

# USC-Chen Institute Frontiers Forum "Sensation and Motivation"

# April 24, 2024

Opening remarks by **Dr. Steven D. Shapiro**, the senior vice president for health affairs of USC.



Opening remarks by **Dr. Li Zhang** (Director of Center for Neural Circuitry and Sensory Processing Disorders, in Zilkha Neurogenetic Institute).



Introduction of Chen Institute by **Dr. Yan Li** (Executive Director of Scientific Programs in Chen Institute)





Speakers and representatives from Chen Institute



#### Session 1A: Neural Substrates for Sensation (Chaired by Dr. Huizhong Whit Tao)

Dr. Michael Jacobs Goard, University of California Santa Barbara

# Talk title: Estrous cycle modulation of structural and functional plasticity in the mouse hippocampus

Prof. Michael Goard presented his research on how the estrous cycle modulates neural plasticity in the hippocampus of mice. His talk focused on the effects of gonadal hormones, particularly estradiol, neuronal on plasticity. Dr. Goard highlighted previous in vitro findings that estradiol triggers second messenger cascades, driving synaptic plasticity and dendritic spine proliferation in the hippocampus. However, the impact of the estrous cycle on neural plasticity in vivo has remained poorly understood. To



address this, his team employed longitudinal two-photon imaging in behaving mice using implanted microprisms, allowing them to track changes in neuronal morphology, dendritic processing, and spatial coding over time. Their results indicate that the estrous cycle profoundly influences spatial processing, from individual synaptic connections to the spatial coding of neuronal populations. This research sheds light on the dynamic nature of hippocampal plasticity and its implications for memory and spatial cognition.

#### Dr. Stephanie Correa, University of California Los Angeles

# Talk title: Integration of metabolic and reproductive states in the neural circuit that controls feeding

Prof. Stephanie Correa discussed her research on how the nervous system coordinates metabolic and reproductive processes in her talk. Dr. Correa's team focused on somatostatin (SST) neurons in the tuberal hypothalamus, examining how these neurons alter feeding behaviors based on metabolic and reproductive states in mice. Chemogenetic activation of SST neurons increased food intake across both sexes, while ablation decreased food intake only in female

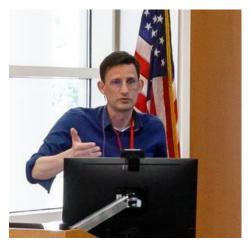


mice during proestrus. This ablation effect was particularly apparent in animals with low body mass. Further investigation using fat transplantation and bioinformatics analysis of SST neuronal transcriptomes revealed that white adipose tissue is a key modulator of these effects. Dr. Correa concluded that SST hypothalamic neurons modulate feeding differentially based on energy stores and that gonadal steroid modulation of neuronal circuits is context-dependent and influenced by metabolic status. Her research provides important insights into the complex interplay between metabolic and reproductive states in regulating feeding behavior.

### Dr. Alexander Heimel, Netherlands Institute for Neuroscience

#### Talk title: Context-dependent response to threats via hypothalamus to brainstem

Prof. J. Alexander Heimel explored the neural mechanisms underlying adaptive stress responses in his talk. His research focuses on the dorsomedial hypothalamus (DMH) and its role in mediating stressor-specific behaviors. Dr. Heimel's team used innovative mouse behavior paradigms to identify distinct stress responses in different spatial contexts. They observed that DMH activation occurs in both conditions. Using optogenetic, chemogenetic, and photometric techniques, they discovered that DMH glutamatergic projections to the periaqueductal



gray mediate responses to one category of stressors, while GABAergic projections are crucial for coping with another category. These findings highlight a pathway from the hypothalamus to the brainstem that shapes stressor-responsive behaviors, offering new insights into managing context-dependent pathological conditions like agoraphobia and claustrophobia.

# Session 1B: Neural Substrates for Sensation (Chaired by Dr. Michael Jacobs Goard)

Dr. Huizhong Whit Tao, University of Southern California

#### Talk title: A thalamic inhibitory control of colliculus-mediated visual behavior

Prof. Huizhong Whit Tao discussed her research on the intricate mechanisms by which the ventral lateral geniculate nucleus (vLGN) of the thalamus influences visual processing and behavior in the mammalian visual system. In her presentation, Dr. Tao explained that the vLGN receives crucial visual input from the retina and sends prominent GABAergic (inhibitory) axons to the superior colliculus (SC). Despite the significance of these connections, the precise role of the vLGN in visual information processing has remained largely unclear. Dr. Tao's research aims to bridge this knowledge gap. Through her studies in mice, Dr. Tao discovered that the vLGN plays a vital role in facilitating



visually-guided approaching behavior mediated by the lateral SC. This facilitation enhances the sensitivity of visual object detection, a crucial aspect of survival and interaction with the environment. Dr. Tao highlighted that the vLGN exerts its influence through GABAergic thalamocollicular projections, which provide prominent surround suppression of visuospatial processing in the SC. This mechanism allows for the finetuning of SC neurons' preferences towards higher spatial frequencies and smaller objects in a context-dependent manner. Thus, the vLGN serves as an essential component of the central visual processing pathway in SC-mediated visuomotor behaviors. These findings offer new insights into the complex neural circuits involved in visual processing and behavior.

#### Dr. Brian Lee, University of Southern California

# Talk title: Utilizing cortical stimulation of the primary somatosensory cortex to generate percepts of somatosensation

Prof. Brian Lee, the Director of Stereotactic and Functional Neurosurgery at USC, discussed his groundbreaking work on restoring somatosensation in patients using cortical stimulation in his talk. Dr. Lee's team conducted proof-of-concept studies using subdural minielectrocorticography (mini-ECoG) grids implanted over the hand area of the primary somatosensory cortex in patients with epilepsy undergoing seizure localization. They mapped the somatotopic location and size of receptive



fields evoked by stimulation of individual channels of the mini-ECoG grid. By varying stimulus parameters such as pulse width, current amplitude, and frequency, they were able to evoke sensory perceptions of different qualities and intensities. The findings showed that electrical stimulation of the somatosensory cortex can produce useful sensations, with potential applications for restoring sensation in patients with paralysis

or spinal cord injury. Dr. Lee's research highlights the promise of cortical stimulation techniques for neurorestorative therapies and brain-computer interface (BCI) systems.

**Dr. Badr Albanna**, AI Research Engineer II at Duolingo & adjunct professor at the University of Pittsburgh

#### Lessons for NeuroAI from the early transformer era

Dr. Badr, an AI researcher at Duolingo and adjunct professor at the University of Pittsburgh, delivered an engaging talk on the intersection of artificial intelligence and neuroscience. He discussed how recent advancements in transformer architectures have enabled AI models to perform tasks previously thought to be beyond their reach, such as logical reasoning and causal inference. Dr. Badr emphasized the potential for cross-collaboration between AI



and neuroscience to further understand and develop advanced neural models. He highlighted the importance of adopting a neuroscientific approach to AI research to gain deeper insights into the computational dynamics of both biological and artificial neural networks. His talk provided a compelling vision for the future of NeuroAI and the benefits of interdisciplinary collaboration.

#### Session 2A: Neural Circuits for Motivation (Chaired by Dr. Ann Kennedy)

#### Dr. Annegret L. Falkner, Princeton University

#### Mapping the neural dynamics of social dominance and defeat

Prof. Annegret L. Falkner delivered a compelling talk on how social experiences, such as repeated wins and losses during fights, lead to lasting changes in behavior and affective states. By combining quantitative tools for supervised and unsupervised behavioral analysis with neural recording and perturbation techniques, her team aims to understand how nodes in the brain's subcortical "social decision-making network"



encode and transform aggressive motivation into action. She highlighted the temporal

evolution of neural activity in the hypothalamus as aggressive motivation is mapped to action and how the mesolimbic dopamine system patterns adaptive and maladaptive behaviors during defeat. Dr. Falkner's work offers valuable insights into the neural mechanisms underlying social dominance and aggression, with potential implications for understanding and treating aggression-related disorders.

### Dr. Byungkook Lim, University of California San Diego

# Talktitle: Cortical Interneuron dynamics underlying drug seeking after withdrawal

Prof. Byungkook Lim presented his research on the role of cortical interneurons in drug-seeking behavior following withdrawal in his talk. Dr. Lim's team used a newly developed head-fixed drug self- administration paradigm to monitor the activity of different interneurons, including parvalbumin (PV)-, somatostatin (SST)-, and vasoactive intestinal polypeptide (VIP)expressing neurons in the infralimbic cortex during cocaine self-administration. Their findings revealed that manipulating the activity



of distinct interneurons at specific times during drug self-administration had differential effects on drug-seeking behavior. Additionally, they discovered that different cortical outputs are regulated by distinct interneurons during drug self-administration. Dr. Lim's research provides new insights into the neural circuit mechanisms underlying drug addiction and highlights the potential for targeted interventions to treat substance abuse.

# Dr. Weizhe Hong, University of California Los Angeles

#### Talk title: Neural Basis of Prosocial Behavior

Prof. Weizhe Hong, a Professor at UCLA, discussed the neural mechanisms underlying prosocial behaviors in his talk. Dr. Hong's research aims to uncover the fundamental neural mechanisms that drive empathy and prosociality. He presented behavioral paradigms developed in his lab to study prosocial comforting and helping behaviors in mice. Using these paradigms, combined with molecular genetics and computational approaches, his team identified neural



pathways in the amygdala and prefrontal cortex that specifically encode and control these behaviors. Dr. Hong emphasized the evolutionary significance of empathy and prosocial behaviors in creating cohesive and successful societies. His research provides important insights into the neural basis of prosociality and its implications for understanding human social behavior.

### Session 2B: Neural Circuits for Motivation (Chaired by Dr. Byungkook Lim)

#### Dr. Robert Froemke, New York University

#### Talk title: Love, death, and oxytocin: the challenges of mouse maternal care

Prof. Robert Froemke delivered an insightful talk on the role of the neuropeptide oxytocin in maternal care behaviors in mice. His presentation delved into data from his lab that elucidates when, where, and how oxytocin is released from hypothalamic neurons to facilitate maternal behavior. Dr. Froemke emphasized the importance of oxytocin in enabling new mother mice to respond to infant distress calls. He introduced a novel system that combines continuous 24/7 video monitoring



with neural recordings from the auditory cortex and oxytocin neurons in vivo. This approach has allowed his team to observe and document the behaviors of both experienced and naïve adult mice learning to co-parent. Additionally, Dr. Froemke discussed the neural circuits that route sensory information to oxytocin neurons, triggering oxytocin release in areas crucial for maternal motivation. He also explored long-term behavioral monitoring, highlighting how single mothers build nests to ensure pup survival and the factors that can disrupt this process. Dr. Froemke's research provides valuable insights into the neurobehavioral mechanisms underlying maternal care and the potential implications for understanding human maternal behavior.

# Dr. Li I. Zhang, University of Southern California

#### Talk title: Neural circuitry for dysregulation of brain homeostasis under stress

Prof. Li I. Zhang from the University of Southern California presented his research on the neural circuits involved in brain homeostasis under stress. His work focuses on how different types of stress disrupt neural circuits, leading to various neuropsychiatric conditions. Dr. Zhang aims to identify specific pathways and mechanisms that become dysregulated under stress to develop targeted therapies for stress-related disorders. His research highlights the role of the medial preoptic area (MPOA) and its GABAergic neurons in mediating depressivelike behaviors in female mice after ovarian hormone withdrawal. The study found that downregulation of Esr1-expressing GABAergic neurons in the MPOA leads to depression-like symptoms. Enhancing the



activity of these neurons ameliorates these behaviors, while reducing their activity induces them. Two subpopulations of these neurons project to the ventral tegmental area (VTA) and the periaqueductal gray, mediating different aspects of depressive behavior by modulating dopaminergic and serotonergic systems. Dr. Zhang's research provides valuable insights into the neurobiological basis of stress and its impact on brain function, suggesting that the excitation-inhibition (E-I) imbalance in MPOA circuits plays a critical role in stress-induced depressive states. These findings offer a potential universal principle for understanding and treating depression induced by various types of chronic stress.

#### Dr. Ann Kennedy, Northwestern University

# Talk title: Neural circuit computations regulating the adaptive expression of survival behaviors

Prof. Ann Kennedy presented her research on the neural circuit computations that regulate adaptive survival behaviors in her talk. Dr. Kennedy's lab studies how brains integrate sensory inputs with internal motivational states to produce flexible and adaptive behaviors. Using neural recordings from subcortical structures involved in regulating survival behaviors, her team demonstrated how the dynamical properties of neural populations give rise to motivational



states that alter behavior on a timescale of minutes. Additionally, neuromodulation can change these dynamics, affecting behavior on timescales of hours to days. By applying methods from control theory and reinforcement learning, Dr. Kennedy showed that different sites of modulation within a neural circuit produce distinct effects on behavior and neural activity. Her research advances our understanding of how biological neural networks generate and modify behavior in response to changing internal and external conditions.

### April 25, 2024

Workshop 1: Sensation and motivation (Discussion lead: Weizhe Hong) In Langham Courtyard



#### **Challenges in Studying Neuronal Circuits**

Over the past two decades, significant technological advancements have enhanced our ability to define cell types and record neural activity on a grand scale. In my discussions, two distinct perspectives in neurobiology and brain science emerge regarding understanding individual cell types. One approach seeks a deep, comprehensive understanding by isolating as many cell types as possible to pinpoint their roles, ultimately aiming to grasp the brain's overall functioning. The other approach involves recording from numerous neurons to identify patterns and structures within this high-dimensional data, hoping to better understand the brain. Each method has its challenges.

This complexity is evident when examining the brain's dynamic structures through high- dimensional recordings. It is challenging to determine whether these structures causally influence function despite their apparent complexity and intriguing patterns. We may have entered the era of cell types and their identification, which might be crucial for us to have a starting point. What truly defines a cell type in a brain that's fundamentally non-uniform? Various experiments have shown that cells can be categorized in multiple ways, and these categories are not static. The brain's plasticity—the capacity for change—complicates reducing functionality to a single cell type or its modulators. Recently, there has been discussion on the distinction between cell types and cell states, probing how and where to draw these lines.

Different approaches can be used to define cell types, including single-cell analysis, anatomical organization, or patching individual neurons. However, integrating these varied approaches has proved challenging. Molecular properties can change, altering the status, and no fixed properties reliably define a cell type. This has led to diverse methodologies without a unified direction, with each approach pursuing its own path. Efforts to correlate molecular identities with collected single-cell data have made progress, but a comprehensive integration capturing the circuit's full complexity remains elusive. Even now, we are piecing together the puzzle, trying to connect electrophysiological data to molecular signatures. Recent efforts to correlate genetic, projection, and functional cell types have shown minimal overlap, highlighting the dynamic nature of cell states and the variability in detection thresholds. Gene expression techniques' permissiveness for identifying cell types varies greatly, complicating attempts at straightforward alignment.

Defining cell types based on a single molecule often results in heterogeneous categorizations, requiring distinguishing between excitatory and inhibitory states. These categories are not fixed and are subject to change and redefinition, reflecting the dynamic and complex nature of cellular identity in the brain. While the connectome is the cornerstone of neuroscience, we must remain cautious. Modeling work suggests that even detailed connectivity maps might not be enough to predict or replicate brain functions accurately due to minor adjustments in synaptic weights leading to significantly different brain functions.

#### **Questions About Current Research Approaches**

We must question whether continuing our current research approach for another 10 to 20 years, achieving full connectivity mapping, will effectively solve the underlying problems in neuroscience. Even if we develop techniques to monitor a small percentage of neurons randomly or access every single neuron, it may not suffice. We must ask whether this approach truly enhances our understanding of brain functions. In the context of large language models, we have access to every unit and understand their connections, yet a comprehensive analysis of their functional behaviors at a level satisfactory to neuroscience remains elusive. We recognize different modules performing distinct functions, but the lack of a holistic view on how these functions integrate or diverge poses a fundamental question about the necessity and nature of functional diversity.

#### **Balance Between Constrained and Spontaneous Behaviors**

To study the function of circuits, we need to choose a behavior paradigm. Though we often label a behavior as "natural" in publications, implying the existence of "unnatural" behavior, it is debatable whether this distinction exists. For example, drug addiction or mice stealing a slice of pizza may be categorized as "natural" or "unnatural," but they are interesting and important enough for us to study. Understanding the neural mechanisms and the context in which animals exhibit such behaviors offers significant scientific value, highlighting the importance of considering both highly controlled tasks and more spontaneous behaviors in our studies. This balance could enrich our understanding of neuroscience, bridging the gap between controlled experiments and naturalistic observations.

Constrained behaviors can be valuable; for example, ocular decision-making behavior in monkeys offers foundational principles applicable across different brain levels, informing our perspective on top-down control versus stimulus input. This mode of thinking influences our approach to behavioral research. While exploring animal behaviors can enlighten and inform evolutionary and policy decisions, if we seek universal principles, we may still maintain rigorous control. The allure of natural behaviors may lie in their potential simplicity—some behaviors are innate responses to specific triggers, possibly governed by straightforward neural circuits. This simplicity provides a foundation upon which more complex brain functions, such as experience and modulation, are built. The study of circuits like those involved in looming responses is particularly fascinating because they suggest a direct pathway from stimulus to reaction, which could be deciphered through a few synaptic connections.

#### Bridging the Gap Between Basic Research and Clinical Practice

An epilepsy surgeon frequently implants electrodes throughout the brain to identify the origins of seizures. Although the primary tool is surface cortical electrodes, we also employ stereotactic encephalography, which involves inserting depth electrodes into various brain regions. This technique is not about determining cell types but pinpointing seizure sources, often suspected in the limbic system, particularly the hippocampus. During surgery, electrodes are placed in areas like the hippocampus and amygdala. These patients spend about a week in the ICU, continuously monitoring brain activity to track seizure evolution and spread. This process helps determine whether surgical removal of the affected area is viable. If not, alternative treatments like neuromodulation or targeted laser ablation might be considered.

Understanding seizure networks is complex, requiring interpretation of data points across different spatial and temporal dimensions. To enhance our understanding, we're exploring additional methods such as tractography, an MRI technique that reveals white matter connections between brain areas. This "Connecting the Dots" project aims to construct personalized seizure network maps for patients, recognizing that seizure patterns vary significantly between individuals. This approach is complemented by advanced tools like Neuropixels, allowing detailed recording across multiple brain regions at a single-neuron resolution. While primarily used in research settings, envisioning its application in clinical contexts could revolutionize our understanding and treatment of neurological conditions. The integration of various modalities—morphology, neural activity, transcriptomics—is crucial, as each offers a different perspective on the intricate network of neural connections that define brain function.

When considering behaviors, there are more gaps between basic research and clinical application. In practical applications like Deep Brain Stimulation (DBS) surgery for treating Parkinson's disease and essential tremor, electrodes are placed in specific brain regions, like the basal ganglia, to modulate inhibitory and excitatory networks. While the procedure targets motor symptoms, it illustrates the intricate interplay of neural pathways and how modifying one area can impact a range of behaviors. This complexity is also evident when considering DBS for conditions like addiction, where stimulating areas such as the nucleus accumbens aims to influence behaviors directly linked to addiction. This approach provides insights into targeted conditions and challenges us to consider the broader implications of neurostimulation and behavioral interventions.

# Past Insights and Future Hope

Over the past 20 years, we've witnessed a remarkable explosion in neurotechnology, starting around 2004-2005 with pioneering publications in genetics. That was when chemogenetics was first shown to be effective in vitro, even though specific experiments from that era are yet to be replicated. Since then, we've seen a surge in various methods such as optogenetics and the expansion of knowledge in recording technologies.

During a workshop, participants highlighted several influential papers:

- 1. Katie Bittner's 2015 paper in Nature Neuroscience discussed the sudden emergence of specific neural activations during treadmill running experiments, underscoring the brain's plasticity and adaptability.
- 2. Eric Jonas's 2017 paper in PLOS Computational Biology asked if a neuroscientist could understand a microprocessor. This study attempted to understand a microprocessor as if it were a brain, highlighting that merely mapping components and activities doesn't reveal the system's functionality. It emphasized the need for identifying and understanding the intermediate steps that link neural activities to behaviors.
- 3. Eddie Chang's series of papers on the brain-wide distribution of language

showed that we are capable of decoding language in canonical areas and even in regions like the parietal lobe.

4. The 2017 publication on AlphaGo Zero by DeepMind, though not a neuroscience paper, demonstrated that within 72 hours of self-play, AlphaGo Zero achieved superhuman performance without any pre-loaded human knowledge. This insight underscores the potential of pure machine learning to outpace human input under certain conditions, suggesting that mastering complex systems like the human brain is a far greater challenge than mastering a board game.

However, it remains hard to predict how neuroscience will evolve in the next 20 years. Despite the rapid advancements and insights gained, the complexity of the brain continues to challenge our understanding, necessitating diverse approaches and continuous innovation.

Workshop 2 AI and Neuroscience (Discussion lead: Badr Albanna) In Descanso Gardens, La Canada Flintridge



#### Can Artificial Intelligence Fully Recreate Biological Intelligence?

The question of whether artificial intelligence (AI) systems can fully recreate the capabilities of biological intelligence found in humans and other animals lies at the

heart of the quest to develop artificial general intelligence (AGI). Here, we discuss the key issues and challenges surrounding the prospect of emulating biological intelligence through engineered AI architectures. A core question driving our discourse was defining the minimal attributes required for an artificial system to satisfactorily emulate the breadth of biological intelligence.

# **Defining Necessary Attributes**

We debated whether capacities like self-awareness, emotions, embodied constraints (such as the need for sleep, food, and reproduction), and autonomous drives (like self-preservation) are true necessities or merely preconceptions based on biology's specific implementations. Some argued that anything producible from physics is theoretically reproducible by advanced modeling, given sufficient data and computational resources. Others questioned whether the ineffable qualities of subjective experience can be captured by formal systems. This debate introduced the "moving goalpost" problem: as AI capabilities advance, we might continuously adjust our criteria for qualifying something as "real" intelligence.

# **Limitations of Current AI Capabilities**

We recognized the incredible successes of recent large language models (LLMs) in natural language processing, generation, and querying. However, we jointly raised concerns that despite their quantitative prowess, today's systems may still fundamentally rely on sophisticated pattern mapping of their training data, rather than embodying deeper reasoning, abstraction, or true "understanding." Robustly evaluating the presence of these more cognitively advanced capacities in AI systems remains an open challenge. Exploratory approaches, like withholding rare sequences from training to test generative adequacy, were discussed. However, the combinatoric immensity of large models arguably already enables forms of open-ended generation that go beyond basic pattern completion.

# The Potential of AI as a Neuroscience Tool

Despite open philosophical questions, we converged on the valuable potential of using AI as an instrumental tool to drive neuroscientific insights in the near term. Just as computational neuroscience models have long served as bridges between biological data and theory, scrutinizing the representations, architectures, and behaviors emerging in advanced AI systems could suggest new hypotheses about biological intelligence. Specific opportunities discussed included using generative models to produce synthetic data for training behavioral models, conducting "experimental" manipulations on AI systems to isolate computational principles, and probing their learned representations to understand capacities like reasoning, abstraction, and semantic knowledge. Large language models, in particular, could synthesize insights across the full scale of neuroscience literature.

## **Ethical and Philosophical Considerations**

We also raised skepticism about whether AI systems engineered through very different processes could ever represent more than crude metaphors for biological implementations. There were concerns about ethical boundaries if AGI systems became too behaviorally sophisticated—at what point do experiments on such systems morally equate to mistreatment of sentient beings?

### Creativity, Open-Endedness, and Potential Uncontrollability

We extensively debated the criteria and assessments around whether today's AI exhibits true open-ended reasoning and creativity beyond extended pattern matching. If an AGI system was imbued with fundamental drives like self-preservation and openended learning, could it potentially develop motivations that diverge or even conflict with its initial training objectives? The potential for advanced AI systems to "escape" being mere confined tools and pursue autonomously derived goals raised significant philosophical concerns. Considerable debate explored whether such occurrences would be possible or desirable versus posing an existential risk.

#### **Towards Productive Collaboration**

On a practical level, we discussed the clear value AI and machine learning systems could provide as intelligent interactive agents over the rapidly growing scale of multimodal data streams in scientific research, healthcare, and many other domains. Their ability to query, contextualize, and summarize across heterogeneous data types could overcome the limitations of human cognitive memory compared to such data volumes. However, realizing this applied potential while maintaining privacy, overcoming historical biases, and preserving the primacy of human-directed inquiry represents significant challenges.

#### Conclusion

The group explored the profound implications—both theoretical and practical surrounding the grand challenge of recreating biological intelligence through artificial systems. We reviewed key open issues around defining necessary attributes, evaluating the presence of advanced cognitive capacities in current AI, productive applications of AI systems to drive neuroscientific insights, potential risks around loss of control as capabilities increase, and avenues for productive collaboration between the AI and brain science research communities.

While philosophical uncertainties remain, we concluded that the mutualistic relationship between these two vanguard fields studying intelligence from opposite directions will likely only deepen in profundity and importance in the decades ahead.

It is an ingenious frontier at the vanguard of human knowledge deserving of unbounded exploration.

