

November 15, 2018

BRAIN Initiative Working Group  
Office of the Director  
National Institutes of Health  
One Center Drive, Room 114  
Bethesda, Maryland 20892-0147

Dear Members of the BRAIN Working Group,

The Endocrine Society appreciates the opportunity to comment on the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) 2025: A Scientific Vision. Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. The Endocrine Society's membership of 18,000 includes clinical, translational, and basic scientists, as well as clinicians in practice. Our members include basic researchers dedicated to developing a fundamental, mechanistic understanding of the roles of hormones on brain development and function, as well as clinical and translational researchers seeking to understand how the actions of hormones influence human behavior.

A central challenge posed by the BRAIN Initiative is to understand how neural circuits and their electrical and chemical activity create unique behavior and complex cognitive capabilities. Although the BRAIN Initiative has made significant progress towards this and other goals articulated in BRAIN 2025: A Scientific Vision, there is still tremendous opportunity to better understand how endocrinology influences the brain, during development and throughout life, to generate mental experience and behavior. We assert that the endocrine concepts identified in our original letter to the BRAIN Initiative Working Group remain fundamental to achieving the stated goals of the BRAIN Initiative and we urge the Working Group to incorporate these concepts in the priority research areas of the Scientific Vision.

**Peripheral organ activity and inputs to the brain:** We are encouraged that the Scientific Vision highlights the importance of neuromodulatory chemicals such as hormones produced in the brain, or by peripheral tissues that may act locally or globally to influence brain circuits. We support the need expressed in the Scientific Vision to "strive for a deeper understanding of these powerful but elusive regulators of mood and behavior" and we encourage the Working Group to prioritize studies that seek to examine the relationship between the brain and other organs. The brain is in constant communication with other organ systems and networks through the action of hormones, driving physiological changes and influencing neuronal networks. For example, nutrient signaling pathways in the brain regulate hepatic glucose production, while other networks regulate neuronal control of bone mass.



**Sex differences as a fundamental biological variable:** Nearly one year after the announcement of the BRAIN Initiative, NIH issued a policy that all grant applications submitted to NIH must take into account sex as a biological variable. A consideration of sex differences remains essential to understanding the structure and function of both normal and pathological brain states. Many if not most sex differences are driven by the action of hormones, and there are important sex difference in the risks and consequences of diseases prioritized in the Scientific Vision, including Alzheimer's and Parkinson's diseases. We urge the BRAIN Working Group to reinforce the study of sex as a biological variable in research projects supported by the BRAIN Initiative. For example, studies that propose to conduct large scale monitoring of neural activity should include data on the sex of the research participant.

**Hormonal influences on the brain across the lifespan:** We appreciate that the Scientific Vision mentions the changes in brain circuitry that may take place across the lifespan and the need to develop tools and resources to understand normal and pathological conditions during development and into adulthood. Hormones are key drivers of changes in brain physiology and circuitry across the lifespan. To understand how circuits are maintained, as described in scientific goal 5a for example, will therefore require knowledge of how hormones impact those circuits throughout life. It will also be critical to consider the hormonal status of individuals (e.g., pre-versus post-puberty, male versus female, stage of the menstrual cycle, pregnancy) when examining or analyzing brain structures.

We encourage the BRAIN Initiative Working Group to emphasize the importance of understanding brain structure and function across the lifespan under physiologically relevant, hormonally stratified conditions. We also recommend that study sections charged with reviewing BRAIN Initiative proposals include relevant endocrine expertise. The Endocrine Society routinely supplies the Center for Scientific Review with the names of experts willing to serve on review panels; we would be happy to provide recommendations for qualified experts to serve on **BRAIN Initiative study sections**.

**In summary**, the Endocrine Society appreciates the ambitious vision set forth in BRAIN 2025: A Scientific Vision, and we look forward to contributing to the ongoing success of the Initiative. Hormone biology is foundational to many of the BRAIN Priority Areas, and our recommendations will help the BRAIN Initiative achieve its goals. Specifically, we encourage the Working Group to:

1. Prioritize studies that seek to examine the relationship between the brain and peripheral organs and networks.
2. Encourage the study of sex as a biological variable in research supported by the BRAIN Initiative.



3. Stress the importance of understanding the impact of hormonal status on brain structure and function over the course of an individual's lifespan.
4. Include relevant endocrine expertise in review panels evaluating BRAIN Initiative projects.

Thank you for considering our comments. If we can be of any further assistance, please contact Joseph Laakso, PhD, Director of Science Policy, at [jlaakso@endocrine.org](mailto:jlaakso@endocrine.org).

Sincerely,

Susan Mandel, MD  
President, Endocrine Society