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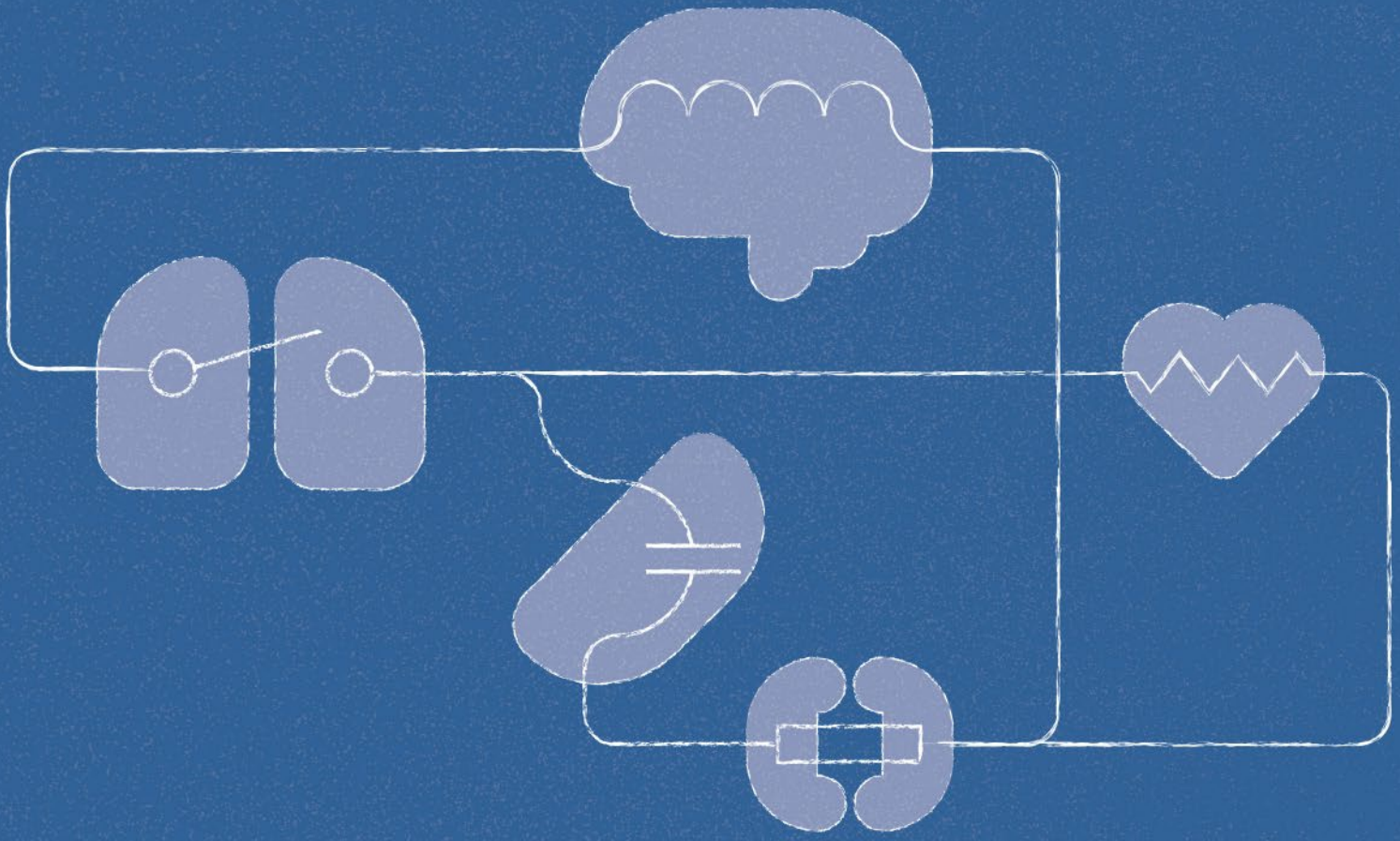

2nd Annual **NIH Investigator Meeting for Interoception Research**

November 11, 2023

Executive Summary

2nd Annual NIH Investigator Meeting for Interoception Research
National Center for Complementary and Integrative Health
Bethesda, Maryland
November 11, 2023

This meeting highlighted recent advances in interoception research relevant to the National Institutes of Health (NIH) Blueprint for Neuroscience Functional Neural Circuits of Interoception Initiative. Invited speakers focused on basic and human subjects research related to functional neural circuit analysis of interoception.

Opening Remarks and Program Updates

Helene M. Langevin, M.D., director of the National Center for Complementary and Integrative Health (NCCIH), opened the meeting by emphasizing that pursuing whole person health requires recognizing that the body's different systems are deeply interconnected. Interoception—the two-way conversation between the brain and internal organs—is integral to whole body health. Walter Koroshetz, M.D., director of the National Institute of Neurological Disorders and Stroke (NINDS), provided an overview of the NIH Blueprint for Neuroscience Research and described NIH's funding efforts in interoception research since 2021. Wen Chen, M.MSc., Ph.D., NCCIH, provided data showing a five-fold increase in interoception research funded by NIH from 2018 to 2023, and described current interoception research funding opportunities.

Keynote Address: Neural Mechanisms of Social Homeostasis

Kay Tye, Ph.D., Salk Institute for Biological Studies, discussed how social homeostasis is mediated by the brain and explains how we relate to, adapt to, and interact in society, both individually and collectively. Dr. Tye and colleagues found that specific dopamine neurons are necessary for promoting rebound sociability following a short period of isolation in mice. Further, the degree to which these neurons modulate behavior was predicted by social rank, suggesting that rank is also a necessary component of a social homeostasis circuit. This effect was reproduced in humans, which showed that acute social isolation evokes midbrain craving responses that are similar to hunger. The "Pain Overlap Theory" proposes that the experience of social and physical pain potentially share some of the same underlying processing systems in the brain. This has been seen in human studies in the insular cortex and anterior cingulate cortex, which are critical to emotional awareness and detecting signals from the organs systems. Dr. Tye described two models being tested to explain how social pain can have a sustained influence on physical pain. Endocannabinoid dynamics play a protective effect on these two types of pain and could be a neuromodulatory mechanism to unite social and physical pain.

Session One: Flash Talks by Junior Investigators

Minel Arinel, B.Sc., Duke University, described her research, which focuses on understanding how gut-mediated signals are encoded across the gut-brain neural circuitry. Enteroendocrine cells (EECs) in the gut epithelium are known to send enteric information directly to the brain through synaptic connections with vagal neurons. In zebrafish, lateralized encoding in vagal ganglia, spatiotemporal encoding across the brain, and photostimulation of EECs determined how nutrients in the gut affect feeding behavior, demonstrating how interoceptive stimuli are sensed along the gut and communicated to the brain through the vagus nerve.

Khalil Ramadi, Ph.D., New York University, provided the rationale for developing an ingestible electronic device for gastric neural/hormonal modulation through electrical stimulation. Dr. Ramadi and his team hypothesized that mucosal stimulation could directly induce the release of ghrelin from the gastric mucosa via endoscopic stimulation. They developed an ingestible electronic device that can modulate systemic levels of neurohormones in a vagal-dependent manner without necessitating wireless power transfer or communication.

Michael Cardenas, B.S., University of Arizona, studies the contribution of interoceptive signals to influence approach-avoidance decision making beyond mere communication of homeostatic needs. He hypothesized that behavior on an approach-avoidance conflict task would shift toward avoidance when the visceral state is dominated by sympathetic versus parasympathetic tone. His research in an animal model indicates that a sympathetic-dominated visceral state communicated through interoceptive afferents is sufficient to modify the behavioral response of the animals.

Senegal Alfred Mabry, B.A., M.P.A., Cornell University, described research to assess whether people with Parkinson's disease (PD) have impaired interoceptive awareness. PD patients participated in a high-intensity cardiopulmonary exercise intervention to improve their motor-gait symptoms. They struggled with sensing changes in their heart rate before, during, and after exercise. Participants also performed a stress task. Those with PD perceived stress at the same level as healthy controls; however, they could not feel their heartbeat during the baseline, stress, and recovery periods despite recorded increases. Imaging revealed that those with PD have differences in insula functional connectivity during stress.

Le Zhang, Ph.D., Yale University, studies how immune cells serve as a major body-to-brain connection in PD. In a subset of patients, PD is initiated by an autoimmune event involving α-synuclein in the gut, and interactions among the immune system and the peripheral and central nervous systems establish the disease in the brain. Rapid eye movement (REM) sleep behavior disorder (RBD) is a preclinical state to PD. Characterization of cerebrospinal fluid (CSF) myeloid cells showed significant cell type proportion changes with increased CSF-specific monocytes in RBD and PD and enriched tumor necrosis factor (TNF) signaling pathways. Comparisons of blood, CSF, and gut immune populations could elucidate the underlying mechanisms of immune regulation in PD and identify the role of the gut-brain axis in regulating immune responses in RBD and PD.

Jose L. Herrero Rubio, Ph.D., Feinstein Institutes for Medical Research, described how disruptions in breathing and awareness sensations alter the way the brain processes ascending respiratory signals. Previous research used neuronal activity to track the breathing cycle throughout widespread cortical/limbic sites, so-called "breathing above the brain stem." Those findings suggested a fundamental role of breathing-related oscillations in driving neuronal activity and provide insight into the neuronal mechanisms of interoceptive attention. Current research suggests that the sensorimotor cortex may play a pivotal role in monitoring the current behavioral state, while the olfactory and cingulate cortices may encode the current effort. Mapping the primary respiroceptive cortices in humans has shown that distinct brain areas are engaged in the motor awareness versus the effort associated with breathing, and that the respiration rate can be controlled volitionally.

Session Two: Technology, Translation, and Reverse Translation in Interoception Research

Karl Deisseroth, M.D., Ph.D., Stanford University, studies how primary cardiovascular conditions can lead to a psychiatric disorder. Precise, noninvasive modulation of electrochemical signals in the heart in vivo facilitate studies of physiology and interoceptive signaling in this phenomenon. Dr. Deisseroth

collaborated with colleagues to optically evoke tachycardia enhanced anxiety-like (apprehensive) behavior in the mouse in a context-dependent manner, showing that both central and peripheral processes are involved in the development of emotional states. The posterior insular cortex was identified as a potential mediator of bottom-up cardiac interoceptive processing. Optogenetic inhibition of this brain region reduced the anxiety-like behavior that was induced by optical cardiac pacing. New high-resolution tools developed by Dr. Deisseroth and colleagues for controlling and mapping specific well-defined elements in intact and fully-assembled biological systems provide an opportunity to gain a deeper understanding of a heart-to-brain axis of communication.

Sahib Khalsa, M.D., Ph.D., Laureate Institute for Brain Research, has used the adrenalin analogue isoproterenol as a visceral psychophysical approach to study interoception and neural circuits. There is a dose-dependent correlation between the continuous subjective ratings of isoproterenol-related interoceptive sensations and the neutral physiological response to isoproterenol, as measured by the change in heart rate. In one trial, patients with generalized anxiety disorder exhibited hypersensitivity to this adrenergic stimulation as well as greater interoceptive sensation and, based on imaging, showed diminished ventromedial prefrontal cortex activity compared with healthy participants. A second study found that adrenergic stimulation caused widespread whole-brain functional connectivity reductions in persons with anorexia nervosa. Dr. Khalsa also described research that identified neural responses to gastrointestinal sensation using a minimally invasive mechanosensory probe by quantifying brain, stomach, and perceptual responses following the ingestion of a vibrating capsule.

Todd Coleman, Ph.D., Stanford University, uses cutaneous electrogastrography (EGG) as a noninvasive technique for recording the gastric myoelectric activity using electrodes placed on the abdominal surface overlaying the stomach. Dr. Coleman's research has shown that, importantly, spatial electrical patterns correlate with symptom severity, which makes this tool clinically useful. An EGG in the form of a novel wearable technology assessed the slow wave patterns of the stomach over time to better understand the associations between spatial patterns and symptoms. Recording of the heart during sleep served as a way to study the parasympathetic nervous system alongside the gastric slow wave. Using high-resolution magnetoencephalography (MEG) and EGG, Dr. Coleman and colleagues were able to visualize greater coupling in the resting state relative to working memory. Finally, to test whether it is possible to modulate the slow wave patterns of the stomach to treat gastric conditions, a novel, inductively powered, gastric pacing technology was developed. Altogether, results from this work highlight the role of gut-brain interactions in cognition and demonstrate the feasibility of these recordings using scalable sensors.

Dana Small, Ph.D., McGill University/Yale School of Medicine, focuses on understanding how sensory, metabolic, and neural signals are integrated to determine food choices and how the dysregulation of these systems contributes to the development of obesity, diabetes, and cognitive impairment. A gut-to-brain neural circuit establishes vagal neurons as an essential component of the reward neuronal circuitry, linking sensory neurons in the upper gut to striatal dopamine release. Under physiological conditions, the pathway is lipid sensing. It can be blunted by habitual intake of high-fat food, and this is associated with reduced dopamine release and shifting preference away from low-fat foods. Administration of oleoylethanolamide (OEA) reverses these effects suggesting a new gut-brain therapeutic target for weight loss. A pilot study found that OEA administration improves weight loss outcomes on a behavioral weight loss intervention, but only in those who are habitual consumers of a high-fat diet. These findings support the translation of a lipid-sensing, gut-derived reinforcing pathway from mice to humans and the potential for a gut-brain target for weight loss and other conditions, such as alcohol use disorder.

Sarah Garfinkel, Ph.D., University College London. Autism spectrum condition (ASC) is a neurodevelopmental condition displaying difficulties in emotion recognition in self and others, comorbid anxiety, and sensory changes. Dr. Garfinkel and others have hypothesized that emotional deficits expressed by individuals with ASC may originate in impaired interoceptive processing. ASC individuals will display impaired interoceptive accuracy while at the same time showing heightened belief in their interoceptive ability. Research has shown that anxiety is associated with enhanced interoceptive sensibility; that is, a tendency for people with anxiety to believe that they are interoceptively proficient. Dr. Garfinkel described a randomized superiority clinical trial of cardiac interoceptive training (Aligning Dimensions of Interoceptive Experience [ADIE]). ADIE combines two modified heartbeat detection tasks with performance feedback and physical activity that transiently increases heart rate. It demonstrated that cardiac interoceptive training can enhance interoceptive accuracy and significantly reduce anxiety in both neurotypical and autistic individuals. These results suggest that trait interoceptive accuracy is malleable, with observable changes in insula connectivity and clinically meaningful reductions in anxiety in autistic adults. Novel therapeutic approaches that target interoceptive mechanisms offer promise for the treatment of other mental health conditions.

Session Three: Brain–Multiorgan System Connections

Ardém Patapoutian, Ph.D., Scripps Research and Howard Hughes Medical Institute, stated that proteins and ion channels that sense mechanical force are hypothesized to play critical roles in somatosensation, hearing, and cardiovascular function, among others. Years of research have elucidated the wide-ranging role of the PIEZO ion channels in somatosensation and interoception, but little was known about the role of mechanotransduction at the molecular level. Dr. Patapoutian's research has shown that PIEZO1 and PIEZO2 are mechanically activated ion channels that mediate touch perception, proprioception, and vascular development. Co-Investigator Dr. Ye Li studied how adipose tissues communicate with the central nervous system to maintain whole-body energy homeostasis.

Julie Pilitsis, M.D., Ph.D., M.B.A., Florida Atlantic University Schmidt College of Medicine, stated that in chronic pain the pathways and mechanisms in interoceptive awareness shifts and acute pain can lead to chronic pain, altering all of the acute responses and pathways. The autonomic nervous system is known to be involved in interoception. The role of the somatic nervous system, particularly through spinal pathways, is less clear. Relying on a patient database of those diagnosed with back pain and scheduled for spinal cord stimulation (SCS) surgery for chronic pain, Dr. Pilitsis and colleagues collected data through intraoperative neuromonitoring, which has yielded a large amount of information about selected muscles that are being stimulated with this device. Dr. Pilitis's research has demonstrated how modulation of the dorsal root ganglia (DRG) and dorsal columns influences pain behavior and brain electrophysiology. Ongoing research will center on how spinal cord stimulation and evoked motor potentials elicited in the lower extremities can be used to create a somatotopy of the dorsal thoracic spinal cord.

John Osborn, Ph.D., University of Minnesota, stated that cervical vagus nerve stimulation (VNS) through an implant is clinically approved for treating drug-resistant epilepsy and depression and for poststroke recovery. Despite more than 100,000 patients receiving treatment with VNS, the physiological effects on peripheral organs in humans is poorly understood. The Research Evaluating Vagal Excitation and Anatomical Links (REVEAL) study involves global research on the effect of VNS on four key systems: autonomic nervous, cardiovascular, immune, and metabolic. A subset of participants with implanted VNS devices will receive a wide range of tests to measure physiological, molecular, imaging, genetic, and neural responses to VNS, along with many other experimental and computational outcomes. Functional

magnetic resonance imaging (fMRI) of the brain will be conducted before and after implantation and during VNS. Imaging of moment-activation responses to VNS will then be used to determine whether upstream CNS modulation is key to changes observed in the peripheral organ systems. Precision functional mapping will be used to map the multimodal networks involved in interoception and allostasis. A supplemental study led by Dr. Ziad Nahas will investigate the effects of VNS on central autonomic network and interoception.

Rui Chang, Ph.D., Yale School of Medicine said that the ability to timely and precisely sense changes inside the body's organ systems is critical for survival. Vagal sensory neurons (VSNs) form an important body-to-brain connection through the vagus nerve, navigating visceral organs along the body's rostral-caudal axis and diving across the organ's surface-lumen axis into appropriate tissue layers. Although the brain can discriminate numerous body signals through VSNs, the underlying coding strategy at the systems level is poorly understood. Dr. Chang's research aims to understand the coding architecture of the vagal interoceptive system, recognizing that three independent key features of interoceptive signals form the visceral organ, the tissue layer, and the sensory modality. Multiple state-of-the-art technologies were developed to determine that VSNs code visceral organs, tissue layers, and stimulus modality—key features of interoceptive signaling—in different dimensions. Together, three independent, feature-coding dimensions specified many parallel VSN pathways that combine to facilitate complex and efficient VSN projection in the brainstem. This research highlights a novel multidimensional coding architecture of the mammalian vagal interoceptive system for effective signal communication.

Richard Lang, Ph.D., Cincinnati Children's Hospital Medical Center stated that his laboratory has focused on the possibility of other extraocular light-sensing pathways in mammals and has been investigating the roles of encephalopsin (OPN3) and neuropsin (OPN5). The opsins are photon-detecting G-coupled receptors that bind to light-reactive chemicals to facilitate vision, phototaxis, circadian rhythms, and other light-mediated responses of organisms. Two light-sensing pathways regulate eye vascular development, suggesting that light could be a development timing clue, mammalian deep tissue light sensing is possible, and opsins work in pairs. OPN3 and OPN5 mediate extraocular light sensing in mice. These two light-sensing tissues function in a regulatory circuit that controls many metabolic parameters, including body temperature. This suggests a new mechanism for regulation of energy metabolism in which intimate coupling to the sunlight cycle is a key feature. In addition, sensory ganglia express OPN3 and OPN5 and their expression as a feature of many sensory neurons, signifying that the sensory ganglia are light sensing. These findings demonstrate that the mammalian system is set up to sense light systemically as a component of normal physiology integrated with the circadian system.

Discussion

Final discussion focused on:

- Further exploration of innervation of the visceral organs and how that affects interoception
- How similar interoceptive signals adapt to the local environment and its receptors
- Whether increasing exposure to blue light contributes to conditions such as increased metabolic disease and myopia
- Understanding the need for neurons to keep spatial information as redundant to the VSNs
- Understanding the interactions of the somatosensory, sympathetic, and parasympathetic systems as they underlie interoception
- How to advance human applications of this knowledge, including reliance on modelling of human data to identify targetable parameters for each cell type or organ