NRC newsletter

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Translational Research in Schizophrenia: Role of Neuregulin 1

By Consuelo Walss-Bass, Ph.D.

Walss-Bass

Abstract: Schizophrenia is a complex disorder with strong genetic underpinnings. Our laboratory identified a novel schizophrenia-associated missense mutation in the transmembrane domain of neuregulin 1, one of the most promising schizophrenia candidate genes identified to date. We are now developing neuronal cell lines obtained directly from individuals with the neuregulin 1 mutation to translate our previous peripheral cell findings to the brain and elucidate the mechanisms underlying the pathophysiology of schizophrenia.

Schizophrenia, like most psychiatric disorders, is a complex disorder characterized by a wide range of symptoms that vary extensively among patients. Individuals may carry different sets of susceptibility genes that, in combination with particular environmental factors, will determine the overall expression pattern and outcome severity of the illness. This complexity in the nature of schizophrenia expression, together with the difficulty of obtaining brain tissue from human patients, has hindered progress towards understanding the molecular mechanisms of schizophrenia and other psychiatric disorders. Isolated populations with relatively homogeneous gene pools make excellent natural laboratories for genetic studies of complex disorders. For the last 16 years, we have worked with individuals from one such population, residents of the Central Valley of Costa Rica, to identify genes involved in schizophrenia. The community was founded

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Cortical Rhythms: Developing Better Tools for Understanding Underlying Mechanisms

By Raymond Y. Cho, M.D., M.Sc.

Cho

Abstract: Oscillatory rhythms in the brain are thought to be a fundamental mechanism for coordinating neural activity within and between neural networks. High frequency cortical oscillations in the gamma band (>30 Hz) are observed in association with a wide range of perceptual, cognitive, and social cognitive processes. There is substantial variability in the recruitment of gamma activity and associated behavioral performance across individuals and across clinical populations. For example, my research team has found that individual ability in cognitive control–a set of processes that allows adapting behavior to ever-changing changing environments and goals–correlates with the amount of recruited gamma activity in the prefrontal cortex. Similarly, impairments in cognitive control in severe mental illnesses such as schizophrenia are associated with frontal gamma oscillatory disturbances. Accordingly, developing reliable measures of gamma oscillations and elucidating the mechanisms that underlie individual differences in sustaining such cortical activity are critical for developing novel treatments in neurologic and psychiatric disorders.

Cortical gamma oscillations are typically measured in the context of task performance. While such cognitively induced oscillations improve our understanding of the mechanisms underlying cognitive and sensory processing, there are confounding factors related to variability in task performance and strategy. A more reliable and stable measure of the cortex's ability to support gamma oscillations would depend solely on intrinsic cortical properties.

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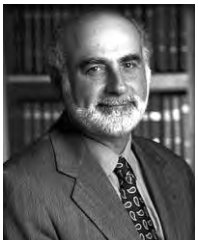
Director's Column

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



This issue of the newsletter features articles by two researchers in the UTHealth Department of Psychiatry and Behavioral Sciences who are studying schizophrenia. Raymond Cho, M.D., M.Sc., director of the department's Integrated Neuroscience and Treatment Program and chief of psychiatry services at Lyndon B. Johnson Hospital, focuses on cortical oscillatory rhythms in patients with schizophrenia. He discusses the tools typically used to measure cortical oscillations in the gamma band and why and how he has modified his approach to yield more precise results. He also points to the neural disturbances associated with the cognitive impairments characteristic of schizophrenia that he is targeting. Consuelo Walss-Bass, Ph.D., director of the Psychiatric Genetics Program in the Department of Psychiatry and Behavioral Sciences, reviews her findings of a mutation in the neuregulin 1 gene and its association with schizophrenia among a remote Costa Rican population. Her current investigations are with human-derived neuronal cells, living outside the body, to learn how the mutation alters signaling pathways and possibly leads to schizophrenia. Drs. Cho and Walss-Bass both received awards from the UT System BRAIN Seed Grants program, announced in 2015.

With the data generated in these seed grant projects (45 statewide, funded at $100,000 each, including 10 at UTHealth), the grant awardees stand to be highly competitive when they apply for NIH BRAIN Initiative grants. (See my column in the winter 2016 newsletter for a list of NRC members who received grants at https://med.uth.edu/nrc/newsletter/.) The seed grant program is one of various new UT System strategies to boost the "Brain Health Revolution" that UT institutions, through collaboration and cooperation—extending outside the UT System as well as in—are committed to lead. The aim is to advance the understanding of brain disorders by a "quantum leap," in the vision of the UT System chancellor, leading to the development of new treatments and cures. This goal for neuroscience is one of eight quantum leaps identified in the System's strategic plan. Never has neuroscience shined so bright in Texas as now.

To outline the challenges neuroscientists face, the UT System hosted the 2016 Texas FreshAIR Neuroscience Conference last October in Austin, Texas. It brought together scientists, pharmaceutical representatives, and thought leaders from throughout the UT System and from private academic health care and industry. More than 70 speakers and panelists addressed topics on 12 focus areas: traumatic brain injury, pain, neurotechnology/neuroengineering, neurodevelopmental disorders, neurodegenerative diseases, mental health, learning and memory, glial biology and disease, computational neuroscience, clinical and drug development, aging and neuroinflammation, and addiction. Huda Zoghbi, M.D., professor at Baylor College of Medicine, director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, and an investigator with the Howard Hughes Medical Institute, delivered a keynote address on "Genetic Approaches to Tackle Neurodegenerative Disorders."

NRC members who joined me on the statewide program planning committee for this very successful event were Drs. Pramod Dash, Louise McCullough, Harel Shouval, and Claudio Soto. Each of us also served as session chairs. A white paper with recommendations for next steps is being developed now, under the direction of UT System Associate Vice Chancellor for Federal Relations, Tom Jacobs, Ph.D. Tom has extensive experience as a program director at NIH and is leading our system-wide efforts on the Brain Health Quantum Leap.

Plans are underway for a new round of UT System grants. In addition to a grant program, other steps to achieving the Brain Health Quantum Leap could include a follow-up Texas BRAIN Conference and the creation of a new faculty recruitment program, "NeuroSTARs," with funds to attract the best and the brightest neuroscientists to UT System institutions. NeuroSTARs would be an expansion of the System's existing highly successful Science and Technology Acquisition and Retention (STARs) pro-

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gram. In that connection, I would like to express a warm welcome to the most recent addition to the Department of Neurobiology and Anatomy, which I chair—Assistant Professor Fabricio H. Do Monte, D.V.M, Ph.D. Fabricio received a UT System "Rising STAR" award for his research on neural circuits regulating fear and reward. He has also received an NIH/NIMH "Pathway to Independence Award." He arrived here in December from Puerto Rico, together with his wife, and we are delighted to have him.

While funding is, of course, as uncertain at the federal level as it is at the state, prospects are encouraging for NIH applications. NIH's Brain Initiative program received a major boost with the passage of the 21st Century Cures Act in December, providing $4.8 billion in new funding for NIH, including $1.6 billion over 10 years for the BRAIN Initiative alone. (And it is worth noting that the UT System is one of only seven universities nationwide recognized as a partner of the NIH BRAIN Initiative.) In his presentation at the inaugural symposium in February of UTHealth's new Stroke Institute (an exciting development that the next issue of the newsletter will cover in more detail), Dr. Tom Jacobs provided some interesting facts and figures regarding NIH funding. Here are a few:

- Of all NIH neuroscience funding to Texas in FY 2016 ($294,919,119), $186,855,079, or about 63 percent, was to UT System institutions.
- Of all NIH grants to UT institutions, 30 percent were for neuroscience.
- In neuroscience funding, among all 11 UT System health-related institutions, UTHealth received the second highest amount ($34,403,847) in total funding.

You can see announcements for NIH BRAIN Initiative funding opportunities in FY 2017 at https://braininitiative.nih.gov/funding/initiatives.htm.

UTHealth NRC members are powerhouses in their productivity, contributions to scientific knowledge, and ultimately, impact on the health of people everywhere affected by neurological and mental diseases and disorders. Congratulations to Jaroslaw Aronowski, Ph.D., professor of neurology. In February he was honored with the 2017 Thomas Willis Award from the American Heart Association for his significant and long-term contributions to the basic science of stroke. He delivered the Thomas Willis Lecture, "Brain Damage and Repair after Intracerebral Hemorrhage" at the AHA/American Stroke Association International Stroke Conference, held in Houston. Congratulations to Louise D. McCullough, M.D., Ph.D., professor and chair of the Department of Neurology, for receiving the prestigious Javits Neuroscience Investigator Award from the NINDS. (Please see the details in the Grants and Awards section of the newsletter.) I also want to congratulate Claudio Soto, Ph.D., professor of neurology and director of the George and Cynthia Mitchell Center for Alzheimer's Disease and Related Brain Disorders, not for a particular recognition, but for his prodigious research progress and success on prion related disease, and the phenomenal $11 million NIH/NIAID grant he received last June.

I hope to see you at some of the NRC's upcoming events. Save the date for the following programs and check our website (https://med.uth.edu/nrc/) for updates:

Our 22nd Annual Public Forum is "Autism Spectrum Disorders in the Age of DSM-5," on Saturday, March 25, 10:30 am to noon, at the Cooley University Life Center. We look forward with great excitement to our 2017 NRC Distinguished Lecture this spring. Our speaker will be the renowned cognitive neuroscientist, Stanislas Dehaene, Ph.D., professor and chair of Experimental Cognitive Psychology, Collège de France. The lecture will be Friday, May 19, 10:30 a.m., in the UTHealth Medical School Building, Room MSB 3.001.

Our newsletter photos over recent months will help bring you up to date on some of the NRC's activities. Note, especially, our awards for Outstanding Graduate Student, Curtis Neveu, and Distinguished Medical Student in the Neurosciences, Henry Caplan. Finally, I am pleased to welcome a new staff member to the NRC, Anne Morris, Ph.D. She is our newsletter editor and will be assisting me with special projects.

Jaroslaw Aronowski, M.D., Ph.D., professor and Roy M. and Phyllis Gough Huffington Chair in Neurology, was named winner of the 2017 Thomas Willis Award, a distinguished international recognition from the American Heart Association for his sustained and long-term achievements in the basic science of stroke and his significant translational contributions to clinical stroke research. Dr. Aronowski also received an NIH/NINDS grant for his research on the mechanisms of neutrophil polarization to ameliorate brain damage after intracerebral hemorrhage.

Charles S. Cox, Jr., M.D., professor and George and Cynthia Mitchell Distinguished Chair in Neurosciences, Department of Pediatric Surgery, received an award from the Department of Defense to assess the efficacy of using stem cell therapy to treat severe traumatic brain injury in adults. He also received a private grant from Cord Blood Registry to explore the use of cell-derived microvesicles to treat inflammation associated with traumatic brain injury.

Valentin Dragoi, Ph.D., Rochelle and Max Levit Distinguished Professor in the Neurosciences, Department of Neurobiology and Anatomy; **Roger Janz, Ph.D.,** associate professor of neurobiology and anatomy; and **John L. Spudich, Ph.D.,** Robert A. Welch Distinguished Chair in Chemistry and professor of biochemistry and molecular biology, received an NIH BRAIN Initiative award to develop and test new viral techniques for optogenetic manipulation of neuronal circuits and specific cell types in non-human primate visual cortex. Dr. Dragoi also received an NIH BRAIN Initiative award as a co-principal investigator for *Dynamic Network Computations for Foraging in an Uncertain Environment* (Co-led by Dr. Dora Angelaki, professor at Baylor College of Medicine) and a grant from the NIH/NEI to examine how sleep influences the processing and coding of sensory information in the visual cortex of non-human primates.

Ruth Heidelberger, M.D., Ph.D., professor of neurobiology and anatomy, has received an NIH/NEI award for her ongoing research program to identify molecular mechanisms that regulate synaptic output at retinal ribbon synapses.

Fabricio H. Do Monte, D.V.M., Ph.D., assistant professor of neurobiology and anatomy, received an NIH/NIMH Pathway to Independence Award to explore how thalamic circuits can integrate reward and fear responses. He also received a University of Texas System Rising STARs Award to investigate the neuronal mechanisms responsible for balancing innate fear and reward responses.

Scott D. Lane, Ph.D., professor of psychiatry and behavioral sciences, received a grant from the Peter McManus Charitable Trust for a laboratory based, outpatient investigation on the *Role of the Orexin Receptor System at the Nexus of Sleep, Stress, and Substance Abuse.*

Louise D. McCullough, M.D., Ph.D., professor, Roy M. and Phyllis Gough Huffington Distinguished Chair, and chair of neurology, received an NIH/NINDS Javits Neuroscience Investigator Award, a seven-year research grant awarded to scientists for their superior research and outstanding productivity. She will receive up to $4.6 million for her investigations of the impact of social isolation on stroke recovery.

Rodrigo Morales, Ph.D., assistant professor of neurology, received a grant from the Alzheimer's Association for a project titled *Contribution of Peripheral Amyloid-beta over Brain Pathology in Alzheimer's Disease.*

Ines Moreno-Gonzalez, Ph.D. assistant professor of neurology, received a New Investigator Research Grant from the Alzheimer's Association to develop a PET imaging test to detect Alzheimer's-like pathology after traumatic brain injury.

Hope Northrup, M.D., professor of pediatrics, has received grants from the Texas Department of State Health Services and the Teratology Society, a professional association, to provide professionals and the public with teratogen information services on birth defects research, including exposure to drugs, alcohol, and medications during pregnancy and breastfeeding.

Joy M. Schmitz, Ph.D., professor of psychiatry and behavioral sciences, received two NIH/NIDA grants. One is to develop evidence-based treatments for cocaine cessation and relapse prevention. The other is a multi-site study to evaluate the efficacy of naltrexone plus bupropion as a combination pharmacotherapy for methamphetamine use disorder.

Dr. Byrne congratulates Curtis L. Neveu, winner of the 2016 Outstanding Graduate Student Brain Awareness Outreach award. This NRC award is for students in The UT M.D. Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences who exhibit exceptional interest and effort in brain awareness and neuroscience outreach activities.

Winner of the 2016 Distinguished Medical Student in the Neurosciences is Henry W. Caplan. The award is to recognize an outstanding fourth-year student who shows excellence in neuroscience research and evidence of pursuing a career in neurology, neurosurgery, neuroradiology, psychiatry or other neuro-related field.

Agnes Schonbrunn, Ph.D., professor of integrative biology and pharmacology, received an NIH grant for research to elucidate basic molecular mechanisms by which receptors for the brain hormone somatostatin control cellular responses. In addition to their role in regulating the secretion of pituitary, pancreatic and gut hormones, somatostatin receptors are widely expressed in many types of hormone secreting tumors. Drugs that target these receptors are used to prevent the deleterious, potentially fatal, effects of tumor secretion and to control tumor growth.

Harel Shouval, Ph.D., associate professor of neurobiology and anatomy, received an NIH BRAIN Initiative award for the project, *Learning Spatio-Temporal Statistics from the Environment in Recurrent Networks.*

Jair C. Soares, M.D., Ph.D., professor and chair of psychiatry and behavioral sciences, received a grant from the John S. Dunn Foundation for the Houston Pediatric Bipolar Consortium, a collaborative effort of UTHealth, Baylor College of Medicine, and Texas Children's Hospital. The consortium will investigate the genetics, brain structure and function, blood biomarkers, and behavior in children and adolescents with bipolar disorder, as well as those at high risk for developing it.

Claudio Soto, Ph.D., professor of neurology and director of The George and Cynthia Mitchell Center for Research in Alzheimer's Disease and Related Brain Disorders, received an NIH/NIAID $11 million, 5-year grant for his study, together with partnering institutions, of the pathogenesis and routes of propagation of chronic wasting disease, as well as the environment's role in prion transmission. Other recent grants include an NIH award for the *Development of a Biochemical Diagnosis for Creutzfeldt-Jacob Disease;* a grant from the Michael J. Fox Foundation for I*mplementation of High Sensitive Detection of Alpha-Synuclein Oligomers for Parkinson's Disease Diagnosis;* and, together with **Paul E. Schulz, M.D.,** professor of neurology, a grant from a private donor to evaluate the efficacy and safety of stem cell therapy for Parkinson's disease. In addition, a postdoctoral research fellow in Dr. Soto's laboratory, Charles Mays, Ph.D., also received a grant from the Creutzfeldt-Jakob Disease Foundation for his project, titled *Design and Development of Anti-Prions as a Novel Therapeutic Strategy for Prion Disease.*

Angela L. Stotts, Ph.D., professor of family and community medicine, received an NIH/NIDA grant for the research to test naltrexone plus bupropion for the treatment of stimulant use disorder involving methamphetamine. In addition, she received an NIDA grant to test the use of a hospital-delivered intervention, combining motivational interviewing and acceptance and commitment therapy to reduce the risk of substance-exposed pregnancies in mothers with infants in the NICU.

Nitin Tandon, M.D., professor of neurosurgery and pediatric surgery, received an NIH BRAIN Initiative award for the project, *A Unified Cognitive Network of Language.* His team is generating a model of the network behavior that enables humans to read letters and words and derive meaning from sentences, yielding new insights into normal language capacity and language dysfunction in patients with neurologic and psychiatric illnesses.

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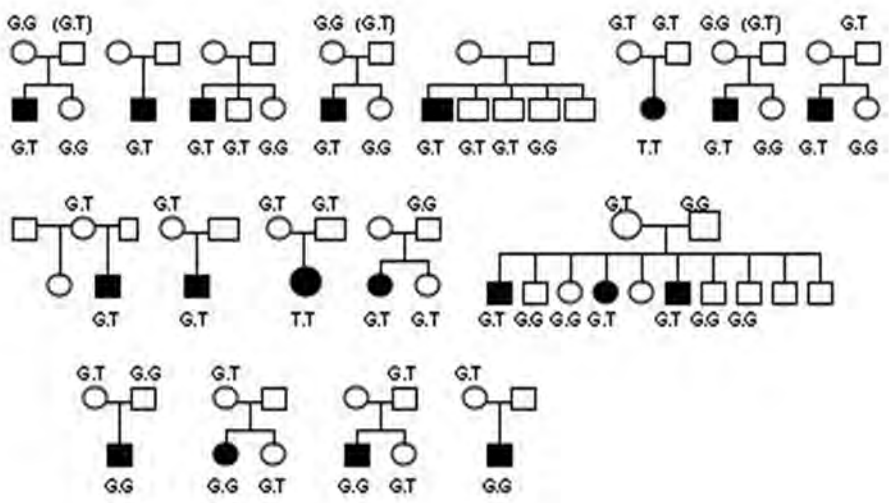
Figure 1. Pedigrees of Subjects from 17 Families Carrying the Neuregulin 1 Gene Mutation in the Central Valley of Costa Rica



Circles denote males; squares denote females. Black circles and squares denote subjects diagnosed as having psychosis, a primary feature of schizophrenia. The T allele reflects the genetic mutation (from guanine, "G," to thymine, "T"). Genotypes in parentheses were inferred. For some individuals no allele information was available and could not be inferred. The first two rows show 13 families who have at least one child with both the diagnosis of psychosis and the mutated gene. The last row shows four families who have a child affected by the illness, but do not have the mutated gene (from Walss-Bass et al. 2006).

in the 1700s by Spanish conquistadors who intermingled with indigenous families in this remote mountainous area, largely untouched by the outside world for 200 years.

As we reported in 2006, our initial studies of this isolated population allowed us to narrow our focus to one gene—and specifically, its mutations—associated with schizophrenia. In collaboration with colleagues at the University of Costa Rica, we identified a novel mutation in the schizophrenia candidate gene neuregulin 1 (Walss-Bass et al. *Biol Psychiatry* 60:548, 2006). This gene has been implicated in the pathology of schizophrenia in many different populations worldwide. Neuregulin 1 proteins perform important roles in such processes relevant to schizophrenia as myelination, neuronal plasticity, development and migration of neuronal and glial cells, synapse formation, and regulation of the inflammatory response. Using sequencing technology, we and our colleagues identified a particular mutation that causes a change from valine (Val) to leucine (Leu) in the protein amino acid sequence. We found the mutation in 13 of 17 families with schizophrenia (see Figure 1). Consulting the detailed genealogical records kept in Costa Rica, we pinpointed a common founding ancestor of the 13 families (see Figure 2).

We hypothesized that the mutation we identified in the neuregulin 1 gene causes an aberration in the function of the protein encoded by the gene. Independent research groups in Belgium and the United States then corroborated our hypothesis (Dejaegere et al. *Proc Natl Acad Sci U S A* 105:9775, 2008; Chen et al. *J Neurosci* 30:9199, 2010). Their research showed, in mouse cells, that the neuregulin 1 protein is not properly cut in cells carrying the mutation, and that this aberration impairs the growth and branching of cortical neurites (Chen et al. *J Neurosci* 30:9199, 2010), which are cellular extensions important for healthy communications between neurons. Subsequently, in our studies of postmortem brains from individuals with schizophrenia, our team found that the neuregulin 1 protein is not properly cut (Marballi et al. *PLoS One* 7: e36431, 2012). Our findings in the human brain validated the observations in mice. Our team also found that people with the identified neuregulin 1 mutation have elevated blood levels of inflammatory markers, immune-cell products called cytokines (Marballi et al. *J Mol Med (Berl)* 88:1133, 2010). Cytokines are produced as a result of stress or infection, and are believed to trigger schizophrenia symptoms in genetically susceptible individuals. Cytokines are thus a very active focus of current research in the biological causes of schizophrenia and other psychiatric disorders. Further, we found that the presence of the neuregulin 1 mutation is associated with alterations in proteins involved in neurite-formation in human blood cell lines (Marballi et al. *J Neural Transm* 121:479, 2014) thus validating the research in animal model described above.

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In*the*Spotlight

Left: *Winners of the NRC's 23rd Annual Neuroscience Poster Session, December, 2016. Winners included students and postdoctoral fellows from Baylor College of Medicine, Rice University, and UTHealth.*
Below: *UTHealth NRC faculty, graduate students, post-docs, and other colleagues—past and present—gathered at the reception that the NRC hosted at the Society for Neuroscience Conference, Nov. 12-16, 2016, in San Diego, Calif.*

Dr. Byrne (right) visits with his longtime friend, Eric R. Kandel, M.D., professor of neuroscience at Columbia University, at the NRC reception.

Enjoying the NRC reception are (from far left) Ye Wang (former post-doc, Dr. Valentin Dragoi's lab); Dr. Dragoi, professor of neurobiology and anatomy; and graduate students Curtis Neveu (Dr. Byrne's lab), Russell Milton (Dr. Dragoi's lab), Ariana Andrei (Dr. Roger Janz' lab), and Brittany Coughlin (Dr. Byrne's lab).

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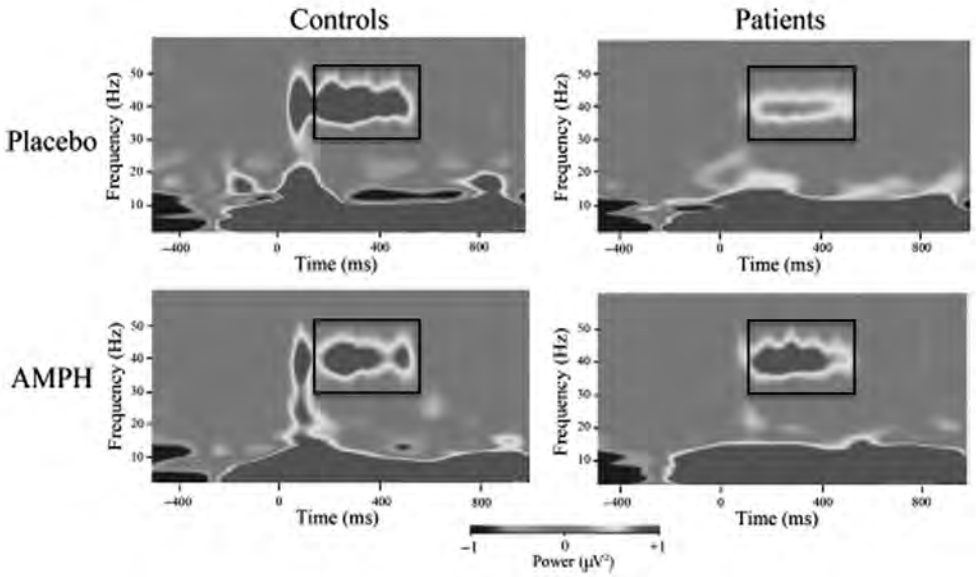
Figure 1. Time–Frequency Plots of Gamma Oscillations in Healthy Control and Schizophrenia Subjects



The warm (darker) color intensity outlined by the boxes shows auditory cortical gamma response to a 40-Hz auditory stimulus. On placebo, schizophrenia patients show the typical reductions in gamma power compared to healthy controls. A single dose of amphetamine (AMPH) reduces gamma responses in controls, whereas it enhances gamma power in patients. These results illustrate how gamma oscillation reductions can be measured in clinical populations and how neuromodulation approaches may potentially remediate such gamma oscillatory disturbances.

For about two decades, the common strategy has been to investigate the brain's sensory areas, indexing the natural cortical resonance properties through the use of sensory entrainment protocols. A commonly employed paradigm is the Auditory Steady State Response (ASSR), which entrains the auditory cortex to periodic auditory stimuli. For example, trains of tones delivered at 40 Hz (gamma band) elicit a steady state oscillating EEG response at the driving frequency (40 Hz). My research team has fruitfully employed this paradigm to detect gamma oscillatory impairments in schizophrenia and has shown that gamma oscillations in patients could be improved with pharmacological interventions (see Figure 1). However, such factors as attention levels may significantly confound measurement paradigms like the ASSR. Further, the use of any paradigms that involve specific cognitive or sensory processes is limited to the specific cortical region associated with the specific cognitive or sensory process. These limitations prompted my research team to seek a more direct way to evaluate cortical resonance properties, a way that is not limited to specific brain regions and does not depend on subject engagement.

Direct Evaluations of Cortical Gamma Oscillations

The establishment of non-invasive brain stimulation approaches has allowed testing of cortical synchronization properties in vivo, safely, and without the aforementioned limitations. Such methods, paired with electrophysiological recordings, can be used to investigate specific cortical regions directly. For example, transcranial electric current stimulation uses weak currents (1-2 mA) that induce measurable and functionally relevant changes in the membrane resting potential without inducing direct discharge and, for brief stimulations, solely by polarity-specific shifts of the resting membrane potential. It is possible to apply a sinusoidal waveform of current of alternating polarities at the desired frequency, thereby directly affecting the probability of neuronal discharge in the underlying area of stimulation in a periodic manner. This approach, called transcranial alternating current stimulation (tACS), has been shown to induce behavioral effects in a frequency-specific manner by entraining corresponding endogenous rhythms. While methodological limitations make simultaneous electrophysiological recordings in humans challenging, concurrent EEG recording is now feasible due to recent advances in hardware and signal processing approaches, allowing measures of regional cortical entrainment. Our ongoing work employs such direct cortical entrainment with weak oscillatory currents in an integrated tACS-EEG approach. We now have the unprecedented possibility to directly investigate individual cortical gamma oscillations in the frontal and other cortical regions. As such, without the confounds associated with task execution, we have a tool for evaluating cortical resonance properties with a sustained modula-

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tory approach that preserves physiological dynamics.

Genetic Polymorphisms and Gamma Oscillations

There has been growing interest among researchers in understanding the components of neural networks that support cortical oscillations and how changes in these components give rise to disturbances in cortical oscillations in populations with neuropsychiatric disorders. Studies of the biophysical and circuitry-based mechanisms of gamma oscillations converge on the critical role of parvalbumin-containing fast-spiking interneurons (PV-FSI). PV-FSI provide strong inhibition at the somata of pyramidal cells. They thus provide a mechanism for coordinating neural network activity, alternating between strong inhibition and release from inhibition in an oscillatory manner. The disturbance in PV-FSI and the associated impairments in gamma oscillations and cognition in neuropsychiatric disorders such as schizophrenia speak to the critical role of PV-FSI.

Accordingly, my research group is examining sets of genetic polymorphisms that perturb critical mechanisms of gamma oscillatory activity. Examples are polymorphisms in components of dopamine and neuregulin signaling pathways. Components of these pathways can impact the excitability of PV-FSI, which provide the fast, repeated inhibition critical for sustaining high-frequency oscillations in cortical and hippocampal circuits. For example, both dopamine D1 and D4 receptors localize to and increase the excitability of PV interneurons. Our computational studies have shown that such increases in FSI excitability can enhance gamma synchrony. This finding is consistent with both animal and human studies showing that increases in dopamine can increase gamma oscillations.

Interestingly, neuregulin pathway signaling increases both dopamine and gamma oscillatory activity. The effect appears to be largely mediated by D4 receptors, which together with the neuregulin receptor tyrosine kinase erbB4, colocalize to PV interneurons. Thus, the dopamine/neuregulin signaling pathways have the anatomic and physiologic properties to modulate gamma oscillatory activity through their actions on PV-FSI. As part of our inquiry into sources of variation in cortical gamma oscillations, we are collaborating with my colleague in the UTHealth Department of Psychiatry and Behavioral Sciences, Consuelo Walss-Bass, Ph.D., on a University of Texas System seed grant to investigate the relationship between polymorphisms in key components of dopamine/neuregulin signaling, in addition to other related pathways in GABA and glutamate signaling.

Conclusions

Elucidating the mechanisms supporting cortical oscillations is important for understanding basic cognitive and sensory processing and their impairments in neuropsychiatric disorders. To this end, it is critical to refine our methods for measuring cortical resonance properties and to identify the genetic bases for variations in cortical gamma oscillations in normal and disturbed cognition. Our efforts require the integration of multiple approaches and disciplines, including neurostimulation, EEG recordings, and genetic approaches. A successful application of this integrated approach holds the promise of a non-invasive, inexpensive way to directly examine cortical gamma oscillations, which together with genetic tests, can identify specific disturbances in an individual patient. Such a toolkit would open exciting possibilities for clear applications in the clinic and the development of novel, precise medicine approaches for patient populations.

About the Author

Raymond Y. Cho, M.D., M.Sc. is an associate professor and director of the Integrated Neuroscience and Treatment Program in the UTHealth Department of Psychiatry and Behavioral Sciences. He is also director of the Integrated Clinical Neuroscience and Treatment Program and Chief of Psychiatry Services at Lyndon B. Johnson Hospital. He earned his M.Sc. in neuroscience and M.D. at the University of Toronto, where he also did a research fellowship in psychiatry. He completed his residency in psychiatry at the University of Pittsburgh. Dr. Cho uses behavioral paradigms, neuroimaging, neurostimulation, and computational modeling approaches to understand and develop novel treatments for cognitive and neural disturbances in serious mental illness, such as schizophrenia. For inquiries about his research, contact him at Raymond.Y.Cho@uth.tmc.edu.

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These findings led us to our current studies, funded in part by a University of Texas System seed grant for the project, "Generation of human-derived neurons for the study of psychiatric disorders," in collaboration with Ying Liu in the Department of Neurosurgery at UTHealth, and Jim Lechleiter and Mike Beckstead at the University of Texas Health Science Center in San Antonio. Because schizophrenia is a brain disorder, it is essential to translate our previous peripheral cell findings to the brain and expand our research to human-derived neuronal cells. With this focus, we are tapping recent technology that can convert a person's skin or blood cells into neurons that are identical in DNA sequence to the person's skin or blood cells. (Essentially, the skin or blood cells are reprogrammed to become stem cells, and from there are transformed to become brain cells, or neurons.) This revolutionary technology empowers researchers to study living neurons belonging to a patient but independent of the brain itself. It thus allows a virtual, non-invasive brain biopsy. A great advantage of using this technology is that it eliminates the effects of external influences, such as use of medications, leaving only the effects of genetic composition, which is unchanged by transformation. We therefore assume that alterations in normal cell function in affected individuals are due to genetic mutations. Thus, by using the human-derived neuronal cells, we can investigate the effect of the neuregulin 1 mutation on the neuronal signaling pathways and their electrophysiological properties. This will allow us to elucidate the mechanisms by which the neuregulin 1 mutation may lead to the development of schizophrenia.

These studies may offer a new view for exploring and treating other psychiatric disorders. As research sheds light on the biological underpinnings of mental disorders, the growing belief is that these disorders occur on a spectrum, with similar molecular pathways altered for schizophrenia, bipolar disorder, depression, autism, and others. Our team aims to conduct a unified investigation across the levels of genetics, brain structure and function, and behavioral outcomes. Our overarching goal is to build on suspected individual biological markers (such as mutations) as targets for the development of novel, sophisticated, and personalized treatments.

About the Author

Consuelo Walss-Bass, Ph.D. is an associate professor in the Department of Psychiatry and Behavioral Sciences at UTHealth, where she is also director of the Psychiatric Genetics Program and the UTHealth Brain Collection. She earned a doctorate in biochemistry from the University of Texas Health Science Center at San Antonio (UTHSCSA), subsequently trained there in psychiatric genetics, and joined the UTHSCA faculty in psychiatry in 2005. She joined UTHealth in 2014. She has a Bachelor of Science in chemical engineering from the Instituto Tecnologico de la Laguna, Torreon, Mexico and a Master of Science in chemistry from the University of Texas at San Antonio. For inquiries about her research, contact her at Consuelo.WalssBass@uth.tmc.edu

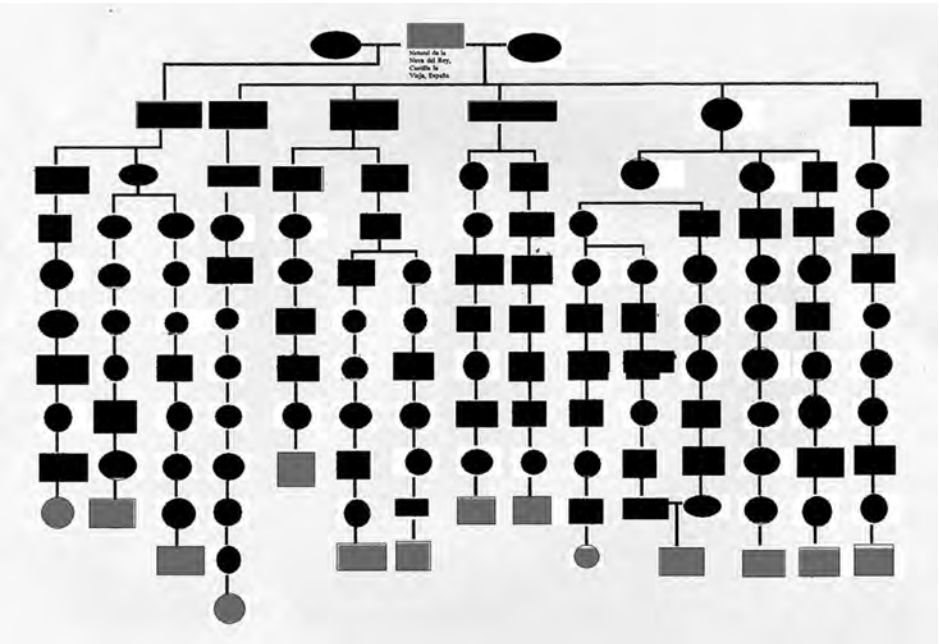

Figure 2. *Ancestral chart of 14 subjects in the Central Valley of Costa Rica who were affected by psychosis and carried the mutated gene. (Indicated in grey, these are from the same subject pool shown in Figure 1.) The chart was constructed through the review of civil and ecclesiastic records. It shows the descent of all subjects from a common male ancestor, born in 1670, who migrated to Costa Rica from Spain.*

Upcoming Events

2017 Public Forum:

Autism Spectrum Disorders in the Age of DSM-5

Saturday, March 25, 2017, 10:30 a.m. to noon

The Denton A. Cooley, MD and Ralph C. Cooley, DDS
University Life Center
7440 Cambridge St., Houston, TX 77054

UTHealth NRC experts on autism, neurodevelopmental disorders, and cognitive neuroscience will discuss autism spectrum disorders and address questions and concerns from the audience.

Moderator: **Pauline A. Filipek, M.D.,** professor of pediatrics and director of the neurodevelopmental neurology clinic.

Panelists: **Katherine A. Loveland, Ph.D.,** professor of psychiatry and behavioral sciences;
Debora A. Pearson, Ph.D., professor of psychiatry and behavioral sciences; and
Anne B. Sereno, Ph.D., professor of neurobiology and anatomy.

The event is free and open to the public. Please register online at med.uth.edu/nrc/22nd-annual-public-forum.

NRC Distinguished Lecture

Friday, May 19, 2017, 10:30 a.m.

UTHealth Medical School Building, Room MSB 3.001

Speaker:

Stanislas Dehaene, Ph.D.
Professor and Chair of Experimental Cognitive Psychology, Collège de France

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Please check our events calendar at http://med.uth.edu/nrc/events. We welcome notices of your neuroscience events (seminars, grand rounds, research colloquia, symposia, and other local or national conferences sponsored by UTHealth, the Texas Medical Center, and Houston area universities and research institutions). Submit the event name, contact information, date, time, and location in an email to nba-nrc@uth.tmc.edu.

UTHealth | Neuroscience Research Center

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Questions? Comments?

Contact us at 713-500-5538
or E-mail: nba-nrc@uth.tmc.edu

This Newsletter is distributed by mail to individuals and groups engaged in neuroscience research within the TMC and worldwide and features research, neuroscience accomplishments and outreach efforts performed at UTHealth. Past issues are available on the NRC website.

If you prefer to receive a digital copy through email, please contact nba-nrc@uth.tmc.edu with your information.

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