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Next-generation brain observatories

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We propose centralized brain observatories for large-scale recordings of neural activity in mice and non-human primates coupled with cloud-based data analysis and sharing. Such observatories will advance reproducible systems neuroscience and democratize access to the most advanced tools and data.

The mammalian brain is the most complex structure tackled by science. The mouse brain consists of about 100 million neurons and 100 billion synapses. The macaque and human brains are 100 and 1,000 times larger. Neurons fall into thousands of distinct types defined by size, dendritic morphology, cell body location, gene expression patterns, and connections with other types of cells. These neuronal cell types span the brain in highly organized networks. Electrical signals coursing through this neural network process information and produce all brain functions, including behavior.

For the last 50 years, neuroscientists have typically recorded activity from one or a small number of neurons at a time in one brain region and in the context of a particular behavior. Recently developed methods allow the recording of thousands of individual neurons across multiple brain regions while keeping track of the recorded cell types (Luo et al., 2018). These methods rely on sophisticated instrumentation and data infrastructure and are rapidly becoming too complex and expensive for individual laboratories.

Systems neuroscience remains a fragmented field. Like in the early days of molecular biology, when a scientist's identity was based on studying genes for a particular trait, system neuroscientists often identify with "their" brain region and behavioral task. Thousands of laboratories are studying a wide range of neural phenomena in diverse species. Although this artisanal approach has led to major discoveries, convergence on a few common paradigms is required for in-depth analysis. The advances made in understanding vision, song learning in birds, and jamming avoidance response in electric fish, among others, by networks of collaborating and sometimes competing laboratories illustrate this point. Convergence is especially important to bridge cell types, circuits, brain regions, and computation to explain behavior.

In the early days of physics and astronomy, discoveries were achieved by individual scientists with little coordination between groups, similar to the current state of systems neuroscience. Over the last century, the experimental methods have become increasingly complex, requiring advanced engineering and fine-tuned operating procedures executed by large-scale collaborations with dedicated professional staff. This evolution has culminated in groundbreaking projects, such as the European Organization for Nuclear Research (CERN) particle accelerator, the Laser Interferometer Gravitational-Wave Observatory (LIGO), and astronomical observatories, including the Keck Observatory and the James Webb Space Telescope. Molecular biology later developed in an analogous manner. Large centers sequenced the genomes of *Homo sapiens* and many biological model systems. Synchrotron light sources, such as the Advanced Light Source, are foundational for determining the structure of proteins.

These facilities are based on the labor of hundreds to thousands of scientists, engineers, and technicians working for decades with commensurate budgets funded by national governments, foundations, and private donors. The payoff is access to unique experimental capabilities that are unattainable by individual laboratories.

Systems neuroscience may be on the verge of a similar transition (Alivisatos and Chun et al., 2015; Koch and Clay Reid, 2012; Mainen et al., 2016): in a manner comparable to how physicists build instruments gazing at distant events at the beginning of time, neuroscientists need to build powerful brain observatories to peer at the dynamic, cellular-level events inside the brain that give rise to the mind. Such observatories would be a game-changing addition to the neuroscience ecosystem, synergistic with the traditional investigator-driven model.

Pilot brain observatories

Any brain function involves the coordinated activity of populations of diverse neurons across many regions. To explore how brain-wide neural circuits guide behavior, it is important to simultaneously record activity from as many neurons as possible, in behaviors that engage these circuits, together with sophisticated data analysis techniques and theoretical models.

Given the many degrees of freedom in animal behavior and neural activity, it is vital that measurements are done in a standardized and well-documented manner. Together with open science practices, standardization will advance reproducibility in systems neuroscience. Reproducible science requires careful gathering of metadata and quality control. These requirements are challenging in academic laboratories, given the career life cycle of graduate students, postdoctoral fellows, and faculty.

The Allen Institute in Seattle prototyped the Allen Brain Observatory for large-scale neurophysiology based on calcium imaging and Neuropixels recordings. This observatory has carried out surveys of the visual system in behaving mice responding to a battery of visual stimuli (de Vries and Lecoq et al., 2020; Siegle and Jia et al., 2021). All data and metadata, such as the coordinates of all recorded neurons, operating procedures, and analysis protocols, are openly and freely available. In addition, the institute opened its platforms for external projects. This program, OpenScope, is funded by the NIH's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. Projects were selected through a blinded review process, and multiple manuscripts are on bioRxiv. This ongoing experiment in the sociology of neuroscience shows that cellular-level neurophysiological observatories can be open to the community and demonstrates demand for such facilities.

At the same time, the Simons Collaboration for a Global Brain, HHMI's Janelia Research Campus, and the NIH BRAIN Initiative recognize the need for large-scale, multi-disciplinary research programs in systems neuroscience (''both individual-laboratory science and team science approaches are necessary in biomedicine''; BRAIN Initiative Working Group 2.0, 2019). For example, the U19 multi-component, cooperative agreements for large-scale team research programs supports 19 multi-investigator research teams, some of which operate observatories for the consortium.

The International Brain Laboratory is a group of academic neuroscience laboratories in Europe and the United States organized in a geographically distributed model compatible with university-based researchers. Data are collected across 10 labs using a standard behavioral task in mice (Aguillon-Rodriguez and Angelaki et al., 2021) and Neuropixels electrophysiology on a brain-wide scale. Standardization across different research institutions in different countries has led to the development of open-source tools, especially in the analysis of neurophysiology data and data sharing. But propagating cutting-edge neurophysiological methods across many laboratories becomes exponentially more challenging as technologies become more complex and costly.

Next-generation brain observatories

It is now time to plan for next-generation brain observatories: centralized facilities that carry out specific neuroscientific experiments using unique capabilities and infrastructure based on submitted and externally peer-reviewed proposals. The output would be neurophysiological and neuroanatomical data with scale and quality that would be game changing. We favor an approach in which all data and metadata are made openly accessible on an aggressive schedule.

Observatories provide six opportunities to advance systems neuroscience technically and sociologically.

First, observatories provide broad access to powerful emerging methods in neurophysiology that move beyond the capabilities of individual laboratories. In mice, complete brain-wide maps of neural activity in the context of specific behaviors are on the horizon. Over the next decade, there will be a major technological push to target simultaneous recordings to many connected brain regions and extract additional information about the types of neurons recorded to link measurements of neural activity with maps of neural circuits. Meeting these goals will require robotics, pre-recording structural MRI, *post hoc* histological analysis, sophisticated signal analysis, and a robust IT infrastructure to wrangle the vast data streams from the various instruments and make these available for further analysis. Pipeline capacity can be scaled, as instruments can often be replicated at relatively low cost for increased output. It is only in such an environment that true technology integration and end-to-end optimization can occur.

Second, economies of scale and professional staff are expected to produce higher quality data at much faster rates than smaller academic laboratories. Specialized infrastructure and human expertise would advance standards in animal husbandry and care. Partnering with observatories will make sense even for PI-led laboratories that, in principle, would have the funding and know-how to perform similar experiments. Investigators can serve as the source of new ideas and methods, including prototype experiments for the observatory, and perform the many follow-up experiments inspired by large-scale data collection at the observatory. The observatory would thus act as a force multiplier for the technological gains produced by the BRAIN Initiative, HHMI, Allen Institute, and others.

Third, observatories will facilitate the emergence of a standardized software and hardware ecosystem. Datasets collected at the Allen Brain Observatory are already used to benchmark new data processing modules. Observatories will incentivize new developments by external groups to be compatible with the observatory hardware and software. Similarly, observatories will develop best-of-class standard operating procedures and propagate these protocols to the scientific community, which will advance reproducible science.

Fourth, observatories are expected to play an important role in training the next generation of neuroscientists. Best practices and standard operating procedures for experimental protocols and animal care procedures developed by observatories would be disseminated, enhancing rigor and reproducibility across the research community.

Fifth, observatories would help democratize neuroscience by providing access to cutting-edge technology to a wide range of researchers who currently lack access to such resources, including non-neurophysiologists (e.g., computational neuroscientists, psychophysicists, clinicians with disease models) and scientists from institutions without the necessary research infrastructure. Observatories will thereby enhance diversity, equity, and inclusion.

Sixth, the open science principles adopted by brain observatories will contribute to the culture and practice of sharing data and metadata in a common format as was pioneered by Distributed Archives for Neurophysiology Data Integration (DANDI) and its use of Neural Data Without Borders (NWB2.0). For example, about 100 published studies are based on the widely available Allen Institute Visual Coding survey (de Vries and Lecoq et al., 2020; Siegle and Jia et al., 2021). Other examples include OpenNeuro (Markiewicz and Gorgolewski et al., 2021), a large repository for human brain imaging data.

Large-scale centralized facilities in physics and astronomy are typically focused on a well-defined goal, such as searching for the Higgs boson. Other facilities provide unique tools for a well-defined experimental purpose, such as gravitational wave observatories or bright X-ray sources for protein crystallography. In neuroscience, precisely defined, unitary goals are more elusive, although canonically important problems can be defined, such as the neural implementation of different forms of learning. Many different species, behaviors, and questions are being pursued. This diversity reflects the brain's many functions and disorders. Next-generation observatories need to focus on the most widely applicable animal system and find the appropriate balance between flexibility and standardization. If the facility is too general (e.g., no constraints on species, behaviors, measurements), it loses economies of scale; if too standardized, it is only of limited interest to researchers.

Of mice and monkeys

It is not possible to build neurophysiological observatories agnostic to the species being studied. The laboratory mouse has emerged as the mammal that will soon be fully mapped at the level of cell types and connectivity. Functional studies in the mouse will link measurements of neural activity and comprehensive anatomical maps, which are already available for the mouse brain (https://connectivity.brain-map.org; https://cic.ini.usc.edu/). The NIH's BRAIN Initiative - Cell Census Network (BICCN) has invested heavily in a census of cell types in the mouse brain (https://biccn.org), which is foundational to any understanding of neural circuits (Luo et al., 2018). This genetic information allows the generation of cell-type-specific driver and reporter mouse lines for cell-type-specific recording and manipulation of neural circuits.

Over the last decade, it has become possible to train mice to perform rich perceptual, decision-making, and motor behaviors. Powerful neurophysiological methods allow large-scale recordings throughout the entire mouse brain; optogenetics provide for manipulation of specific types of neurons during behavior in transgenic mice (Luo et al., 2018). These considerations argue for a focus on mice. Lessons learned with murine observatories are likely to apply to observatories for other species.

A deeper understanding of the human experience and the specific circuits giving rise to human behavior in health and disease requires animal models that bridge the cognition gap between mice and humans. The macaque monkey remains the key animal model filling this gap. The scientific opportunities for an observatory focused on non-human primates include the study of high-level vision, blinding diseases, aging, social behaviors such as bond formation and communication, higher-level cognition, and a range of neurological and psychiatric diseases.

The development of neurotechnology is another area that would benefit from a non-human primate neuroscience observatory. Realistic use of any neurotechnology in humans will require testing and refinement in monkeys first. The observatory would also provide a platform for translating tools developed in rodent models to non-human primates, something that is currently difficult to do in individual laboratory settings. The observatory would provide these tools and specialized resources to the broader neuroscientific community for circuit-based studies.

Working with non-human primates, especially macaques, remains challenging for individual laboratories and academic institutions. Macaques are large and highly social animals and require housing that simulates their natural habitats. Ensuring conditions that allow species-appropriate behaviors is good animal welfare and is also imperative for rigor and reproducibility. Maintaining species-appropriate animal care is better achieved at specialized institutions. Siting observatories at the National Primate Research Centers would facilitate the acquisition and sharing of foundational knowledge about the non-human primate brain and its control of behavior in health and disease.

Large-scale recordings with Neuropixels probes

Neuropixels probes have emerged as the new standard for extracellular recordings (Jun and Steinmetz, 2017). The main advantage of Neuropixels over previously available silicon probes is their high electrode density over many millimeters (100 sites/mm on a 10 mm shank). This makes it possible to record spiking activity across multiple brain regions with a single probe and—when multiple probes are used—across nearly the entire mouse brain. Furthermore, Neuropixels' regular site geometry makes it straightforward to co-register physiology and anatomy.

Many variants exist, including Neuropixels 2.0, in which denser columnar sites allow improved drift correction while the four-shank geometry provides better coverage of individual brain regions, and Neuropixels NHP, which has the same set of 966 selectable electrodes as Neuropixels 2.0 but on a 45 mm long silicon shaft for recordings in non-human primates. On the horizon is Neuropixels NXT, which has a much smaller probe base relative to the number of channels to permit more probes to be simultaneously inserted into the brain, especially in chronic experiments.

Neuropixels technology is a general-purpose tool for recording simultaneous neural activity at the sub-millisecond timescale across the entire brain.

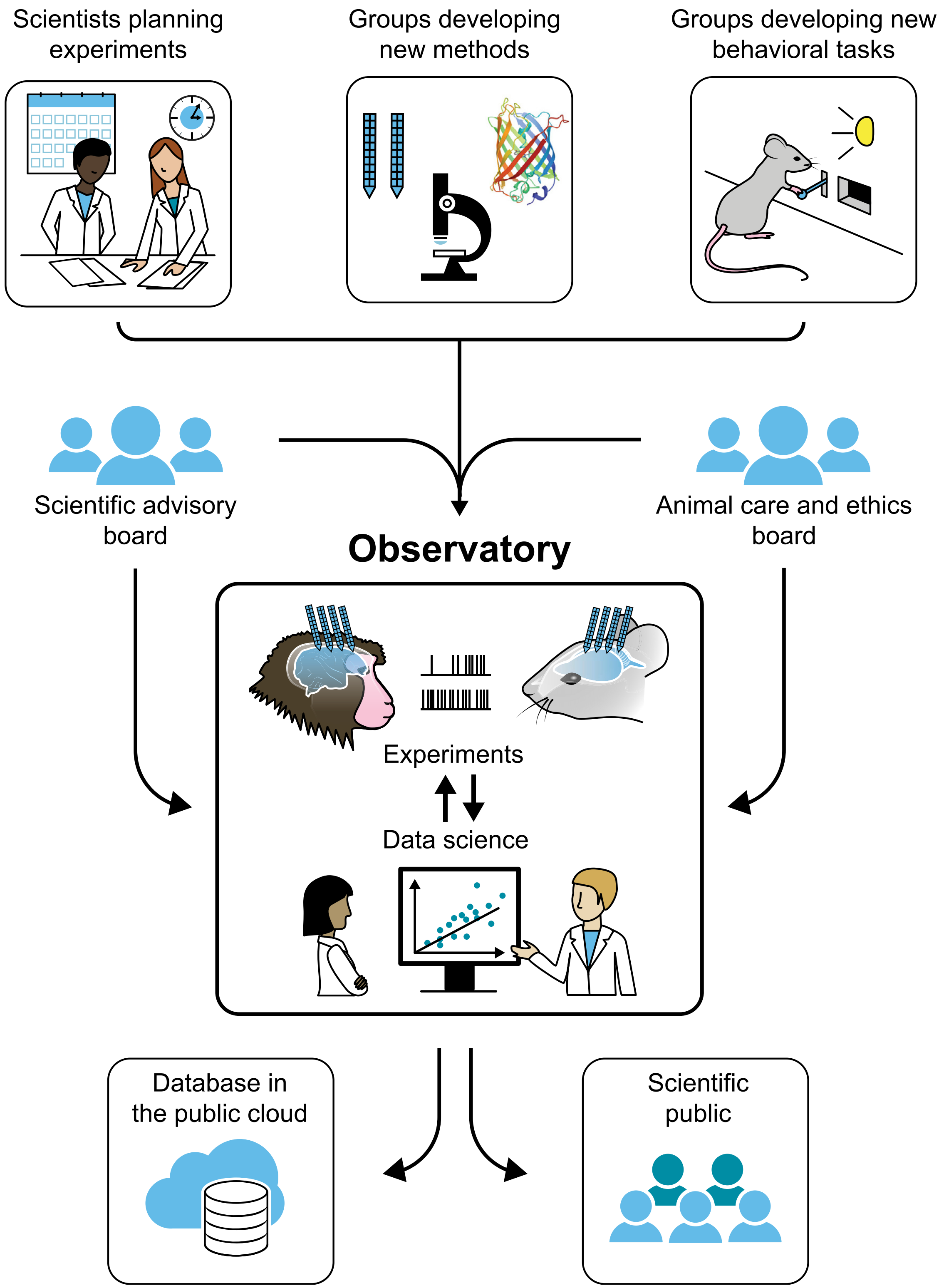

Figure 1. Organization of a brain observatory
The scientific community drives scientific goals by proposing specific experiments (e.g., Box 1), contributing new methods, and developing new behavioral tasks to be implemented by the observatory. Various boards provide governance and community-guidance and set long-term goals and oversee ethics and animal care. Separate observatories would perform recordings from laboratory mice and non-human primates. Data will be made widely available to the scientific public. Drawing by Bénédicte Rossi.

Of pilots and surveys

Observatories could subserve two project categories (tracks) for different, but overlapping, communities, each of which would be able to apply for peer-reviewed access to the facility.

TRACK 1

This track includes small, focused projects based on existing, standardized behavioral paradigms led by a single investigator or a small team. These projects could test specific computational hypotheses, focus on specific disease models, such as Alzheimer's disease, Parkinson's disease, schizophrenia, and aging, or probe the mechanisms of neuroactive compounds, such as psychedelics.

TRACK 2

This track is focused on larger projects proposing a new behavioral task or experimental paradigm and neurophysiological surveys across many brain regions. These would be initiated by a group of investigators who jointly pilot and develop experimental designs and the associated conceptual and computational framework and for which large-scale, brain-wide electrophysiological recordings would be foundational and transformative. The paradigm would be optimized for implementation at scale. The design and data output from such an endeavor could become a starting point for future track 1 projects.

Advanced microscopy

The development of sensitive protein-based probes for neural activity (e.g., GCaMP) has revolutionized cellular imaging of neural activity *in vivo*. Coupled with new microscopy methods, it is now possible to monitor very large (>10,000) neuronal populations during behavior (Luo et al., 2018). Neurons can be imaged densely—that is, all neurons within the field of view—and longitudinally over the course of learning. Imaging with genetically targeted fluorescent indicators provides great flexibility to selectively monitor specific cell types based on gene expression patterns or axonal projection patterns.

Flexible behavior with standardized software and hardware

The observatory will provide flexible configurations for head-restrained behaviors, subject to steric constraints imposed by the recording apparatus. In addition, flexibility must be based on standardization of the underlying components, including laboratory instrumentation control software and hardware components. Standardization of software and hardware will facilitate a wide range of behavioral tasks with relatively low switching costs from one experiment to the next (e.g., comparative ease to reposition and reprogram different components, such as virtual reality systems, manipulanda, cameras, visual-audio-tactile-olfactory stimuli). Scientists everywhere will benefit from these standard tools and the dissemination of open methods that accompany them.

Data product

The output of the brain observatory must be open and meet the findable, accessible, interpretable, and reusable (FAIR) principles. Electrophysiological data would be spike sorted and packaged together with metadata. The observatory might also implement analyses such as generalized linear models, dimensionality reduction techniques, and behavioral modeling. Data would be made widely available to the community through user-friendly portals and by leveraging community standards (e.g., NWB2-compliant) for extensible analysis packages.

Selecting projects

A management team and scientific advisory board would solicit applications and organize the vetting of proposals from prospective teams (Figure 1). Criteria would include impact, feasibility, commitment to open science, and diverse, equitable, and inclusive participation from the community. Ongoing evaluation and impact metrics would be established and continuously refined to ensure quality, rigor, and platform improvement.

Brain observatories are inherently geared toward a community model of planning and executing on team projects to address challenging questions that cannot be done by individual investigators (Box). To ensure the most impactful and accessible outcome, mechanisms for support should emulate those fostering national laboratories or independent research organizations with commensurate missions, facilities, and budgets to accommodate the scale of research needed.

We believe that such centralized, independently operated, and community-guided observatories are a necessary next step in understanding the brain, the most complex piece of highly active matter in the known universe.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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