "Neurosciences: A basic understanding of dementia" section.

**Agnes Schonbrunn, Ph.D.,** Professor of Integrative Biology and Pharmacology, was invited to give the 16th Annual Nicholas T. Zervas, M.D. Lectureship at the Massachussetts General Hospital, Harvard University in May. Dr. Schonbrunn gave a talk titled, "Somatostatin Receptors as Therapeutic Targets: The promise, the limitations, and the opportunities."

**Jair C. Soares, M.D.,** Professor and Chair of Psychiatry and Behavioral Sciences, received the Houston Pediatric Bipolar Consortium award from the John S. Dunn Foundation for collaborative efforts by the UTHealth Medical School and Baylor College of Medicine to conduct an integrated investigation of genetics, brain structure and function, blood biomarkers and behavior in children and adolescents with bipolar disorder, as well as those at high risk for the development of the illness.

**Claudio Soto, Ph.D.,** Professor of Neurology, recently received three NIH grants: 1) An R42 grant from the National Institute on Aging to study blood-based diagnostics for Alzheimer's Disease in collaboration with Amprion; 2) An R01 grant from the National Institute of Neurological Disorders and Stroke to study the absorption, metabolism and biodistribution of prions after oral ingestion; 3) An R01 grant from the National Institute of General Medical Sciences to examine the cross-seeding of protein misfolding as a disease mechanism. In addition, Enrique Armijo, a graduate student in Dr. Soto's laboratory, received a BD Biosciences Research Grant.

**Angela Stotts, Ph.D.,** Professor of Family and Community Medicine, was awarded the 2015 Distinguished Professional Woman Award from the UTHealth Committee on the Status of Women in June.

## The NRC would like to welcome two new additions to the UTHealth Community:

Barbara Stoll, M.D., H. Wayne Hightower Distinguished Professor in the Medical Sciences and Dean, McGovern Medical School at UTHealth

Louise McCullough, M.D., Ph.D., Chair of Neurology & NRC Executive Committee Member

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cycle. The molecular and biochemical basis of biological timing indicates that the core machinery of circadian clocks is a cell-based mechanism that relies on a specific set of genes (the *clock* genes) and their protein products interlocked in recurrent transcriptional/translational feedback loops. Over the last two decades, it has become clear that circadian clocks control such fundamental biological processes as the cell cycle and metabolism. However, how clocks modulate neuronal activity and network properties and eventually behavior on a daily basis remains elusive. The long-term goal of my research is to understand how daily changes in ambient light intensity and circadian clocks interact to control functional circuits and signal processing in the retina. We use the retina because it is a tractable model for the rest of the brain and a great example of daily plasticity in a self-optimizing network.

## The retina as a model system to study the daily plasticity of neural networks

Light intensity may vary over a billion-fold range from bright sunlight to darkness. The ability to adapt to a constantly changing environment is a key feature of the mammalian retina. This amazing capability depends on a specific functional architecture, including two types of photoreceptors, rods and cones. In addition, a wide variety of adaptive processes not yet fully understood are driven by ambient light intensity and circadian clocks. Altogether these mechanisms lead to a total functional reorganization of the retina on a 24 hour basis.

A wealth of evidence supports the presence of autonomous circadian clocks within the retina. For instance, the clock components (i.e., the clock genes and proteins) are expressed in retinal tissue, and knocking out the essential and non-redundant clock component transcription factor *Bmal1* specifically in the retina, abolishes retinal rhythms in transcriptional activity and electroretinogram kinetics. Thus, intrinsic circadian clocks act locally to control retinal function and physiology. We and others have obtained evidence that the retina is a heterogeneous tissue in terms of clock activity. Clock genes and proteins are found in most neuronal cell types in the retina but rods may be an exception, and there is an important disparity in the expression of the clock components among cell types. Thus, the overall temporal architecture of the mammalian retina seems to reflect the cellular and regional heterogeneity in clock function within retinal tissue. This raises the interesting possibility that each clock cell type may function independently of the other types and control specific aspects of retinal function through a private signaling pathway. We are currently working to identify two clock pathways that control specific neural circuits in the mouse retina: one clock pathway controls photoreceptor electrical coupling and interactions, and the other regulates contrast sensitivity.

## Daily regulation of photoreceptor electrical coupling

Photoreceptors are electrically coupled via gap junctions. This electrical synapse represents the first synapse of the visual system. In addition, rod-cone coupling is the entry-point for an important alternative rod pathway. Pioneering studies in the 1970s and 1980s in salamander and turtle retinas have laid down the basic properties of photoreceptor electrical coupling and their impact on photoreceptor light responses. However, much remains to be learned about photoreceptor coupling in mammals, in part because of the small size of mammalian photoreceptors (< 5 μm) and the related difficulty in recording from them. During the last decade, we and others have used several derivative measures of photoreceptor coupling, including tracer coupling, and analyzing the light response properties of second-order neurons. These studies have suggested that photoreceptor coupling in mammals may be dynamically regulated by light/dark adaptation and time of day: coupling may be weak in the light and stronger under dark-adapted conditions in the day and even stronger in the dark at night.

Recently, we developed a perforated-patch clamp technique to record from single photoreceptors in the isolated mouse retina. This new technique has allowed us to use the variability of the single photon response amplitude and the receptive field size as proxies of photoreceptor coupling. We can also use the extent of tracer coupling following tracer injection within single cells. Results obtained with this approach so far have been consistent with a day/night and light/dark regulation of photoreceptor coupling and have provided important clues about the functional impact of the regulation of electrical coupling on neighboring photoreceptors (Jin et al. J *Physiology* 593:1597, 2015). Yet, single-cell recording and other indirect approaches fail to provide an absolute value of the coupling strength. The gold standard in the field of coupled cells is to measure the gap junction conductance between two cells, a direct measure of electrical coupling strength, using two electrodes and a paired recording technique. Due to a recent technical advance in the lab, we are now able to simultaneously record from pairs of

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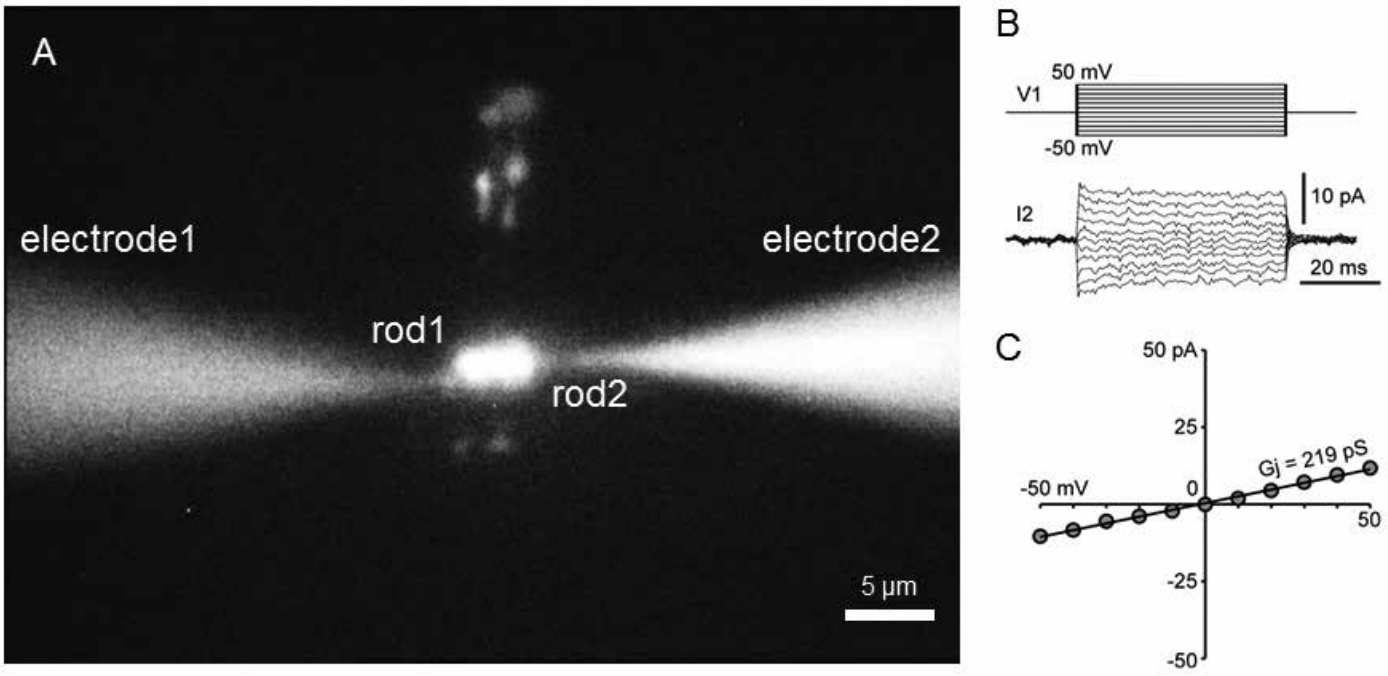


***Figure 1. Simultaneous recording from a pair of adjacent rods in a mouse retinal slice. (A) Lucifer Yellow included in the pipettes, diffused into the cells and revealed their morphology. (B) The voltage of one rod (rod2) was held constant (Vh = -35 mV) and changes in membrane current (I2) were measured in response to voltage steps applied to the other rod (rod1, V1). (C) The junctional conductance was estimated from the slope of the transjunctional current - transjunctional voltage relationship. Changes in transjunctional current were linear with voltage, reflecting the ohmic behavior of the rod-rod gap junction. Recording obtained during subjective day.***

adjacent mouse photoreceptors (Fig. 1). So far we have found that rod-rod coupling strength is ~ 100 pS during the day in the dark and ~ 600 pS at night in the dark. In addition, adaptation to bright daylight reduces rod-rod coupling to ~ 0 pS. Finally, no coupling is detected between rods in mice that lack the gap-junction-forming protein connexin36 (Cx36), demonstrating that rod photoreceptor coupling requires Cx36, similarly to what has been demonstrated in cones.

Experiments are still in progress but results already indicate that photoreceptor coupling is not an "all-or-none" or "open-or-close" principle, but rather a graded process controlled by time-of-day and light-adapted conditions. Using genetic and pharmacological approaches, we are currently characterizing the signaling pathways that control photoreceptor electrical coupling in the mouse. The pathway includes the neuromodulators, melatonin and dopamine, and Cx36 gap junctions. Using photoreceptor type-specific clock-deficient mice, we are also testing the hypothesis that a circadian clock in the cones—and not in the rods—controls the circadian rhythm of photoreceptor coupling through melatonin/dopamine. Our current working hypothesis is that rod-rod, rod-cone, and cone-cone coupling are all synchronously controlled by the cone clock pathway, and so far we have found no evidence to contradict this hypothesis. In parallel, we are evaluating the functional impact of the modulation of photoreceptor coupling on downstream neurons. In particular, we are focusing on the modulation of the signal-to-noise ratio of dim light responses in rods and rod bipolar cells, and of the amount of rod-mediated signals that enter cones and cone pathways.

Our work will establish the cell signaling pathways and molecules that regulate the circadian and light/dark modulation of gap junctions between photoreceptors. It would be interesting to compare daily plasticity-related mechanisms in photoreceptors with those in other brain areas. Interestingly, melatonin is a signaling molecule that is secreted in a time-of-day dependent manner and diffuses throughout the body, including all brain areas. In addition, Cx36 is the main connexin isoform expressed in neurons of the CNS. It is possible that the molecular

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# In*the*Spotlight

*The UTHealth Neuroscience Research Center Reception at the 45th annual meeting of the Society for Neuroscience, Chicago, IL, was held at Exchequer Restaurant & Pub on October 20, 2015. This casual event brings together past and present UTHealth NRC members, graduate students and postdocs to provide a means of promoting collaborations and scientific exchange.*


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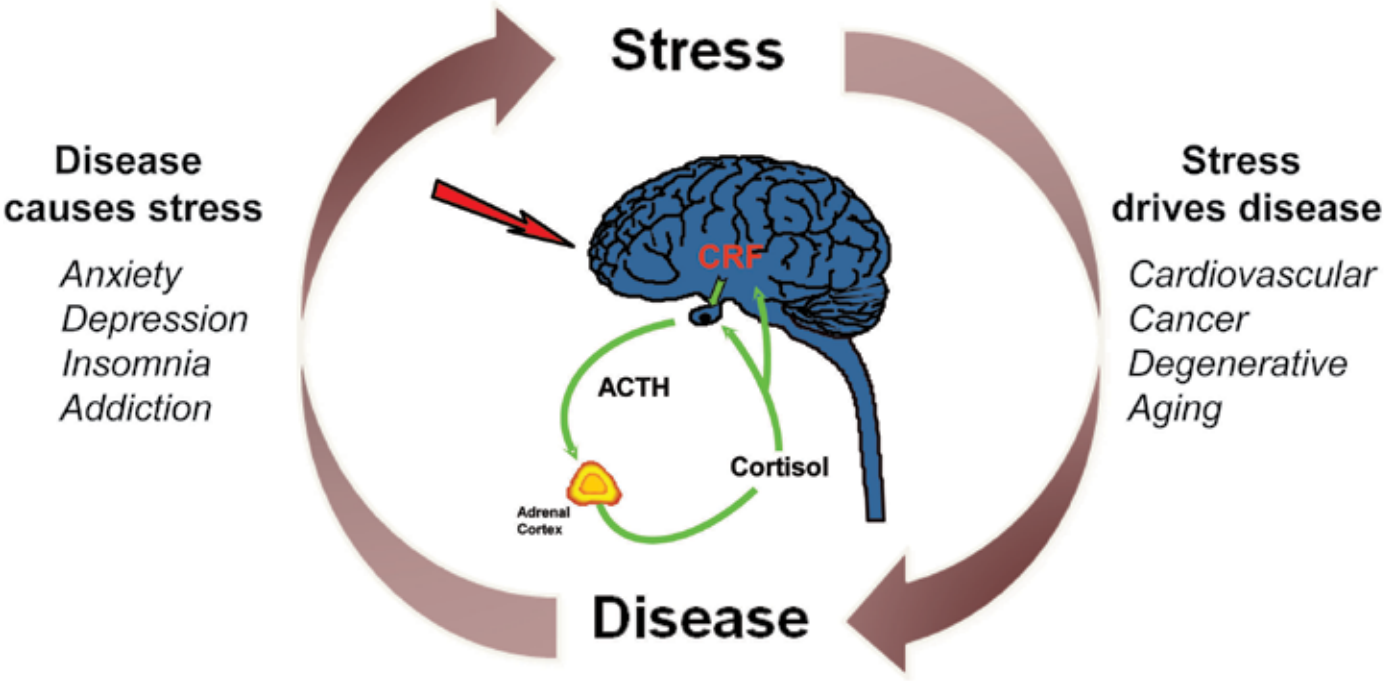


***Figure 1. The Vicious Cycle of Stress. Elevated levels of stress can exacerbate many common diseases including Alzheimer's Disease. Disease processes can also activate stress pathways that produce neuropsychiatric co-morbidities, including depression, anxiety, and insomnia. The likely driving force behind this relationship between stress and disease is aberrant activity of the Hypothalamic-Pituitary-Adrenal axis which controls release of cortisol into the bloodstream.***

ing factor (CRF), which travels to the pituitary and causes the release of ACTH, which, in turn travels through the bloodstream and causes the release of cortisol from the adrenal glands, completing the endocrine hypothalamic-pituitary-adrenal (HPA) axis. Cortisol is a hormone that alters the function of every cell in the body, modifying transcriptional programs to increase energy supply and decrease reproductive and immune function to allow for escape from a current dangerous predicament. In nature, this response is adaptive – it helps survival – but in the modern world chronically high levels of stress cause neuropsychiatric diseases such as depression and insomnia, and can also exacerbate diseases such as cancer and AD.

### A background in stress biology and Alzheimer's Disease

I completed my postdoctoral training in the lab of Wylie Vale. Wylie, a Houstonian who worked with Roger Guillemin at Baylor College of Medicine, discovered CRF as the neuropeptide that releases ACTH (Vale et al., *Science* 213:1394, 1981). He later discovered two G-protein coupled receptors for CRF, termed CRFR1 and CRFR2 (Perrin et al., *Endocrinology* 133:3058, 1993; Perrin et al., Proc *Natl Acad Sci U S A* 92:2969, 1995). While I was in the Vale lab, I generated the first generation of transgenic reporter mice for CRFR1 and CRFR2 (Justice et al., J *Comp Neurol* 511:479, 2008). These reporter mice have been of great value to the field because they allow for both post-mortem and in vivo identification of CRF-responsive cells, which had been previously been difficult to identify because of a lack of specific antibodies that recognize CRFR1 or CRFR2. The next generations of these tools now allow the use of new molecular techniques available to probe neural function (see below).

In 2009, I moved to Baylor College of Medicine as an Instructor in the lab of Hui Zheng who is known for the identification of the function of amyloid precursor protein (APP) in mice (Zheng et al., *Cell* 81:525, 1995). Together, we set out to understand the connection between stress and AD. Surprisingly, many of the AD model mice commonly used in laboratory settings have high levels of anxiety and related stress phenotypes. We found that these phenotypes are due to elevated levels of CRF and a perturbed stress axis (Guo et al., *Neurobiol Aging* 33:2678, 2012). This finding was of considerable interest to the

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field because it revealed that ongoing neurodegenerative disease could cause stress disturbances, perhaps explaining why late-life depression and elevated cortisol levels are associated with greater incidence and faster progressing AD.

### Post-Traumatic Stress Disorder and Alzheimer's Disease

While I was investigating altered stress responses in AD model mice, a clinical group in Houston led by Paul Schultz of the UTHealth Department of Neurology published epidemiological findings that veterans who suffer from PTSD have a higher incidence of dementia, in particular AD (Qureshi et al., *J Am Geriatr Soc* 58:1627, 2010). After establishing a model of PTSD in mice, my lab pursued how PTSD might impact AD progression. We found that PTSD-like inducing trauma causes the chronic elevation of Aβ levels, the toxic peptide responsible for amyloid plaques in AD (Justice et al., *J Neurosci* 35:2612, 2015). In addition, AD model mice are more susceptible to PTSD-like symptoms after trauma (Justice et al., 2015). Thus, stress disruptions both indicate advancing neurodegenerative disease and exacerbate ongoing disease processes. But how are these two linked? The answer came from a surprising finding using an in vitro system. When exposed to soluble toxic Aβ species, cultured neurons from mice in which CRF neurons are fluorescently labeled with expression of red fluorescent protein, became acutely hyperactive. Thus it appears that Aβ release in the brain activates CRF neurons to drive HPA axis activity and cortisol release (Justice et al., 2015). Referring to Selye's original conception of the generalized stress response, one interpretation of this result is that the CRF system/HPA axis is activated by the failure to maintain proteostasis (indicated by the presence of excess improperly produced and folded Aβ), constituting the translation of a cellular stress to a physiologic stress response. The body is attempting to deal with the stress of ongoing neurodegeneration.

In the next phase of this study, I have teamed up with Dr. Paul Schulz to investigate whether patients with a history of PTSD or PTSD/TBI have biomarkers, including circulating cortisol levels, which indicate elevated risk for AD.

### Bringing modern neuroscience tools to the stress response

With the generation of reporter and Cre recombinase transgenic mouse lines for CRF, CRFR1 and CRFR2, we are poised to take advantage of the many new tools that have become available in neuroscience and molecular biology. Using cell specific expression of channelrhodopsin, we will be able to acutely activate cells with laser light in behaving animals to determine how acute activation of stress responsive CRF circuits drive stress, anxiety, and fear-related behaviors. This strategy has the potential to identify a role for new circuits that express CRF receptors but have yet to be shown to function in the stress response. We are also using designer receptors exclusively activated by designer drugs (DREADDs) to selectively excite or inhibit CRF receptor expressing circuits to determine how these contribute to the stress response. Finally, as part of the UTHealth BRAIN Initiative, we are performing ribosome profiling and next-generation sequencing of CRF neurons to determine how transcriptional responses change in the context of acute and chronic stress. The application of newly developed techniques in these classic neural and endocrine pathways will likely open up many new avenues in stress research.

### Conclusion

Stress is a part of every individual's daily life. Some people thrive on stress, while others succumb to stress and develop debilitating neuropsychatric diseases. Given enough stress, especially in the context of war, most individuals will suffer from chronic stress related diseases such as PTSD. Stress can also impact the progression of other diseases that are not caused by stress, such as cancer and AD. My lab is focused on understanding how chronic activation of stress responses produces stress related disease and how stress can exacerbate existing disease. The long-term goal is to identify new pharmacological targets to inhibit stress responsive neural and endocrine pathways, which might alleviate stress-related symptoms and perhaps slow neurodegenerative disease progression.

### *About the Author*

*Nicholas J. Justice, Ph.D. was an HHMI predoctoral fellow at the University of California San Francisco from 1996-2003 where he studied developmental neurobiology in Drosophila with Yuh Nung Jan. He then studied as a postdoctoral fellow with Wylie Vale at the Salk Institute in San Diego. In 2009 he moved to Houston to take a position as Instructor at Baylor College of Medicine where he worked with Hui Zheng in the Huffington Center on Aging. In 2013, Dr. Justice joined UTHealth as an Assistant Professor at the Center for Metabolic and Degenerative Diseases at the The Brown Foundation Institute of Molecular Medicine.*

pathways that are involved in the control of photoreceptor coupling may be a fundamental feature of all neural networks.

### Intrinsically photosensitive retinal ganglion cells and the daily control of contrast sensitivity

Intrinsically photosensitive retinal ganglion cells (ipRGCs) are a type of ganglion cell—the output neurons of the retina— that express the photopigment opn4/melanopsin and thereby are intrinsically photosensitive. Thus, they provide a third class of photoreceptor in addition to rods and cones. IpRGCs play key roles in non-image-forming vision, such as the pupillary light reflex and entrainment of the circadian clock in the hypothalamus. Interestingly, recent findings indicate that ipRGCs may support spatial visual perception as well. However, how ipRGCs influence circuits and functions encompassing spatial information remains unknown.

We recently reported that the core components of the circadian clock are expressed in ipRGCs, suggesting that ipRGCs may contain a functional circadian clock (Liu et al. *PLoS One* 7:e50602, 2012). To test the functionality of the ipRGC clock, we have developed a mouse line that is deficient for circadian clock activity specifically in ipRGCs by knocking-out the essential clock component Bmal1 specifically in ipRGCs ($Bmal1^{f/f}$;$Opn4^{Cre/+}$ mice). $Bmal1^{f/f}$;$Opn4^{Cre/+}$ mice have a normal retinal gross morphology, electroretinogram responses, and acuity but show a strong deficit in contrast sensitivity. Contrast sensitivity refers to the ability of the visual system to distinguish between an object and its background. Recent data indicate that contrast sensitivity is under the control of a circadian clock in the retina: it is high during the day and low at night. Our $Bmal1^{f/f}$;$Opn4^{Cre/+}$ mice show low contrast sensitivity regardless of the time-of-day, suggesting that the circadian clock in ipRGCs is a key regulator of a retinal circuit that controls contrast sensitivity (unpublished data).

To better understand the role of ipRGCs in the control of contrast sensitivity, we have started collaborative work with Dr. Jiaqian Wu of the UTHealth Department of Neurosurgery/IMM funded by the UTHealth BRAIN Initiative pilot grant. We have acutely purified ipRGCs and are in the process of generating a transcriptome database for this cell type by RNA sequencing. We hope to identify genes and/or splicing isoforms that are differentially expressed between wild-type and clock-deficient ipRGCs. The data will provide critical clues on the signaling pathways and circuits linking the ipRGC clock (and ipRGCs) and contrast sensitivity.

In summary, understanding how neural networks adapt to a changing environment is a Herculean task. However, much can be learned by studying fine-scale features of specific circuits. The retina with its easy access, well-known anatomical organization, and well-controlled stimulus (i.e., light) offers a unique model in which to study daily plasticity in intact, well-identified neural circuits. Our multidisciplinary approach to daily plasticity in the retina holds the promise to better understand how retinal circuits reconfigure to optimally process visual information during day and night. This research will also be of great benefit to understand the general rules governing the activity of neural circuits in the CNS.

### *About the Author*

*Christophe P. Ribelayga, Ph.D., is an Assistant Professor in the Ruiz Department of Ophthalmology & Visual Science at the McGovern Medical School at UTHealth. Dr. Ribelayga has a broad background in retinal physiology and circadian biology. He earned a Bachelor of Science degree in Animal Biology from the University Henri Poincare in Nancy, France and a Master of Science degree in Molecular & Cellular Neuroscience from the University Louis Pasteur in Strasbourg, France. As a graduate student at the University Louis Pasteur, he studied the circadian and seasonal (photoperiodic) regulation of melatonin synthesis in the rodent pineal gland, with a focus on the last enzymatic step of the melatonin synthetic pathway. As a postdoctoral fellow at The University of Alabama at Birmingham and later as a research faculty member at The Ohio State University, he studied the control of the light responses of retinal cells, such as cones and horizontal cells, by circadian clocks in the retina. Dr. Ribelayga moved to The University of Texas at Houston in 2009 and has since developed a research program that evaluates circadian signaling in the retina. His research is funded by the NEI, NIH, Research to Prevent Blindness, UTHealth, and the Hermann Eye Fund.*

# Upcoming Events

## Public Forum:
*"Stem Cell Therapy for Neurological Diseases"*

**Saturday, February 20, 2016, 10:30 am to Noon.**

UTHealth Cooley University Life Center
7440 Cambridge St., Houston, TX

This free, educational event will be moderated by Dr. Sean Savitz, UTHealth Professor of Neurology, and Frank M. Yatsu, M.D. Chair in Neurology. The event is open to the public and registration will be available online through our website.

## Brain Night
at The Health Museum

**Thursday, March 17, 2016, 6:00 to 8:00 pm**

The Health Museum, 1515 Hermann Drive, Houston, TX.

Free event for children and their families; open to the public. More details available on our website.

## Distinguished Lecture in the Neurosciences

**Thursday, March 31, 2016, 4:00 pm**

UTHealth Medical School Building, Room MSB 3.001

Lecture given by Kathleen T. Brady, M.D., Ph.D., Distinguished University Professor, Associate Provost of Clinical and Translational Research, and Director of the South Carolina Clinical and Translational Research Institute at the Medical University of South Carolina.

For upcoming neuroscience events in the Texas Medical Center, please check our online events calendar at

**http://med.uth.edu/nrc/events**

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