2023 BSAC Report, RIKEN Center for Brain Science

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Introduction

The members of this advisory committee, the Brain Science Advisory Council (BSAC, hereafter), are honored to participate in the second BSAC review of the RIKEN Center for Brain Sciences (CBS, hereafter). RIKEN founded the internationally renowned Brain Science Institute (BSI, hereafter) in 1997, which was terminated in March, 2018. Neuroscience at RIKEN was successively reformed and rebuilt as the CBS under the initiative of Dr. Yasushi Miyashita. The CBS was established with the dual missions of understanding the human brain and mind, and finding solutions to social challenges, by incorporating basic, applied, and translational research. The first BSAC was held in 2019 and evaluated the direction and activity of the new CBS. The first BSAC highly endorsed the selection of Dr. Miyashita as the first director of CBS and recognized the unique advantages of the outstanding multidisciplinary scientific environment at RIKEN. Past and current suggestions were clearly articulated, and strong leadership was taken to strengthen multidisciplinary research in CBS, particularly in the areas of systems and computational neuroscience.

During the transition from BSI to CBS, the number of PIs was reduced from 35 to 27 to align with new research directions. A future plan to recruit new PIs, who were expected to play a critical role in the CBS, was proposed. The first BSAC highly evaluated this difficult transition to implement the new initiatives of CBS and at the same time, proposed **10 recommendations** in their 2019 report.

Since then, the director of CBS has changed to Dr. Ryoichiro Kageyama, a world-renowned developmental neuroscientist, who has continued to implement the research directions formulated under Dr. Miyashita's leadership. Dr. Kageyama has demonstrated tremendous leadership over the past few years and has both developed and implemented a number of management strategies that have benefited the scientific and working environment of CBS. The BSAC highly endorses all the efforts made under the leadership by Dr. Kageyama, who coordinated a number of goals for improvement of the scientific environment at CBS in response to the 2019 BSAC recommendations. These are summarized in TOR1 below. In brief, CBS recruited several new PIs and improved its research environment despite the difficulties caused by the COVID-19 pandemic, which started from early 2020. During this period, the RIKEN headquarters (HQ, hereafter) was reformed, and Dr. Makoto Gonokami was appointed as the President of RIKEN. He set **"RIKEN's Vision on the 2030 Horizon"** as a new platform to advance science within RIKEN. The platform materialized as the "**TRIP** (Transformative Research Innovation Platform of RIKEN platforms) Concept" to effectively generate new fields of knowledge across research fields by organically linking cutting-edge research platforms. Specifically, three platforms, (1) High-quality data acquisition, (2) Pioneering prediction science with AI x Mathematics, and (3) Expansion of a Computationally Viable Region, were presented, and the new CBS policy is expected to align with this TRIP Concept. In addition, the 10-year Japanese Flagship Project, **"Brain/MINDS"**, for which the CBS has played a major role as the central organizing institution, and another flagship project, **"Brain/MINDS Beyond"** will terminate at the end of FY 2023, and

currently a new national brain science project is planned to start from FY 2024. CBS is planning to play a leading role in the new project.

The second (current) BSAC review of the CBS was held in August, 2023, to evaluate the activity of CBS since the first review. The CBS Director, Dr. Kageyama, presented their current administrative activity and how they responded to the BSAC 2019 recommendations. The Director also presented their plan for the next 5th Mid- to Long-Term Plan period, including their proposal to lead the next national flagship brain science project. A number of research outcomes were also presented by the PIs.

For this review, **three terms of references (TORs)** were established by RIKEN HQ for the evaluation of the CBS:

1. Evaluate the responses to the 2019 BSAC recommendations.
2. Based on the results of the Center's self-analysis, evaluate operations and R&D activities for the 4th Mid- to Long-Term Plan period (FY2018-2024).
3. Evaluate the policies of the 5th Mid- to Long-Term Plan period (FY2025-2031) and recommend new directions for operations and R&D that should be implemented and promoted.

After the last BSAC review, CBS responded to almost all the recommendations and succeeded in improving the research environment. The BSAC highly applauds all of these efforts. The BSAC was also deeply impressed by the cutting-edge research presented by both established and junior PIs, including the newest recruits. The BSAC feels that they had enough information and time to fully evaluate the CBS and overall agreed with the future directions of the Center. At the same time, the BSAC proposed several recommendations both to the RIKEN HQ and CBS for further development of neuroscience and related cutting-edge sciences in RIKEN, which are summarized at the end of this report.

TOR1 Evaluation of responses to recommendations (EOR) of BSAC 2019

In making the following comments on the BSAC 2019 recommendations, we note that these were written prior to the worldwide pandemic and the financial complications of the global increase in energy costs associated with the war in Ukraine and other matters. The BSAC 2023 is truly impressed by how well the CBS has managed to integrate these recommendations into its strategy and to efficiently implement them despite these global pressures.

EOR 1: Purchase of 7T MRI scanner

IMPLEMENTED

CBS managed to purchase the 7T MRI scanner. The process was delayed due to the pandemic, but it has now been functional for 1 year. Research work with it should be up-to-speed in the coming months. Points for further consideration are noted in ***Recommendation 7***.

EOR 2: Yearly increases of the CBS internal budget

NOT IMPLEMENTED

BSAC 2023 does not fully understand the reasons why it has not been possible to increase the CBS core (RIKEN-provided) budget, and noted that research activity had become increasingly dependent on the substantial input of funds via Brain/MINDS. As external funding is linked to pre-determined projects, this limits the ability of CBS to respond to new priorities and retain its pioneering position in global neuroscience. The BSAC is impressed by the administration within CBS. The pro-active attitude towards helping scientists with any administrative issue is remarkable and should be preserved. The future goals of CBS align perfectly with RIKEN's Vision on the 2030 Horizon. Moreover, CBS is integrating the TRIP Concept to serve society in a future-looking way, ultimately contributing to "control of the future". This will include efforts to provide high quality "big" data to the research field and to society, such as the gene expression atlas of the marmoset project. Points for further consideration are noted in ***Recommendation 1***.

EOR 3: Fulfill the 7-year plan via recruitment

IMPLEMENTED, BUT WITH REMAINING UNCERTAINTIES

We applaud the efforts in recruiting new faculty that resulted in excellent new appointments. We are delighted to hear that the "salary-cap" within RIKEN has been removed; this will help in the recruitment of excellent senior faculty in the future and might also serve as a retention mechanism for outstanding current faculty. Points for further consideration on "age-cap" are noted in ***Recommendation 10.***

EOR4: Intellectual exchange and community building

IMPLEMENTED

We are enthusiastic about the installation of two relevant active programs. The CBS Brain Science Seminar Series has begun with a remarkable record of speakers. We are also impressed by the balanced speaker line up. The CBS Young Investigators' Seminar Series is popular among students and postdocs. We are very pleased with these innovations, and the postdocs spoke well of this initiative.

EOR5: Gender diversity

IMPLEMENTED

We applaud the progress made by CBS in hiring outstanding female PIs, such that it now has a higher female PI quota than other (if not all) RIKEN centers or major Japanese universities with science divisions. Still, the 22% female PIs is relatively low by international standards. Points for further consideration are noted in ***Recommendations 3 and 10.***

EOR 6: Mentorship

IMPLEMENTED

The committee applauds the efforts that CBS has taken to implement mentorship committees. The postdocs like the process a lot and find it helpful. We commend Dr.

Hitoshi Okamoto who has made an amazing start in organizing these mentorship activities. Points for further consideration are noted in ***Recommendation 9.***

EOR 7: Integrating international scientists

IMPLEMENTED

BSAC 2023 is impressed that CBS has almost doubled the number of international scientists, i.e., from 28% to 48%. We also applaud CBS's efforts to enable international PIs to participate in leadership committees and responsibilities, including the CBS Steering Committee and CBS Search Committees. However, we note that the use of the Japanese language in committee meetings can be a barrier to their full participation. We applaud that RIKEN Science Council meetings are held in English. CBS should consider whether the CBS Steering Committee meetings could be conducted in English for easier integration of non-Japanese colleagues. Points for further consideration are noted in ***Recommendations 9 and 10.***

EOR 8: Non-human primate and marmoset work

IMPLEMENTED

We are excited by the achievements of Brain/MINDS and, specifically, RIKEN's contributions to the adoption of the marmoset as the non-human primate (NHP) species of choice with a massive scaling up of the facilities for housing and conducting research using this species. We also note that RIKEN will be the likely place of marmoset research in any extension of the national project. In connection with this, we applaud that RIKEN HQ and CBS extended the term of non-tenured CBS PIs to nine years in principle, mindful of the length of time many non-human primate projects take to realize impactful results.

EOR 9: Hiring PIs with clinical experience

IMPLEMENTED

We are impressed that CBS has made several recruitments as well as strategic links to clinical centers; these will also help in the continuation of the Brain/MINDS-project. The efforts made so far are sufficient.

Nonetheless, we note that CBS is a fundamental science institute rather than a medical research institute and its basic research should not be diluted. Numerous strands of ongoing research in CBS have, and will have, major clinical implications that can be pursued via such strategic links. We endorse this action. Points for further consideration are noted in ***Recommendation 4.***

EOR10: Hiring PIs with computational expertise

IMPLEMENTED

PIs with computational expertise have been hired. Such scientists need to be monitored to ensure that opportunities for successful interactions with experimental scientists are fully explored and implemented when possible. Points for further consideration are noted in ***Recommendations 2 and 10.***

TOR2: Based on the results of the Center's self-analysis, evaluate operations and R&D activities for the 4th Mid- to Long-Term Plan period (FY2018–2024).

BSAC 2023 commends the leadership and members of CBS on their continued record of research of the highest international standard, their impact on global brain science, and their contributions to human society. The quality and number of scientific publications produced over the review period are impressive, with a number of particularly striking results. These and other outputs have helped to cement CBS's position as the flagship center for neuroscience research in Japan and a leading center worldwide.

Scientific Excellence

The BSAC heard research from a number of the groups at CBS but it was not our task to evaluate individual laboratories. Below, we highlight some of the work of researchers within the CBS to provide a flavor of the types of research being undertaken. It should be noted that this is not an exhaustive list of the research in all laboratories, and many other excellent researchers are not named here.

(i) Research to reveal high-level cognitive functions of the human brain

Human cognition is a core target of CBS research, which will be accelerated by the availability of the newly installed 7T MRI system. The newly recruited PIs are well aligned with this new direction.

Combining MRI with electrophysiological measurements and interventions, Dr. Miyamoto showed in macaques that confidence, a measure of metacognition, is represented by the prefrontal cortices, whose information is integrated by the posterior parietal cortex, ultimately driving the anterior cingulate cortex to output the final decision. Dr. Miyamoto now extends his research to social metacognition of both human and NHP using MRI and behavioral analysis, enabling cross-species comparisons, for which 7T MRI is optimal because of its high spatial resolution to depict and detail the NHP brain.

To investigate the neural mechanisms of sleep-learning interactions, Dr. Tamaki succeeded in simultaneously measuring magnetic resonance spectroscopy (MRS) and EEG during sleep. The new 7T MRI system has a large advantage in MRS. To further depict the neural substrates of sleep-learning interaction, Dr. Tamaki is now preparing 7T MRI optimization targeting hippocampal plasticity.

7T MRI will provide richer information with a shorter duration for decoding, which is a critical procedure for information extraction from the brain, particularly by separately imaging the surface and deep layers of the cortex. Utilizing decoded neurofeedback, combined with interventions such as transcranial magnetic or ultrasound stimulation, Dr. Shibata is working on human learning at conscious and unconscious levels, and Dr. Lau is approaching the theme of consciousness by studying the subjective experience of perception or emotion, showing that the prefrontal cortex is important.

Thus, the CBS is ready to approach human cognition with well-motivated and talented PIs armed with the cutting-edge 7T MRI to complement the existing 3T MRI capabilities. To support these research activities, it is critical to develop cutting-edge MR technologies, including layer imaging and the imaging of the MRS. Points for further consideration are noted in ***Recommendation 7.***

(ii) Multi-layered studies based on animal models, spanning levels from molecules, cells, circuits, systems, and organisms to society

The breadth of the CBS in terms of research questions, techniques, and model species is exemplary. For instance, within CBS, faculty are studying humans, NHP, various species of rodents, *Drosophila*, and zebrafish. This multi-disciplinary, multi-level approach to neuroscience is also reflected in the academic backgrounds and training of the faculty, which range from physics and math to psychology and physiology. Neuroscience is not a traditional academic discipline, and progress towards understanding the brain is likely best accomplished through a diversity of perspectives, skills, and approaches. The committee was impressed by the extensive networks of collaboration amongst faculty members, bridging disciplinary training, and sharing concepts and techniques between different experimental systems.

A particular strength of CBS is the animal model group that investigates fundamental underlying questions of brain function. This group shows expertise in developing and sharing tools to examine brain functions. For instance, Dr. Murayama's group has been a leader in developing wide field 2-photon imaging techniques to not only answer his group's questions on perception and cognition, but also to share this technology with others. Looking forward, it would be important to engage with computational and modeling scientists to take full advantage of the large and rich data sets that could be collected using this incredible technology. Moreover, a clear data management plan will be necessary.

In terms of invertebrate species, Dr. Kazama's group has continued to uncover fundamental information on the neural basis of sensory perception in *Drosophila*. Dr. Takeishi's work on *C. elegans* examining odor learning is in its beginning phases but holds great promise. We are enthusiastic about the progress of these researchers using invertebrate species. Dr. Moore's group has impressively progressed in deciphering the molecular program underlying dendrite differentiation.

Research using rodent models continues to be a world-leading strength of CBS. For instance, Dr. McHugh's lab has made pioneering contributions to understanding the fundamental mechanisms of memory engrams and how novel external information is processed in the brain using mouse models. The discoveries made by his lab are recognized throughout the world. Dr. Johansen's lab explores the neural mechanisms underlying emotion. His lab has uncovered the role of key circuits in emotional learning and has made important links to human researchers examining emotion. This cross-pollination of approaches and findings from model species to humans is key to making

progress in the future. Dr. Yoshihara's group discovered a unique function of the long mysterious brain region, the claustrum. The role of this brain region has long eluded experimental investigation as it is difficult to target. His group used cutting-edge techniques to reveal that this region orchestrates cortical activity. Moreover, in addition to using rodent models, several groups are using zebrafish (Drs. Yoshihara and Okamoto) to study the fundamental properties of odor learning and social interactions.

CBS remains an international leader and a hub of Japanese neuroscience in terms of fundamental discoveries using model species. We applaud its continuing effort to value basic research, realizing that fundamental research discoveries are the fastest and most direct paths to patient recoveries. Until there is a better understanding of the basic mechanisms underlying brain function, there is little chance of translational success.

One of the key animal models at CBS is NHPs, particularly marmosets. The efforts to create a genome-wide, high-resolution atlas of gene expression in the marmoset are applauded, as they will be a jewel in the CBS crown. This open-source resource, led by Dr. Shimogori, will be widely used by researchers around the world and will increase the international visibility and reputation of CBS. The development of this key resource is critical for the leading role of CBS in Japan's Brain/MINDS and future national neuroscience project efforts.

There is a vital role of theory, modeling and data analysis within experimental brain scientists using different model species. Although interactions between theory groups and experimentalists exist, they should be strengthened.

(iii) Data-driven research led by theoretical and technological advances
Theoretical neuroscience research has a long and globally significant history at BSI, not least through the pioneering contributions and influence of Prof. Shun-Ichi Amari.

This tradition has been continued at CBS. The BSAC was pleased to note the successful recruitment of three young Unit Leaders working in theoretical and data-driven neuroscience: Drs. Isomura, Kang, and Matsuda. These new PIs are now established (despite the challenges posed by starting up during the COVID-19 pandemic), and we were pleased to see clear connections already established with experimental groups, notably between Dr. Isomura and Drs. Okamoto, Kang and McHugh, with Dr. Matsuda having published a recent collaborative analysis of fNIRS data with Dr. Komaki. These new recruits complement the strengths of Dr. Toyoizumi's laboratory, which continues to publish influential and insightful works. Notable progress from his laboratory has included a consideration of the impact of the different phases of sleep-related network activity on information-maximization principles of synaptic plasticity (Yoshida and Toyoizumi, 2023) and a brain-inspired predictive machine learning approach to dimensionality reduction (Isomura and Toyoizumi, 2021).

Technological advances pioneered at CBS continue to generate rich datasets of potentially groundbreaking significance. We note particularly the fluorescent mitophagy sensor developed by Dr. Miyawaki highlighted in the CBS report, which we had the pleasure to see for ourselves during our visit. These and similar world-leading developments at CBS provide valuable opportunities for further collaboration between the experimentalists and data-oriented theorists at CBS.

The shared office space occupied by the three newer theorists provides an excellent opportunity for them and their students and postdocs to interact, exchange ideas, and benefit from their pooled expertise. CBS should work to capitalize further on the strengths of these newer theory- and data-focused recruits by giving consideration to the following:
(1) The nucleation of a physical theory center core (similar to those at Columbia University and UCL) that includes trainees affiliated with senior laboratories (such as Dr. Toyoizumi's) alongside the junior groups;
(2) Exploring ways to promote further interaction with experimentalists at CBS---particularly those with data-intensive emerging technologies; and
(3) creating links to machine learning and AI experts center for AIP and iTHEMS.
One challenge to such planning may be the short-term nature of the Unit Leaders' appointments. Points for further consideration are noted in ***Recommendation 10.***

(iv) Research to develop diagnostic and therapeutic methods for neuropsychiatric disorders
Brain diseases constitute another focal point of research at CBS. The goal of the team led by Dr. Motomasa Tanaka is to elucidate the molecular mechanisms governing protein aggregation and the resulting physiological consequences in neuropsychiatric disorders. The team's expertise lies in the structural analysis of the formation, disaggregation, and propagation of amyloid fibers. Recently, Dr. Tanaka's investigations on protein aggregation shed light on an innovative cellular mechanism that underpins neuronal dysfunctions triggered by an exacerbated cellular stress response resulting from the accumulation of anomalous translation products within neurons. Dr. Saido, a senior Team Leader, is a prominent figure in the field of brain aging and Alzheimer's disease (AD) research. His team's previous achievements encompass the identification of a pivotal enzyme, neprilysin, responsible for the degradation of amyloid beta peptide within the brain. Moreover, they have unveiled the intricate mechanism through which the neurotransmitter somatostatin activates neuronal neprilysin, both in vitro and in vivo. Dr. Saido's pioneering work includes the creation of App knock-in mice, a widely adopted model for AD across the globe, effectively positioning him as the most extensively cited researcher within CBS during the year 2022. Additionally, he is vigorously engaged in the endeavor to develop NHP models of preclinical AD, a pursuit poised to yield substantial benefits for the broader research field.
Dr. Hayashi-Takagi, who joined CBS as Team Leader in 2019, has been dedicated to investigating the molecular mechanisms that underlie the onset and pathology of schizophrenia. Her recent breakthrough involves the observation of a notably elevated

count of extra-large (XL) spines in various mouse models of schizophrenia. She employs state-of-the-art techniques to visualize individual synapses within the brains of living animals, operating across multiple scales. These endeavors are yielding novel scientific achievements. Her contributions have garnered substantial recognition, including her leadership of the MEXT Group Grant (Grant-in-Aid for Scientific Research on Innovative Areas), solidifying her position as an exceptional researcher of great distinction within the field.

Dr. Ito-Ishida, who recently joined CBS as Team Leader, has been steadily advancing her research on neurodevelopmental disorders, focusing on MeCP2, a gene known to cause Rett syndrome. She is now setting up her own laboratory and adopting a multidisciplinary approach to elucidate the complex causal relationships between molecular irregularities and the resulting behavioral disorders. A pivotal aspect of her research centers on the exploration of mosaicism within the female brain of Rett syndrome model mice, which offers a promising avenue for comprehending the complexities of neurodevelopmental disorders unique to females. This endeavor holds the potential to enhance our understanding of female-specific neurodevelopmental conditions.

(v) The national project "Brain/MINDS"
CBS has played a leading role and is a core hub in Japan's Brain/MINDS project and may continue to play a leading role in the next National Brain Project. The overall goal of this project is to elucidate the neural circuits underlying higher-level brain function in marmosets as a model for human disease and to understand the neural basis of complex behaviors.

Response to self-analysis
We limited our comments to the issues to which we had recommendations.

S-(2) International personnel and research environment
The BSAC recognizes the ongoing efforts of the CBS to link with international organizations, including productive exchanges with UCSF and MIT. To maintain its global excellence, the BSAC recommends the CBS explore additional opportunities with other organizations, particularly in Asia. By further developing global networks, these links could further strengthen hub areas of excellence at the CBS in areas such as Alzheimer's disease.
Interviews with junior researchers, including students and postdocs, indicated overall satisfaction with the scientific environment at CBS but a lack of awareness of basic introductory information. Points for further consideration are noted in ***Recommendation 9.***

On a related note, it would be helpful for CBS to increase transparency in terms of the ratios of foreign nationals and women among the constituent members. As CBS has a good record compared to other RIKEN institutes and centers, these data could be helpful

and should be up-to-date and disclosed to the public to highlight CBS's continuing efforts. Points for further consideration are noted in ***Recommendations 3 and 9.***

W1 insufficient gender diversity

The overall percentage of female researchers increased from 25.5% to 31.1% between 2019 and 2023, but as of August 2023, the percentage of female PIs will remain at 22%, showing a "leaky pipeline" in the career paths of female researchers. In particular, only two female PIs have tenure, and one of them is in the support section, so there is a need for female participation in higher-level positions. It is expected that more creative research will be developed at CBS with the participation of excellent women scientists. Key performance indicators (KPIs) should be set based on data on how to promote the expansion of human diversity, and the budget needed to analyze the current situation and raise awareness should be viewed as a RIKEN-wide issue. Points for further consideration are noted in ***Recommendation 10.***

T-(1) T-(2) T-(3) Financial challenges

(Drastic decrease in CBS internal budget, reduced flexibility in budget execution, and increased expenditures due to rising labor costs and prices). Points for further consideration are noted in ***Recommendation 1***.

T-(4) Decreased employment mobility due to changes in the labor law

While BSAC acknowledges that the changes highlighted will require more careful planning around laboratory and center staffing policies, we feel that they also provide an opportunity to support the career advancement of postdoctoral researchers. The majority of the postdocs we met hoped to go on to long-term careers in academic science. CBS, through the newly established central mentorship program as well as the individual PIs, could support this ambition by helping postdocs understand when they are ready to apply to academic positions or what further milestones might be needed to bring them to that point. Many postdocs will want to consider an international job search, perhaps spanning multiple continents. CBS could tap the considerable international experience of its PIs to help identify opportunities as they arise and provide guidance about the global variety of academic systems, while also reinforcing and publicizing routes to broader careers in, for example, industry, research administration, or government. At a practical level, training and assistance with the preparation of research statements, talks, and interview skills, as well as grant applications and laboratory management, will help these trainees secure and establish their own positions and reinforce CBS's impact on Japanese and international brain science. **[*See recommendations 9 and 10*]**

TOR 3: Evaluate the policies of the 5th Mid- to Long-Term Plan period (FY2025-2031) and recommend new directions for operations and R&D that should be implemented and promoted.

CBS Vision – Neuroscience: Understanding ourselves

The ambitious goal of CBS is to bridge understanding of the physical brain at multiple levels (molecular, cellular, and circuits) with cognitive processing and brain function. The current four major themes will be consolidated into three integrated themes directed at understanding the human brain and brain pathologies while utilizing computational and AI approaches for data analysis, data sharing, and the development of new theoretical concepts for modeling brain function and pathologies.

CBS proposes a research focus in three major areas, as follows:
1) Towards understanding the multilayered mechanisms of the human mind;
2) Investigating the pathological mechanisms of neurological and psychiatric disease toward the development of new diagnostics and treatments;
3) Developing innovative technologies and theories to understand the principles of brain functions and contribute to the advancement of AI.

Overall, these represent cutting edge areas of research that will open new avenues of knowledge of the human brain and understand the cause and treatments for human diseases of the brain and mental illness while contributing to new technological advances and commercial links with industry to develop products of societal benefit. If appropriate, a description of some examples of expected breakthroughs achieved after 7 years could make the plan more appealing for securing further funding, recruiting aspiring researchers, and gaining public support for the CBS program.

The current faculty are well aligned with these three focus areas, and opportunities for strengthening existing collaborations and developing new collaborations are highlighted below.

1) Towards understanding the multilayered mechanisms of the human mind

Through the vision of the previous Director Miyashita and with the additional support of the previous national project, Brain/MINDS, CBS is now a powerhouse of systems, computational, and circuit neuroscience. Teams are studying various mechanisms of human cognition and gaining valuable insights from circuit and behavioral analyses in animal models, as described in TOR2.

The BSAC was extremely impressed with the advances in the technological application of wide-field imaging, together with dense recordings using Neuropixel probes and miniscopes in awake, behaving animals to measure multiscale brain activity across the brain during behavior. This, coupled with functional brain imaging and the installation of the new 7T MRI, as well as computational modeling, will provide unprecedented access and analytical tools to realize the goal of bridging the tangible and intangible mechanisms of brain function.

2) Investigating the pathological mechanisms of neurological and psychiatric disease toward the development of new diagnostics and treatments

The BSAC heard exciting new research related to a variety of human clinical pathological diseases, as described in TOR2.

The BSAC suggests capitalizing further on CBS's links with the University Hospitals and medical schools to include The University of Tokyo, Juntendo University, Kyorin University, and Keio University to promote opportunities for physician-scientist research training. This could provide excellent ways to strengthen collaborations with clinicians such as those named in the Brain Medical Science Collaboration Division (Dr. Shigeo Okabe). Analysis of the clinical behavioral and clinical pathological phenotypes of the precious marmoset disease models will be vitally important for understanding disease progression as it relates to the human disorders being studied. Specialists in neurology (both adult and pediatric neurology), psychiatry, radiology, neurosurgery, anesthesiology, neuropathology, and other disciplines, including clinical psychology and pharmacology, could provide important translational insights.

Areas 1 and 2 research also require the integration of an understanding of the cell biological mechanisms of brain function, which will also lead to a better understanding of human disease and the development of diagnostics and treatments. In this regard, the laboratories of Drs. Kamiguchi and Kageyama are conducting world leading research into cellular proliferation and axonal pathfinding. The recent addition of Dr. Nagai is an excellent addition. However, the BSAC suggests that cellular and molecular neurobiology may still need to be bolstered in order to deliver diagnostic and therapeutic outcomes. An area of particular importance may be to consider recruitment in the area of neuroimmunology, where the marmoset model could make a significant contribution. Research in dementia and Alzheimer's disease is increasingly converging on neuroimmunological mechanisms of pathology as well as diagnosis and treatment. Additional resources for researchers to accelerate translation will require access to iPSC's and human organoid technologies, as well as disease biobank resources. The BSAC recommends developing these resources through local and national collaborations. Points for further consideration are noted in ***Recommendation 5.***

The installation of a PET scanning system for molecular imaging of disease-related molecules is strongly recommended for the future development of disease-related studies. This technology will be key to capitalize on past achievements of the CBS group and extend their findings to develop the next generation of potential therapies. Points for further consideration are noted in ***Recommendation 8.***

3) Developing innovative technologies and theories to understand the principles of brain functions and contribute to the advancement of AI

CBS researchers have produced world-leading technologies, such as bioluminescent and fluorescent probes by Dr. Miyawaki, wide-field two-photon imaging by Dr. Murayama, and efficient unsupervised learning algorithms suitable for hardware implementation by Drs. Isomura and Toyoizumi. These and other PIs are well positioned to lead the development of innovative technologies both for understanding the brain and brain-

inspired AI. Recent progress in AI technologies is phenomenal, since achieving supra-human performance in image analysis several years ago, recent large language models are providing novel opportunities for knowledge discovery and experimental designs. To incorporate rapid progress in AI for neuroscience, and further lead the development of next-generation AI, CBS would need to actively recruit new PIs with strong computational and mathematical backgrounds and also strengthen its ties with other centers of RIKEN, such as AIP, iTHEMS, and BDR. Points for further consideration are noted in ***Recommendations 2 and 6.***

RIKEN TRIP alignment

RIKEN set the TRIP Concept to effectively generate new fields of knowledge by organically linking cutting-edge research platforms. CBS's research on big multi-modal data collections, including data from animal behavioral experiments, large-scale 2-photon imaging, the development of genetic and molecular tools for imaging neural activity, large-scale neurophysiological recordings and neuroanatomical tracing, and non-invasive neuroimaging with 3T and 7T MRI, well fits the "High quality data production platform" of TRIP. Decoding brain activity from neural recording and connectome data using AI, analyzing neural circuits with mathematical models, understanding human communications using hyperscanning fMRI/EEG, and establishing a multimodal database align well with the "AI x Math" platform. As a third platform, CBS aims to digitally reconstruct the brain, build new theories of the brain, and develop new brain-inspired AI using quantum states, to be aligned with the platform of "Expanding the Computationally Viable Region". The focus of the third platform is on developing quantum computing hardware, integrating it with the Fugaku supercomputer, and furthermore, developing the neuromorphic hardware for resource-efficient (computation within a stochastic context), high-performance computation, and introducing neuronal networks for cybernetics applications. This third part would be the most ambitious and appealing to RIKEN, and society as a whole. Its achievement would give CBS the opportunity to play a major role in the future direction of RIKEN. But the pathway to this goal was still rather ambiguous and not clearly presented. BSAC recommends that the CBS clarify the milestones toward this goal, actual research plans (including collaboration with other RIKEN institutes and construction of data sharing systems regarding the national project), and identify major collaborators, or set a realistic goal to be matched with the scheme of "Expanding the computationally viable region" in the brain sciences. Points for further consideration are noted in ***Recommendation 6.***

Global Trends in Neuroscience

Global trends in Neuroscience are rapidly evolving. More and more attention is being paid to "the brain environment," composed of non-neural as well as neural cells. The discoveries of the brain's lymphatic and glymphatic systems provide novel insights into mechanisms maintaining brain homeostasis. The role of non-neuronal cells, including microglia, astrocytes, and oligodendrocytes, in modifying neuronal circuits and neuronal health/longevity is very important to pursue. In the disease research field, the role of

immune cells in neuroimmunological diseases such as multiple sclerosis, neuromyelitis optica and other autoimmune disorders is being elucidated and having an enormous impact on their therapies. It is particularly noted that immunotherapy against Alzheimer's disease using Aβ antibodies has shown promising effects in slowing the progression of the disease, demonstrating that changing the brain environment would be a novel and promising strategy to treat brain diseases. Research using brain organoids is rapidly growing. These innovative technologies are particularly instrumental in the studies of neurodevelopmental diseases or variants of unknown significance (VUS), as well as diseases with multiple genes and small effect sizes (eg: schizophrenia and depression).

The BSAC encourages the CBS to take these scientific trends into consideration and think critically about incorporating them into their future scientific program by forming collaborations with external institutions and/or hiring experts in these fields.

Alignment with future National Brain Project

In FY2024, a new national Brain Science Project tentatively coined the "Integrated Brain Science Program" may be launched as a 6-year term project. The following five subprojects are proposed as the main pillars:

- Development of innovative technologies and expansion of research infrastructures
- Elucidation of the dynamics for human higher brain function
- Elucidation of the pathogenetic mechanisms underlying neurological and psychiatric disorders
- Reproduction of brain models in a digital space
- Identification of seeds for new diagnostic and therapeutic tools for neurological and psychiatric disorders

A novel focus is on the "digital brain," which integrates animal and human data to predict brain disorders. While reproducing the human brain at a cellular level may not be possible and would take much more than 6 years, some macroscopic models to explain and predict brain disorders is expected.

The CBS aims to serve as the core institute for the new national project and support community activities by participating in the following tasks:

- Expanding its resources and technological infrastructure
- Promoting interspecies comparative analyses
- Deciphering the mechanisms of brain dysfunctions
- Modeling and predicting brain dynamics

All of these would be toward understanding diseases, exploring biomarkers, and understanding intelligence and individuality.

Appendix:

Summary of recommendations to RIKEN HQ

Recommendation 1. *The BSAC highly recommends that RIKEN HQ consider a major increase (perhaps a 30% increase is required) of the CBS Budget from RIKEN central funds.*

Reason: These funds would be used to allow CBS to play a central role in implementing RIKEN's Vision on the 2030 Horizon. Moreover, CBS is integrating the TRIP Concept to serve society and the prediction of the future, contributing to "control of the future". This will include efforts to provide high-quality "big" data to the research field and to society, such as the gene expression atlas of the marmoset project.

Recommendation 2. *The BSAC recommends RIKEN HQ consider capitalizing on the potential synergies between CBS and AIP (RIKEN Center for Advanced Intelligence Project).*

Reason: The potential to work together across institutes could accelerate advances aligned with the TRIP concept, in particular: "Pioneering "prediction science" with AI", and "Expansion of the computationally viable region".

Recommendation 3. *The BSAC strongly recommends that RIKEN HQ work to rectify the gender imbalance amongst its researchers.*

Reason: The ratio of female scientists in RIKEN is low. We note that, up until now, RIKEN has not had an center led by a female director. While we note that CBS has progressed further than other centers in this regard, focused policy effort at the central level will benefit all parts of RIKEN including CBS.

Summary of recommendations to CBS

Scientific Vision and Collaborations

Recommendation 4. *The BSAC suggests capitalizing further on CBS's links with the University Hospitals and medical schools to include The University of Tokyo, Juntendo University, Kyorin University, and Keio University to promote opportunities for physician-scientist research training.*

Reason: This could provide excellent ways to strengthen collaborations with clinicians such as those named in the Brain Medical Science Collaboration Division (led by Dr. Shigeo Okabe). Analysis of the clinical behavioral and clinical pathological phenotypes of the precious marmoset disease models will be vitally important for understanding disease progression as it relates to the human disorders being studied.

Recommendation 5. *The BSAC recommends the integration of an understanding of the cell biological mechanisms of brain function, including the development of biological resources to accelerate translation, such as access to iPSC's and human organoid technologies, as well as disease biobank resources.*

Reason: Cellular and Molecular neurobiology will lead to a better understanding of human disease and the development of diagnostics and treatments. The resources

supporting these studies can be obtained through local and national collaborations and the recruitment of new faculty.

Recommendation 6*. BSAC recommends that CBS clarify the milestones toward their goals of developing a digital reconstruction of the brain, building new theories of the brain, and developing a new brain-inspired AI using quantum states.*
Reason: Providing actual research plans (including collaboration with other RIKEN centers and the construction of a data sharing system regarding the national project) and major players to work on it, or setting realistic goals that can be matched with the scheme of "Expanding the computationally viable region" in the brain sciences would support successful advances in this area.

Research Infrastructure

Recommendation 7. *To promote studies with 7T MRI, CBS should provide their scientists with the possibility to operate the MRI scanners anytime by themselves by providing training courses for these scanners that enable safe and efficient handling of the scanners. CBS should also invest in the expert personnel related to 7T MRI capabilities such as the recruitment of MRI physicists who have expertise in MRI sequence development.*
Reason: We understand that the scientists cannot *directly* control the MRI scanners at CBS but are required to do so through the facility manager. This may be counterproductive. It is noteworthy that at other international institutes, scientists have direct access to and control of the scanner. Furthermore, the replacement of the MRI Unit Leader is still ongoing. CBS needs to identify highly-qualified potential candidates and approach them directly as suitable international senior scientists in the field may not apply unless approached about such an opportunity. The newly appointed MRI Unit Leader should be capable of developing, installing, and optimizing cutting-edge MR technologies in tight collaboration with other 7T MRI research groups within and outside of Japan.

Recommendation 8. *BSAC recommends that CBS purchase a PET scanner for marmoset experiments.*
Reason: Molecular imaging with PET is a quickly developing field and will be key to capitalizing on the past achievements of the CBS group and extending their findings to develop the next generation of potential therapies.

Human Resources and Training

Recommendation 9. *CBS should continue to support trainees through the development of a "Welcome package", "Early career research training" and "career development" for the postdocs onboarding at the start of their position and provide support for them to take their next career step to obtain the faculty position.*
Reason: Many postdocs seemed to have problems in settling in at the start (particularly foreign postdocs), grant writing and finding jobs (felt by all postdocs), although the CBS leadership thinks these are provided currently. Supporting postdocs to prepare

applications for faculty positions, providing opportunities for practice job talks and chalk talks may be helpful.

Recommendation 10. *BSAC recommends more flexible conditions for recruitment, and duration of employment, including dual career couples and female faculty to increase diversity and inclusiveness, and empower the Center's human resources.*
Reason: In selected outstanding cases, the BSAC recommends that there be a mechanism to remove the "age cap" and either extend a current working contract beyond official retirement age or enter a new temporary contract with such scientists. We also think it is necessary to provide a longer guaranteed duration for computational Unit Leaders (particularly those hired during the COVID-19 pandemic) to give them time to establish deep links with experimentalists, other theorists and other RIKEN centers. Furthermore, careful alignment with local Universities to identify employment opportunities for partners may be necessary to recruit dual-career couples. Moreover, we recommend that at least one female scientist join the leadership team. One way to realize this goal would be through targeted recruitment of a new female scientist with the appropriate seniority and ambition. CBS should also consider holding CBS Steering Committee meetings in English for easier integration of non-Japanese colleagues.