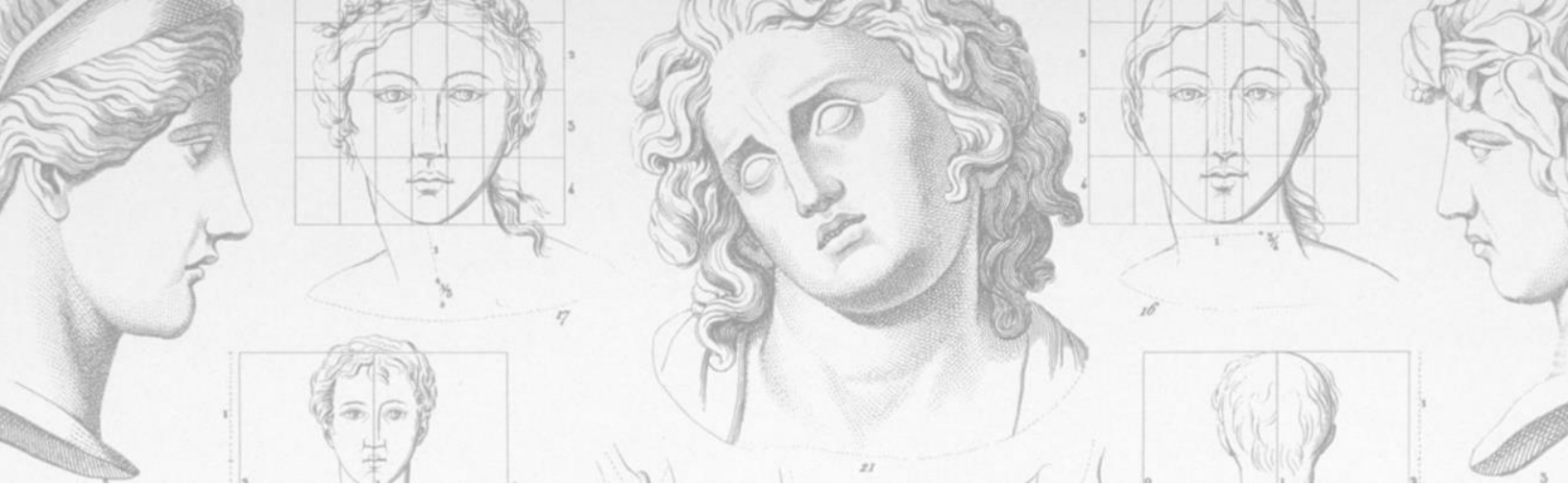

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Keio Medical Science Prize, Keio Medical Science Foundation (2003)
Presidential Lecture, International Brain Research Organization (2003)
Asahi Prize, Asahi Cultural Foundation (2004)
EBBS lecture, Federation of European Neurosciences Societies (2004)
Medal with Purple Ribbon, Cabinet Office, Government of Japan (2004)
Presidential Special Lecture, Society for Neuroscience Annual Meeting (2005)
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Fujiwara Prize, The Fujiwara Foundation of Science (2013)
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Yasushi Miyashita has been studying the memory and metamemory system in primates to reveal the dynamics of the cortical global networks and local circuits that underlie the memory of objects. He has made three major discoveries: first, the memory neurons that encode and retrieve associative long-term memory of objects in the temporal cortex; second, the top-down signal from the prefrontal cortex to the memory neurons in the temporal cortex for memory retrieval; and third, the metamemory centers in the frontopolar and anterior dorsolateral prefrontal cortex that interact with the temporal lobe memory centers. These discoveries clarify where and how mnemonic representations are organized in the primate brain and which mechanism underlies the on-demand reactivation of the representation during voluntary recall. His work also provides mechanistic insight into the long-standing question of how we comprehend the meaning of what we see. Finally, his recent work on metamemory has enriched our understanding of how our metacognition (cognition of cognition) is implemented in the brain and how retrospection becomes possible.

Yasushi Miyashita

Early Life and Education: Mathematical Beauty or a Mystery of the Human Mind?

I was born in 1949 in Ochanomizu, Tokyo, 1 km from both the Imperial Palace and the University of Tokyo. I grew up in a part of Shinjuku that is now about 1.5 km from the current Tokyo Metropolitan Government Building. But when I was a child, there were still wooded leafy parks and playgrounds here and there in the area. My parents were schoolteachers who specialized in humanities. Before I went to kindergarten, while my parents were at work during the daytime, I went to the grounds of a shrine and temple with an elderly couple who took care of me. There, I enjoyed running around with a white mixed-breed dog. Once I started going to elementary school, I would also spend time in my father's library, where I enjoyed looking at the illustrations and artwork in the books. Although I forgot most of them by the time I grew up, one exception was *Hyakunin Isshu*, a classical Japanese anthology of 100 poems by 100 different poets. This traditional Japanese anthology also served as the basis of a card game consisting of 100 pairs of a poem card and a picture card, which my family and I enjoyed playing, particularly while on New Year's holidays. In later years, as I organized my father's books after he passed away, I found myself remembering some of the artwork in the books from such poets as Rimbaud and Verlaine in Japanese translation. In particular, I had clear memories of Aubrey Beardsley's artwork in *Salomé* by Oscar Wilde. The experiences of individuals during their childhood remain deep in memory. In my case, for example, you can sometimes see motifs from *Salomé* that I borrowed for the opening line in my presentation slides for a scientific meeting.

In upper-elementary grades, I diligently practiced swimming to become the school's representative at the regional tournament. In the process, I learned that I had no talent for swimming. Around that time, I started spending less time with my father's books and instead went to a nearby public library, where I read George Gamow's books from cover to cover. As with other books, earlier in my life, I was initially attracted by the artwork, but once I started to read them, I became absorbed by the content of *Mr. Tompkins in Wonderland* and *One Two Three . . . Infinity*. I consider myself fortunate to have been fascinated by the mysteries of special relativity theory (depicted in *Mr. Tompkins in Wonderland*) and infinite set theory (depicted in *One Two Three . . . Infinity*), particularly the concept of cardinal numbers, during my younger years. I still feel some emotion when I encounter

a logic problem or discussion that uses the diagonal argument that I first learned when Gamow demonstrated the difference between two sets with different cardinal numbers (e.g., $\aleph_0$ and $\aleph_1$). During junior high school, I dedicated myself not to swimming but to gymnastics, particularly the horizontal bar. As with swimming, I ended up learning that I had no talent for gymnastics. At the same time, however, I was attending extracurricular classes in German and French, for the simple reason that I wanted to sing songs by Schubert and Édith Piaf. Moreover, NHK (Nippon Hoso Kyokai; the Japan Broadcasting Corporation) Radio had started offering German and French courses, which I also took. NHK currently offers television and radio courses in Chinese, Korean, Italian, Spanish, Russian, Arabic, and Portuguese, which would have attracted me if available at that time. During junior high and high school, I read basically everything I could get my hands on, but I sometimes was attracted by more academic books. The 12 volumes of Vladimir Smirnov's *A Course of Higher Mathematics: Advanced Calculus* had already been published in Japanese translation and were easy to read, so I held a reading club with my friends to read some of the volumes, such as the one on partial differential equations and the Hilbert space. At the same time, I held a journal club with other friends on Maurice Merleau-Ponty to learn stylish French by referring to a Japanese translation of *La Structure du comportement* (*The Structure of Behavior*) and *Phénoménologie de la perception* (*Phenomenology of Perception*). Although I was not convinced of all the arguments therein, my basic awareness of issues raised by these books may have determined the direction of my life.

At the time that I was considering enrollment in a university, I had not yet made up my mind about the future direction I would take. Although one of my high school teachers recommended that I enter law school to become a lawyer or statesman, I vaguely imagined myself working in academia. But lacking sufficient direction to imagine a specific theme of my life's work in academia, I vacillated between the physical beauty of the world's order, which I felt could be mathematically expressed, and the mysteries of the human mind, as described by poets and philosophers. At the end, I decided to study physics at the University of Tokyo as an undergraduate student.

After entering university, I continued to be uncertain about a course of study. However, the civil unrest of Mai 68 in France and the global anti–Vietnam War movement in the United States triggered a university-wide strike at the University of Tokyo, which provided me with time to consider my options. I tried my hand at everything from Bourbaki's *Éléments de mathématique* series to cultural anthropology and sociology; my favorites were Max Weber, Karl Mannheim, and Talcott Parsons. I have especially strong memories of tutorials in a student-initiated voluntary course given during the strike by Professor Shozo Omori, a professor at the University of Tokyo and a renowned phenomenologist and philosopher. In an introductory

seminar for students working in science, he discussed the philosophical foundation of natural science, based mainly on *The Logic of Scientific Discovery* by Sir Karl Raimund Popper. In fact, for more than 20 years, until I became a professor at the University of Tokyo School of Medicine in 1989, whenever possible, I participated in the annual meetings of the phenomenology and modern hermeneutics seminar conducted by Professor Yoshihiro Nitta of Toyo University. In later years, I had opportunities to work with Dr. Kei-ichi Noe, who was a colleague in this seminar and later became a leading Japanese philosopher. We co-organized symposia and lectures at the Science Council of Japan, exploring the points of contact between philosophy and natural science.

My wish to find a way to study the mysteries of the human mind using a clear natural scientific method was the *basso continuo* of my adolescence. I will never forget the impact of reading the chapter entitled "Neuronal Circuit" in *A Course of Biophysics* (Yoshioka Shoten, 1966), written by Professor Masao Ito, for the first time during high school. This introduction to the concept of the "Neuronal Circuit" strongly shook my heart. Before that, I could not imagine how I could reach the worlds of *The Structure of Behavior* and *Phenomenology of Perception*, given the properties of neurons and synapses generally presented in textbooks and popular books explaining the molecular, subcellular, and cellular properties of neurons in the brain. Reading that chapter made me an Ito fan, and I read his books written for the general public immediately after they were published. These included *Physiology of Neurons*, which was first serialized in the monthly journal *KAGAKU* (*Science*) published by Iwanami Shoten and later published as a book entitled *Neuron no Seirigaku* (*Physiology of Neurons,* 1972), in which more than one-third of the chapters were devoted to conceptualization and methodological discussion of neuronal circuit analysis. Eventually, I visited Professor Ito, who at the time was an associate professor in the Department of Physiology II at the University of Tokyo School of Medicine, to consult with him about my future career. I was not greatly interested in clinical medicine, which I thought evolved through the accumulation of practical knowledge and practice, and was less directed toward structured theorization and a systematic worldview. Nevertheless, I considered it fine to be enrolled in the Medical School (I was qualified according to university rules) if enrollment provided me with an option to conduct brain research. However, Professor Ito advised me to conduct physiological research under his supervision after I established an academic foundation in the Department of Physics. He kindly introduced me to Professor Setsuro Ebashi, another great physiologist and molecular biologist whom I respected. He had discovered troponin and had elucidated the roles of calcium in muscular contraction. Professor Ebashi's advice to me was the same as that of Professor Ito.

Ultimately, I decided to pursue my training as a vocational researcher in three steps: training in physics and mathematics during my undergraduate

studies, training in physiology in my graduate studies, and training in psychology during my postdoctoral fellowship. In Japanese, it can be expressed that physics explores the *kotowari* (essence) of the physical world, physiology the *kotowari* of the biological world and its functionality, and psychology the *kotowari* of the inner world and mind. I therefore decided to pursue my training in all three *kotowaris* (i.e., of the physical world, of the biological world, and of the inner world and mind). At that time, however, I was uncertain about how I would be able to develop my own academic field after these educational experiences.

The Ito Laboratory

I could hardly wait to study in Professor Masao Ito's laboratory. Of course, I enjoyed my physics studies as an undergraduate student. Like many of my classmates, I was absorbed by quantum field theory, particularly gauge theory and second quantization. However, unlike many physicists who were interested in biological phenomena, I did not believe that quantum statistical mechanics, which derive many important macroscopic physical rules from interactions among simpler elements, had the potential to provide a basic understanding of neural circuit dynamics through interactions among neurons and, ultimately, reach the world of *The Structure of Behavior*.

I started my graduate studies in the Ito laboratory in 1974. When I first met Masao, he was an associate professor at the University of Tokyo School of Medicine, and his laboratory was on the second floor of the School of Medicine Building 1. By 1974, he had already become a full professor, his laboratory had moved to the third floor of the same building, and many researchers from around the world were working in his laboratory. Those whom I directly met included Drs. S. M. Highstein, J. I. Simpson, B. Ghelarducci, M. Dufosse, P. J. Jastreboff, C. Batini, I. Orlov, R. T. Kado, C. D. Balaban, P. Tongroach, V. Chan-Palay, L. Karachot, and T. K. Hensch. Among them, Steve Highstein (1939–2014) later became a professor at Washington University School of Medicine in St. Louis, Missouri, after his residency in the Department of Neurology at Mt. Sinai Hospital in New York. Although Steve conducted his research mainly at Washington University, he often spent the summer at the Marine Biological Laboratories in Woods Hole, Massachusetts. This gave me the opportunity to enjoy yachting with him at Woods Hole, which remains a pleasant memory of my student days.

Professor Ito promoted the internationalization of Japanese neuroscience in various ways. As part of his efforts, he organized a number of international workshops to which Japanese and international researchers were invited. In August 1975, while still a student, I attended an international workshop held at a famous summer resort in Japan, Nikko, where I listened for the first time to presentations and discussions by leading women researchers, including Drs. Ann Graybiel and Victoria Chan-Palay.

The experience made a strong impression on me, as did Masao's determination to promote internationalization and diversity.

Within the Ito laboratory, Associate Professor Keisuke Toyama was responsible for educating the graduate students through journal clubs and seminars. Journal club took place at lunchtime every day, and a meeting to discuss our progress was held every Monday. In the journal club, laboratory members introduced a wide variety of topics covering many different biological fields in English. In addition to these activities, Professor Toyama let us take turns reading a variety of books, including *Man on His Nature, 2nd edition* (1951) by Sir Charles S. Sherrington, *Receptors and Sensory Perception* (1955) by Dr. Ragnar Granit, and *The Organization of Behavior* (1949) by Dr. Donald Hebb. Through these books, the thoughts of these legends in the history of neuroscience deeply affected my later research.

In the Ito laboratory, I devoted myself to studying the function of the cerebellar flocculus, a phylogenetically old area in the cerebellum, in the adaptive control of the vestibulo-ocular reflex. Professor Ito was an advocate of the theoretical hypothesis in systems neuroscience stating that the cerebellum is a "learning machine" responsible for motor learning (Ito, 1970, 1984). This hypothesis is now called the Marr-Albus-Ito model of the cerebellum (Marr, 1969; Ito, 2006). This theory provides the basis for a comprehensive understanding of the functions of the cerebellum, including both the phylogenetically old vestibulo-cerebellum and the phylogenetically newer neocerebellum, which is the part of the cerebellar hemisphere that has evolved the most in humans. To experimentally verify this comprehensive theory, Professor Ito selected the vestibulo-cerebellum, whose anatomical input-output connectivity has been well analyzed and is known to control a simple motor circuit, the tri-synaptic arc of the vestibulo-ocular reflex. This research strategy impressed me a lot.

In daily experiments, I was responsible for a project aimed at elucidating the role of the inferior olive. The core concept of the Marr-Albus-Ito theory is that input from the inferior olive to the cerebellum supplies an error signal that modifies the activity of the cerebellum as a learning machine (Ito, 1974). My mission in this project was to collect experimental evidence addressing this core concept. I sought to accomplish my mission using two approaches. One approach was to record the activity of Purkinje cells to elucidate how inferior olivary input affects the dynamics of the local network within the cerebellum. The other was to use lesioning to obtain causal evidence of the role of inferior olivary input. In later years, the two-pronged strategy of that project would significantly affect my own research strategy toward the elucidation of higher brain function.

Purkinje cells, the only output cells in the cerebellum, receive input from two sources: climbing fibers and mossy fiber-granule cell-parallel fibers. Climbing fibers originate in the inferior olive and directly input to Purkinje cells. In the experiment, we simultaneously recorded both climbing

fiber-derived neural firing (complex spikes) and parallel fiber-derived neural firing (simple spikes) in Purkinje cells, and we analyzed how complex and simple spikes change over time along with the progression of adaptive changes in the vestibulo-ocular reflex at the behavioral level (Dufosse et al., 1978; Masao arranged the author names of a paper in alphabetical order). We then investigated whether the observed changes were consistent with the patterns of change theoretically predicted by the Marr-Albus-Ito model. The results of the experiment were quite consistent with the theoretical prediction (Ito et al., 1979). This experience again had a strong impact on my view of the role of theory in systems neuroscience.

In addition to recording single-cell activity for analysis of local network dynamics, I eagerly committed to a lesion experiment. At that time, neither optogenetic techniques, such as the use of ArchT, nor pharmacological neural inhibition techniques with muscimol, both of which we use frequently now (Miyamoto et al., 2017, 2018; Setsuie et al., 2020), were available to inhibit neuronal activities. Therefore, electrocoagulation was the only choice for lesioning a brainstem nucleus. However, the inferior olive is surrounded by a large number of nuclei within the brainstem that are essential for life. Consequently, when using electrocoagulation to destroy the inferior olive or cut the visual input fibers running from the pretectum to the inferior olive, even a slight inaccuracy in the targeting threatens the life of the animal. It was an extremely difficult experiment. Eventually, we reached a conclusion. Both the destruction of the inferior olive and the cutting of the visual input from the pretectum to the inferior olive led to the loss of adaptability of the vestibulo-ocular reflex (Ito and Miyashita, 1975; Miyashita et al., 1980), which provided experimental support for the Marr-Albus-Ito model of the cerebellum.

My experience in the Ito laboratory deeply affected my later research. It was there that I realized the power of empirical studies of brain function. I was convinced that, in principle, it should be possible to approach the world described in *The Structure of Behavior*, starting with studies of individual neuron activities and network dynamics. Although I had not understood at that time the great distance between "in principle" and "actual" understanding, this experience led me to select systems neuroscience as the field in which I would conduct my life's work. It was also in the Ito laboratory that I became aware of the importance of both correlational approaches, such as recording single-cell activity, and causal approaches, such as lesion experiments, and their complementarity in empirical studies of brain function. This led me to apply a combination of correlational and causal approaches at various phases of my later research. In addition, I had come to believe that to acquire an understanding of a large research target, such as the motor learning function of the cerebellum, I should focus on elucidating the mechanism of a model (or "prototype") system that includes the simplest function among those implemented in the target system. Later in

life, I thoroughly investigated the simplest model or paradigm (i.e., prototype model) every time I started to study a new higher brain function. An example of the simplest model I chose for the neurophysiological study of declarative (or explicit) memory was the "pair-association memory" paradigm (Sakai and Miyashita, 1991; Miyashita, 2004, 2019), in which I considered the associative nature of long-term memory to be highlighted in its simplest form. Using the same principle, I chose and developed the feeling-of-knowing (FOK) paradigm (Kikyo et al., 2002; Miyashita, 2004) and postdecision wagering confidence paradigm for metamemory (Miyamoto et al., 2017; Miyashita, 2019) for my neurophysiological studies in systems neuroscience. I could not have developed these paradigms for neurophysiology without my experiences in the Ito laboratory. Finally, it was there that I learned the importance and difficulty of presenting and publishing highly original new findings at a high level of international visibility. Masao fought a lot of battles against his competitors at conferences and through publications. In the battles around the cerebellar learning theory and the discovery of the long-term depression of cerebellar Purkinje cell synapses (with which I was not involved), he won the most important ones, but it took many years.

By 1980, Professor Ito's scientific interest had shifted to long-term depression of cerebellar Purkinje cell synapses. I understood the importance of this phenomenon well, as it was the last piece of the hypothetical elements in the Marr-Albus-Ito model of the cerebellum. However, the time had come for me to leave Masao and to start my own research program. I had already decided on the general direction of my future research: I wanted to explore the human inner world, tapping into the world described in *Phenomenology of Perception*. But I knew that I had not yet received sufficient training in psychology to do so. Accordingly, I wondered where I should train myself while working as a postdoc. The laboratories of Drs. Evarts and Wurtz at the U.S. National Institutes of Health (NIH) were options I considered first. I respected Drs. Ed Evarts and Bob Wurtz as great pioneers who were running cutting-edge laboratories using monkeys. In 1983, I had an opportunity to visit NIH, where Mickey Goldberg and Oki Hikosaka kindly welcomed me. I was deeply impressed by Mickey's proud words, "My lab is the best small lab in the world. Smallest and best!" Since then, Drs. Goldberg and Hikosaka have become my best friends in the primate physiology community. However, the studies being conducted in the laboratories of Drs. Evarts and Wurtz were already too firmly established for me; I wanted to conduct my investigations in a less mature field, where I was free to find a new research target of my own. Motor control of the upper limbs or the oculomotor control had already been developed as complete model systems in primate physiology and thus awaited thorough physiological investigation. What I needed was basic training in psychological thinking and experimentation. I sought the opportunity to obtain such training

in the Department of Experimental Psychology at University of Oxford. But one of the subliminal reasons I decided to go to Oxford may have been my longing for the origin of neuroscience, which was traceable back from Masao Ito, to Sir John C. Eccles, and finally to Sir Charles Sherrington.

Department of Experimental Psychology at Oxford

In April 1984, I became a visiting lecturer in the Department of Experimental Psychology at University of Oxford. My wife Naomi and I initially lived at Halifax House on South Parks Road, a guesthouse for the university at that time, until we found a terraced house in Cunliffe Close facing Banbury Road. We enjoyed our life in Halifax House, although I made a mistake at the very start. It was Easter Monday when I went for the first time to the Experimental Psychology/Zoology Building (i.e., Tinbergen Building) on South Parks Road; of course, it was closed. Noticing I was in trouble, a bearded gentleman helped me enter the building through a side entrance. This was the first time I met Professor Larry Weiskrantz. I am ashamed to say that I did not know that this gentleman was the head of the Department of Experimental Psychology and a discoverer of blind sight.

I enjoyed my life in the Department of Experimental Psychology. At afternoon teatimes, I very much enjoyed talking with the other researchers, which included legendary pioneers, such as Professors Larry Weiskrantz and Donald Broadbent, as well as young up-and-coming researchers of the time, such as Dr. Dick Passingham. However, this was only possible when my experiment was going well and I could join them at 4 p.m. I did not initially develop a rapport with Jon Driver, because he seemed to be difficult; that is, until our departmental Christmas party, where he showed up wearing a stuffed bunny on his waist, and I finally could have a sort of chat with him, a distant memory for me.

I learned a lot at the Department of Experimental Psychology. I was fortunate enough to receive training in behavioral testing in monkeys from Professor Alan Cowey, in lesion experiments from Dr. David Gaffan, and in neurophysiology from Dr. Ed Rolls. Chantal Stern and Mike Hasselmo, who are currently at Boston University, were graduate students working on the same floor as me and gave me a lot of practical tips for experiments. Dr. Gaffan taught me some fundamental principles and know-how for monkey experiments, which I had previously lacked. I learned from him that, in designing experimental behavior tasks, it's crucial to maximize monkeys' spontaneous behavior by taking their ecology into account and to measure their behavior as quantitatively as possible using advanced information technology devices. For example, David and Ed took leadership roles in employing touch panels in the laboratory more than 20 years before the iPhone was equipped with such an interface. My interaction with David continued after I returned to the University of Tokyo. I have a

pleasant memory of a dinner at David's home, with Drs. Mort Mishkin and Betsy Murray, when I visited Oxford University again in 1994. At the EBBS Symposium to mark David's retirement held in Queen's College, Oxford in 2011, I had the opportunity to catch up with old friends, including Drs. Mark Buckley, Madeline Eacott, and John Duncan, and to get acquainted with rising stars such as Dr. Mathew Rushworth. Although I learned a lot in the Department of Experimental Psychology, my background at that time limited the experiments that I could contribute to at Oxford and ultimately get published, to those related to neurophysiology. I owe most of my publications during this period to the supervision of Dr. Rolls (Miyashita et al., 1989).

Discovery of Memory Neurons in Tokyo

Discovery of Pictorial Short-Term Memory Neurons

In 1985, I returned to the University of Tokyo School of Medicine, where I took a position as a university lecturer and launched my monkey laboratory. I started my journey from a small corner of the Department of Physiology, with only two Japanese macaque monkeys (*Macaca fuscata*) and one DEC PDP11 computer. As my goal, I borrowed the phrase "My lab is the best small lab in the world," which I had heard from Micky Goldberg a few years before, and I worked like a horse. Because the experiment control software programs that are now commercially available from many companies had not yet been developed, I wrote an assembler program for the PDP11 (and later for the VAX11) with functions related to experimental sequence control, video display control, monkey behavior control, and recording time series of spike firing.

Then, I had to ask: what's the target of study? After wavering, I decided to search for neurons responsible for visual memory in the visual association area in the monkey temporal cortex. I had rationales. My experiences at Oxford made me aware of the depth of the study of memory. Pioneers in the physiology in memory, including Professors John O'Keefe and Tim Bliss, tended to select the hippocampus as their target area of study, with good reason. I asked myself, "What should I select, particularly considering a linkage with general cognition?" I repeatedly read the papers of Professor Brenda Milner (e.g., Scoville and Milner, 1957; Milner, 1968, 1972) and had become convinced that the cortical association areas, rather than the hippocampus, should be studied to explore the seats in the brain that are related to ultimate storage of long-term memory as well as the dynamic expression of short-term and working memory. This belief mostly arose from the fact that, in patient H.M., the retrograde amnesia was relatively mild, or sometimes absent, despite severe anterograde amnesia (Scoville and Milner, 1957; Milner, 1968; Squire et al., 1975; Squire and Wixted, 2011). Then, which cortical association area should I study? Visual research was the

major battlefield on which the largest number of excellent researchers were competing across the world. I therefore wanted to compete in that field. In addition, I was familiar with the field of visual research. When I was a graduate student, Dr. Keisuke Toyama, an associate professor in the Ito laboratory, was a physiologist recording neuronal activities in the primary visual cortex of cats. Professor Toyama encouraged us to read the classic papers on visual physiology, including those written by Drs. Hubel and Wiesel, as well as articles and reviews on neuronal activities in the inferior temporal cortex written by Dr. Charles Gross (Gross et al., 1969, 1972) who was one of my heroes. Moreover, I was a long-term follower of Dr. David Marr, starting from the monumental paper on his model of the cerebellar cortex (Marr, 1969), to many MIT AI MEMOs for computer vision and related papers (Marr, 1976, 1980; Marr and Poggio, 1979), and finally to his book *VISION* (Marr, 1982).

I then had to design a specific experiment. I wanted to use monkeys as subjects and to have them perform tasks that enabled me to make quantitative measurements under conditions in which their behavior could be controlled as rigorously as possible. Ultimately, I decided to start with a delayed matching-to-sample (DMS) task. The DMS task is a form of conditional discrimination and is quite popular for studying learning and memory in animals. During the task, a trial is begun by presenting the subject with a stimulus (a visual object in a visual task), the "sample" stimulus, which the subject is required to remember. The subject is then required to identify from a subsequent set of stimuli, the "choice" stimuli, one that "matches" the sample. In my laboratory, I placed a computer-controlled video display with a transparent touch pad in front of each monkey to rigorously control the presentation of visual stimuli and the monkey's responses (although quite popular now, it was a unique setup in the mid-1980s). I wanted to set the duration of presentation of each visual stimulus in each trial to be as short as possible. I also wanted to set the delay time to be as long as possible. Delay time, the duration of the period between the sample and choice stimuli, during which nothing except a fixation spot is displayed on the screen, is a key factor in memory load. The two Japanese macaques, Tami and Chie, were great! (By the way, "ta" and "chi" are adjacent phonemes in the Japanese language.) Both monkeys were cooperative in the experiments and performed hundreds of trials each day. I worked to maintain their motivation by preparing their favorite foods (bananas, potatoes, and raisins) in the laboratory. In this way, I started my experiments on the physiology of memory using a DMS task with 0.2 seconds of visual stimulus presentation and 16 seconds of delay time.

During my basic training at Oxford, I learned the importance of controlling the sample size of stimuli—that is, the differential impact on behavioral testing with a small stimulus set and that with a large stimulus set (e.g., see a later paper by Eacott et al., 1994). Initially, I considered using many pictorial

stimuli that could serve as trial-unique stimuli. These stimuli needed to be eye-catching to attract the interest of the monkeys. Through trial and error, I created fractal patterns utilizing a fractal algorithm, which enabled me to produce countless different visual graphics using a small number of parameters (Miyashita et al., 1991). This in turn enabled me to design an experiment in which trial-unique graphic stimuli were used in DMS tasks.

From 1985 to 1986, I immersed myself in experiments, devoting myself to recording single-neuron activity using microelectrodes from morning to evening, every day. I worked with Han Soo Chang, a neurosurgeon in the Department of Neurosurgery at the University of Tokyo Hospital, who was studying as a graduate student in the Department of Physiology. In the Ito laboratory, as in many other electrophysiology laboratories around the world, electrical signals reflecting spike firing obtained with microelectrodes were monitored as audio signals that were output from speakers after being amplified and input into a computer. Every day, we concentrated on the sounds of spike firing coming from speakers while monitoring the behavior of the monkeys.

Then, one day in 1986, I heard a series of consecutive strong spike firing sounds that continued for 16 seconds. It was so sudden that I was not sure what had happened. The strong sounds of spike firing occurred only once and never again during the succeeding trials for more than 10 minutes. Nonetheless, I was certain the sounds reflected highly specific spike firing. The sound must have been produced when the neuron fired strongly in response to a particular picture during the recording; I could not think of another reason for the sound. Therefore, although it was unusual, I had no choice but to repeatedly show that particular picture to the monkey to reproduce this phenomenon. I quickly re-wrote the PDP11 software to repeatedly show a particular picture every 10, 20, or 30 trials. The main concern was that the neuron being recorded would move away from the tip of the electrode while I was rewriting the program. Thirty minutes later, I conducted the test again, and the strong consecutive spike sounds returned. I was convinced that there were neurons in the inferior temporal cortex that strongly responded only to a particular picture and continued firing during the 16-second delay time after the picture disappeared from the screen.

Subsequently, however, it was not easy to reproduce this finding. There was no way to predict which neuron would respond to what picture, and most neurons did not respond to any of the pictures tested (rigorously speaking, most neurons responded to some or several stimuli, but only with much weaker firing than the strong firing that I found on the "discovery day." I was convinced that those weaker firings represent "suboptimal" responses of the neuron, just like the "suboptimal" responses seen in the earlier visual areas). I was a skilled electrophysiologist and had a technique for keeping each single neuron at the tip of an electrode for an hour or even longer, but throughout that hour or so, during which I tested more than 100 pictorial

stimuli, most of the neurons examined did not encounter the "optimal" pictures to which they would strongly respond. I finally overcame this difficulty by reducing the sample size of stimuli, and I successfully reproduced the finding within a practical testing time during which a single neuron could be kept stably at the electrode tip.

In July 1987, only two years after returning from Oxford and starting my own experiments, I wrote a paper on this finding and submitted it to the journal *Nature*. This paper, entitled "Neuronal Correlate of Pictorial Short-Term Memory in the Primate Temporal Cortex" (Miyashita and Chang, 1988), was accepted in November 1987 and published in January 1988.

Discovery of Visual Long-Term Memory Neurons

From the time that I discovered short-term memory neurons, I wondered whether a neuron responds to a particular picture by coincidence or as a result of learning. Through experiments conducted under various conditions to reproduce the finding in short-term memory neurons, I became convinced that the response was a result of learning. I formulated a hypothesis that these neurons constitute a neural basis that is responsible not only for short-term memory but also for storage of long-term memory of visual objects ("long-term memory neuron hypothesis"). Immediately after I posted the paper on short-term memory neurons to *Nature*, I fully engaged in a study to test this hypothesis. I had to conduct this study myself because Han Soo Chang had already left the Department of Physiology and returned to the Department of Neurosurgery. Whereas I had discovered short-term memory neurons serendipitously, to test the long-term memory neuron hypothesis, I had to proceed logically. I constructed the logic of the associativity of long-term memory and collected physiological evidence to demonstrate that logic. I already knew what kinds of neurons needed to be recorded and where in the temporal cortex I could find such neurons. I collected data quickly, all of which beautifully supported my hypothesis, and I submitted a paper on this theory along with the supporting evidence to *Nature* in July 1988. This paper, entitled "Neuronal Correlate of Visual Associative Long-Term Memory in the Primate Temporal Cortex," was accepted in September and published in October 1988 (Miyashita, 1988). I am proud of this single-author paper, which was the first to report neurons that encoded long-term memory engrams in the cortical association areas.

This paper convincingly demonstrated the existence of long-term memory neurons with high probative value. However, I wanted to further broaden our understanding of this finding in two directions. First, I wanted to extend the finding by discovering the neuronal correlates of memory retrieval, as the October 1988 paper dealt with neuronal representation of long-term memory engrams (i.e., the mechanism of memory storage). Second, because the logic in the October 1988 paper was based on artificial experimental

conditions (i.e., associativity was defined based on the order of displayed pictures), I wanted to confirm the finding under experimental conditions that were commonly used in psychology. These two aims could be achieved by introducing a behavioral task called a *pair-association memory* task into the electrophysiological study of monkeys. Pair-association memory tasks are standard memory tasks that were formulated in human neuropsychology and are included in psychological test batteries, such as the Wechsler Memory Scale–Revised (WMS-R), which are widely used around the world. In the WMS-R, the task is included under the category of the verbal and visual *paired-associate learning* test. Typically, people are asked to learn unrelated word pairs (e.g., elephant–rose) (verbal paired-associate learning test) or picture pairs (visual paired-associate learning test). At a later time, memory of those pairs is tested by having subjects recall one of the words/pictures in response to the word/picture it was paired with during encoding (e.g., recall the word that was paired with "elephant"). In our task, monkeys learned a large number of picture pairs and were trained to recall the paired associate of the presented cue stimulus.

It took two years to complete this study, and our findings were published in *Nature* in 1991 (Sakai and Miyashita, 1991). In this paper, we reported that monkeys could learn the *pair-association memory* task using visual stimuli, and that *pair-coding neurons* responsible for memory storage and *pair-recall neurons* responsible for memory retrieval could be identified within the framework of the task. Kuniyoshi Sakai, who was the first doctoral student in my laboratory, contributed prominently to this study.

The observations of this study were confirmed and developed in subsequent studies. Dr. Albright's group demonstrated how the pair-coding property of the neurons develops in the course of the paired-associate learning in monkeys (Messinger et al., 2001; Albright, 2012). Another group also demonstrated a development of single-unit activity through visual stimulus association learning in monkeys (Erickson and Desimone, 1999). We demonstrated forward processing of encoding of stimulus-stimulus association memory in monkey inferotemporal cortex, and clarified the difference of memory encoding between the perirhinal cortex and area TE (Naya et al., 2003). Regarding the retrieval signal, we further clarified that the pair-recall neurons are activated with precise timing when the necessity for memory retrieval and its initiation time were signaled by an independent color switch rather than by the cue stimulus itself, suggesting the involvement of the pair-recall neurons in neural circuits underlying the on-demand reactivation of the representation under cognitive control (Naya et al., 1996). Therefore, the discovery of the pair-recall neurons has been frequently cited as some of the best neurobiological evidence supporting the "*reactivation*" theory of remembering (Buckner and Wheeler, 2001; Badre and Wagner, 2007; Danker and Anderson, 2010). The *reactivation theory* posits that domain-specific cortical regions and neurons are reactivated during vivid

remembering and contribute to the contents of a memory. This theory has a long history, but it became popular after many functional magnetic resonance imaging (fMRI) studies found that certain brain regions that process incoming (bottom-up) perceptual information are also involved in representing that information during remembering (e.g., O'Craven and Kanwisher, 2000; Ishai et al., 2000). Finally, our 1991 study enabled us to identify the roles played by the memory neuron groups we discovered in various neuropsychological and clinical contexts, including human memory disorders. In 1993, for example, a study by Drs. Murray, Gaffan, and Mishkin (1993) reported that learning of a visual pair-association memory task by monkeys was impaired by a lesion in the temporal cortex (Murray et al., 1993), thus demonstrating the causal roles of the memory neuron group that we discovered. I synthesized these new discoveries into a neurophysiological theory of memory (Miyashita, 1993, 2004).

The discovery of the neural correlate of cortical long-term representations in explicit memory also opened up a door for neurobiologically reexamining some long-standing debates that had been mostly addressed only by behavioral or psychological approaches. One example is the issue of storage versus retrieval and the nature of memory impairment (for a review, see Squire, 2006). When memory impairment occurs, particularly after brain damage, including electroconvulsive therapy, head injury, and drug-induced amnesia, a question arises whether the impairment reflects impaired information storage ("storage deficit" view) or impaired accessibility ("retrieval deficit" view). Beginning in the 1970s, a considerable amount of work targeted the issue, but all the evidence was indirect based on behavioral analysis. We tackled the question directly with my monkey model of paired-associate learning (Higuchi and Miyashita, 1996) by applying the split-brain technique (one half of the hemispheres supported behavior, and the other half allowed for an evaluation of the lesion effects on pair-coding neurons). The study demonstrated that an ibotenic acid lesion of the rhinal cortex (perirhinal and entorhinal cortex) impaired the formation and maintenance of the associative representations between pairs of visual stimuli in area TE (adjacent lower-order neocortex). Thus, the findings demonstrated a strong case for the "storage deficit" view, providing some of the best evidence that memory loss involves an actual loss of the synaptic changes that support a memory.

Impact of the Discovery of Memory Neurons on the Neuroscience Community

After being recognized for my discovery of short-term and long-term memory neurons, I was assigned to take over Professor Masao Ito's position at the university, and in 1989, I became the professor of the Department of Physiology in the University of Tokyo School of Medicine. I was more

frequently invited to international symposia and had more opportunities than before for discussion with the world's leading scientists. At the 13th European Conference on Visual Perception (ECVP90) held in Paris in September 1990, I met many rising stars with whom I have stayed friends for many years, including Drs. Bill Newsome, Patric Cavanaugh, and Shimon Ullman. I was particularly impressed by the achievements of Dr. Newsome, whose monumental work demonstrated a causal linkage between stimulus-selective neuronal firing and its behavioral impact in perception through microstimulation within area MT in monkeys. I remember a long discussion with Bill during the banquet at the senate held at ECVP90; our conversation was even more memorable than the taste of Sauternes and foie gras (although I no longer eat foie gras) at the banquet. In fact, at that time, Bill suggested that I should electrically stimulate my memory neurons and observe the behavioral impact of the stimulation, just as he did with direction-selective neurons in area MT. I never forgot his suggestion. But it took more than 20 years for me to complete the experiment and publish the results (Tamura et al., 2017): optogenetic stimulation of the memory neurons indeed provided strong behavioral impact as demonstrated by the stimulation-dependent shift of psychometric function for recognition. Both conceptual and technological refinements, including optogenetics in monkeys, were necessary during the 20-year interval.

The Fourth Conference on the Neurobiology of Learning and Memory, held at the University of California at Irvine the following month, in October 1990, also made a deep impression on me. I was so glad to meet Professor Jim McGaugh for the first time at this meeting. More importantly, I was overwhelmed by Professor Larry Squire, who served as a leader of the introduction and discussion sessions in the meeting, because of his long-range perspective and outlook based on clear rationales and broad knowledge. Since then, I have learned a lot from him at every turning point in my research.

To enable Japanese neuroscience to contribute to an international research alliance, we held a symposium entitled "Computation, Cognition, & Consciousness" at the International Institute for Advanced Studies in Kyoto from August 31 to September 3, 1994. The lectures from both experimental and theoretical neuroscientists, including Drs. Marcus E. Raichle, Michael Petrides, Edmund T. Rolls, Christoph von der Malsberg, and Jack D. Cowan, were amazing. In addition, I also invited philosophers specializing in mind-body problems, including Drs. Daniel C. Dennett, Owen Flanagan, and Junichi Murata, who were keen to engage in interdisciplinary exchanges with empirical scientists, particularly neuroscientists. In so doing, I was trying to realize my youthful dream of stimulating exchanges between philosophers and neuroscientists. In particular, a lecture by Dr. Daniel C. Dennett, entitled "Consciousness in Human and Robot Minds," led to a heated discussion among participants. Furthermore,

Dr. Michael Gazzaniga's lecture, "Consciousness Is an Instinct," deepened the discussion and impressed both neuroscientists and philosophers. The texts of these lectures were published in *Cognition, Computation, & Consciousnes* in 1997 by Oxford University Press.

Discovery of the Top-Down Signal from the Prefrontal Cortex

The discovery of memory neurons gave me an important basis for my life's work. This prompted me to proceed further toward my distant dream of understanding how activity of the mind, as a psychological reality, emerges from the activity of the entire brain. Technically, as will be mentioned later, one of my new research directions was to measure whole-brain activity using neuroimaging, in particular, fMRI. Another new direction was to delve into such whole-brain activity toward the level of cellular network dynamics. To do that, I then took aim at the causal cognitive role of interaction between two brain regions and its physiological mechanisms in memory retrieval.

The theoretical basis of memory retrieval has long been discussed in a broader context of cognitive control (Tulving, 1985; Norman and Shallice, 1986), positing that the central function of memory retrieval is to bring knowledge to mind that is relevant to current goals and actions. Sometimes knowledge relevant to our goals comes to mind automatically, in a bottom-up fashion, simply by processing cues in our environment ("automatic retrieval"), typically when stimulus-stimulus or stimulus-response associations are strong. Often, however, relevant experiences from the past or facts about the world do not readily come to mind. In these instances, we must strategically search memory or trigger a strategic retrieval attempt and monitor its outcome ("controlled retrieval"; for more recent views on automatic and controlled retrieval, see Buckner and Wheeler, 2001; Badre and Wagner, 2007). The prefrontal cortex was considered to play a central role in controlled retrieval because patients with frontal cortical lesions often show retrieval difficulties, in particular when the specific context (or source) of an episode must be remembered or when minimal cues are provided to aid retrieval (Stuss and Benson, 1984; Schacter, 1987; Shimamura, 1995). On these grounds, I hypothesized that in controlled retrieval, a search signal for memory retrieval originates in a frontal lobe process and is sent to the memory neurons in the temporal lobe. I called this hypothetical signal "top-down signal for memory retrieval." I also formulated a "strong version" of the top-down signal hypothesis whereby both bottom-up signals from the retina and top-down signals from the frontal lobe converge at temporal cortical memory neurons. If it is verified, the "strong version" of the top-down signal hypothesis would provide a neurobiological basis for the classic cognitive control theory of automatic and controlled retrieval (Norman and Shallice, 1986) as well as the "reactivation theory of remembering" that was

described in the previous section, "Discovery of Visual Long-Term Memory Neurons."

Until our discovery of pair-recall memory neurons in the temporal cortex in 1991, there had been no clue or experimental starting point to investigate the neurobiological basis of controlled retrieval, more specifically, no starting point to seek a top-down signal for memory retrieval as a physiological reality. The discovery of pair-recall neurons provided a starting point. I made a plan to demonstrate the existence of a top-down signal for memory retrieval and to analyze its specific characteristics using a physiological approach. To do that, I needed to conduct experiments in monkeys, but I wondered how to make monkeys perform controlled retrieval. I realized that I had to start by developing an experimental paradigm for monkeys.

Since my time in the Ito laboratory, I had been interested in the human split-brain studies conducted by Drs. Sperry and Gazzaniga (Gazzaniga, 1966, 1995) and I had used a split-brain monkey model in my study of the "storage vs retrieval deficit" debate of memory impairment (Higuchi and Miyashita, 1996). One day, when I was trying to develop an experimental paradigm of controlled retrieval for monkeys, I came across a case report written by Dr. Gazzaniga's group on memory retrieval in a patient with a partially split brain (Sidtis et al., 1981). This report detailed the process of controlled retrieval in this patient who had undergone partial posterior callosal commissurotomy (i.e., a posterior split-brain patient), based on the patient's verbal report. For example, when the word "Knight" was presented to the left visual hemifield (i.e., to the right primary visual area) of patient J.W., he answered, "I have a picture in mind but can't say it . . . Two fighters in a ring . . . Ancient wearing uniforms and helmets . . . on horses trying to knock each other off . . . Knights?"

Having got a clue from this article, I developed a partial split-brain (posterior split-brain) model that enabled me to make monkeys perform controlled retrieval. Because monkeys could not work in a verbal recall task, I designed a modification of the visual pair-association memory task. In this task, monkeys learned many pairs of different pictures, and a trial started when a randomly selected picture (cue picture) from a pair was presented to the right or left visual hemifield of the monkey. Then, choice pictures, including the paired associate of the cue picture, were presented to the right or left visual hemifield or both hemifields, depending on the recall conditions ("intra-hemispheric" recall or "inter-hemispheric" recall). Our behavioral experiment tested the inter-hemispheric transfer of memory engram of the paired associates and also tested the ability of inter-hemispheric cued-retrieval in the posterior split-brain monkeys. The experiment provided statistically robust evidence that memory control signals are produced in the frontal lobe of the cerebrum (i.e., brain regions dependent on the circuit that sends interhemispheric commissural fibers through the anterior part of the corpus callosum, including the genu), whereas long-term memory

engrams of visual objects are located in the temporal lobe. We published the results in *Science* (Hasegawa et al., 1998). Please note that case studies in humans provide us with very interesting anecdotal findings, but it is difficult to statistically test the results. This behavioral evidence from monkeys also clarified the involvement of long-term memory engrams that reside in the memory neurons in the temporal lobe, and their functional roles in whole-brain neuronal circuits for controlled retrieval.

I was then ready to conduct an experiment to detect a top-down signal at a microelectrode tip during controlled retrieval. I designed this experiment to test the "strong version" of the top-down signal hypothesis whereby both bottom-up signals from the retina and top-down signals from the frontal lobe converge at temporal cortical memory neurons. Several aspects of this experiment required a high level of technical skill. For the experiment, the partial split-brain (posterior split-brain) monkeys learned and performed the modified visual pair-association memory task that was described in the previous paragraph. The monkeys were required to maintain fixation while they performed the pair-association memory task under both "intra-hemispheric" recall and "inter-hemispheric" recall conditions. A microelectrode recorded single-neuron activity in the temporal cortex over the course of several hours. If my "top-down signal for memory retrieval" hypothesis was correct, the top-down signal from the prefrontal cortex should be recorded in the "inter-hemispheric" recall condition. Here the cue stimulus is presented to the hemifield ipsilateral to the recording site. In this condition, the cue signal should travel a long way to reach a neuron recorded in the temporal cortex. The signal would first be sent to the contralateral primary visual area, then up to the contralateral frontal cortex, and, after being processed and traversing the anterior corpus callosum, eventually would reach temporal cortex as a top-down signal. The bottom-up signal should be recorded in the "intra-hemispheric" recall condition. In this condition, the cue stimulus is presented to the hemifield contralateral to the recording site and thus sent directly to the ipsilateral primary visual area and to neurons in temporal cortex. This task was difficult to conduct without highly motivated and cooperative monkeys. Hyoe Tomita, a graduate student in my laboratory, completed this difficult experiment and provided strong evidence for the hypothesized top-down signal for memory retrieval. We published the results in *Nature* (Tomita et al., 1999).

This experiment was the first to detect the top-down signal at the microelectrode tip and enabled analysis of the specific characteristics of the top-down signal. For example, we found that top-down signals conveyed categorical information about each picture, whereas bottom-up signals conveyed information specific to individual pictures. Through this study, we opened up a new way to characterize top-down signals using a rigorous electrophysiological method. Furthermore, the study also found that both the top-down and bottom-up signals converge onto a single temporal cortical

neuron, which directly supported the "strong version" of the top-down memory retrieval hypothesis. Thus, it lent novel neurobiological support to classic ideas, such as controlled retrieval theory and reactivation theory of remembering as discussed previously (Miyashita and Hayashi, 2000). The figures included in this paper were cited in *Principles of Neural Science, fifth edition* (Kandel et al., McGraw-Hill Medical, 2013), and the paper has been recognized as a groundbreaking article that substantiated the concept of top-down signals.

Toward a Comprehensive Understanding of the Cortical Memory System: Local Circuits and Global Networks

The discovery of top-down signals in controlled retrieval ignited an ambition to conduct a comprehensive analysis of brain-wide cortical mechanisms related to declarative memory (explicit memory), with the goal of elucidating the whole picture of the activities of both local circuits and global networks within the monkey cortex. I endeavored to fulfill that ambition for over 15 years. During that time, my achievements included the discovery of recall signals for automatic memory retrieval, which are transmitted between areas in the temporal cortex in a retrograde manner (Naya et al., 2001); elucidation of the roles of the premotor area of the frontal lobe in output control in a sequence of memorized items (Ohbayashi et al., 2003); elucidation of the roles of temporal cortical memory neurons in working memory, particularly in the presence of distracters (Takeda et al., 2005); optogenetic proof that readout from memory neurons in the temporal cortex causally affects memory-based judgments (Tamura et al., 2017); and analyses of local circuit dynamics that enable encoding and retrieval in the memory neurons in the temporal cortex (Takeuchi et al., 2011; Hirabayashi et al., 2013a, 2013b; Takeda et al., 2015; Koyano et al., 2016). The initial concept of this long-term project was explicitly described in a review article published in *Science* in 2004 (Miyashita, 2004), and the findings were summarized in a review article published in the *Nature Review of Neuroscience* in 2019 (Miyashita, 2019).

In the course of these studies, we had to develop several new technologies ourselves. For example, to investigate local neuronal circuit dynamics within the cortical association areas (e.g., the perirhinal cortex or area TE), it was necessary to determine in which of the six layers of the cerebral cortex the neurons of interest were located, while recording single-neuron activity in monkeys during a cognitive task. At that time, however, there was no technology to make this possible. Therefore, Teppei Matsui and Kenji Koyano, who were graduate students in my laboratory, and I developed a new method to accomplish this using high-field MRI. The tip of a microelectrode inserted into the monkey cortex is typically invisible in conventional MRI because of a partial volume effect, but we demonstrated that the

position of the electrode tip can be detected in high-resolution structural MR images with enhanced detectability. With this technique, the electrode image is made very thick by the enhancement caused by the interaction between the static magnetic field and the electrode metal, while the spatial resolution along the electrode is preserved. Using this method with fast spin echo 4.7T MR imaging, Matsui et al. (2007) were able to identify microelectrode tip locations with single-voxel accuracy (less than 100 μm) (Matsui et al., 2007). At present, 7 T MRI enables determination of tip locations at a voxel size of 50 μm or less.

In addition, we developed another, perhaps more easily accessible, method than the MRI method, which uses current-source-density (CSD) analysis and a linear-array multichannel electrode. The CSD is a reflection of the net transmembrane currents in a local neuronal ensemble and is calculated from stimulus-evoked local field potentials recorded at different depths within the cortical tissue (Nicholson and Freeman, 1975). We found that, within the temporal association cortex, the earliest current sink induced by an optimal visual stimulus provides a good estimate of the position of the granular layer (layer 4) (Takeuchi et al., 2011). Therefore, this method enabled us to assign a large number of simultaneously recorded neurons into a supragranular layer (layers 2/3), granular layer (layer 4), and infragranular layer (layers 5/6). We then analyzed the time series of simultaneously recorded neuronal spikes using spike-spike time series correlation and the Granger-causality method, which enabled us to determine the flow of signals between neurons (Hirabayashi et al., 2010, 2013a, 2013b; Takeuchi et al., 2011; Hirabayashi and Miyashita, 2014; Takeda et al., 2015).

The development of these new technologies enabled us to elucidate the dynamics of the neuronal circuits underlying memory retrieval. Here, I briefly summarize the findings of my studies on the cortical semantic memory system for visual objects. [Note: it would be more accurate to call it "semantic-like memory" because the study was conducted in monkeys. For the conceptualization of "semantic-like memory," please refer to Miyashita, *Nature Review of Neuroscience* (2019)].

It is now generally agreed that semantic memories of visual objects are stored and represented in a distributed network encompassing multiple cortical areas. These cortical areas are hierarchically organized such that the perirhinal cortex (PRC) (Brodmann area 35/36) is at the apex of the brain-wide network. Various attributes of visual objects are represented in the downstream areas of the PRC. For example, a major downstream area adjacent to the PRC, area TE, is a unimodal visual association area in monkeys, where information about the shapes of visual objects is represented (Gross, 1992; Miyashita, 1993; Tanaka, 1996). In terms of memory storage, the PRC integrates various attributes represented in area TE and other areas into the images of an individual object through an association

mechanism (Yoshida et al., 2003; Hirabayashi et al., 2013b; Hirabayashi and Miyashita, 2014). In terms of memory retrieval, when we see an object, the representation of the object's identity that is activated in the PRC triggers backward sequential activation from the PRC and retrieval of object-associated features, which are represented in the PRC and other downstream cortical areas, eventually activating all attributes of the object, one after another (Naya et al., 2001; Takeda et al., 2015). The origin of the backward retrieval signal is in the PRC, and the first backward retrieval signal is generated in layer 5 of the PRC (Koyano et al., 2016) by a direction-specific interaction between a neuron encoding an object that is a cue to memory recall and a neuron encoding a to-be-recalled object (Hirabayashi et al., 2013a; Hirabayashi and Miyashita, 2014). The backward retrieval signal is transmitted from the infragranular layer in the higher-order cortical areas to the infragranular layer in the lower-order cortical areas (Takeda et al., 2015). The basic machinery that enables the retrieval of semantic-like memory is serial activation via backward projections from the PRC, which drive retrieval of nested associations. Moreover, in each area, the activity is transmitted from the infragranular layer to the supragranular layer (Takeuchi et al., 2011). It then reads out the attribute information that is represented in each area. The circuit dynamics that send signals from the infragranular layer to the supragranular layer was also a new discovery, shedding new light on the functional principles of local neuronal circuit dynamics within the cerebral cortex (Takeuchi et al., 2011; Miyashita, 2019). These ideas differed from the standard mode of signal transduction found in the primary sensory areas (conventionally known as a "canonical circuit") that sends signals from the supragranular layer to the infragranular layer (Douglas and Martin, 2004; Harris and Shepherd, 2015).

We also investigated molecular mechanisms of memory circuit formation in the primate. Because the number of monkeys available for such molecular studies was limited, a new research strategy for monkeys was required that was different from the methods used with rodents. Hiroyuki Okuno and Wataru Tokuyama, graduate students in my lab, developed a new efficient assay strategy using a split-brain monkey (Okuno et al., 1999; Tokuyama et al., 2000). To eliminate genetic and cognitive variations between individual animals, we used split-brain monkeys for intra-animal comparisons in PCR-based mRNA quantitation. The monkeys learned a pair-association task using one hemisphere and a control visual task using the other, to balance the amount of visual input to each hemisphere. We found that several molecules, particularly BDNF, was upregulated selectively in the PRC during pair-association learning, but not in areas involved in earlier stages of visual processing (Tokuyama et al., 2000; Tokuyama et al., 2002). The results not only revealed molecular substrates for memory circuit formation in the primate temporal cortex but also confirmed the

unique position of the PRC in memory formation in the primate. Some of my students were also interested in synaptic/spine mechanisms that support memory formation (Matsuzaki et al., 2001)

These discoveries were reported in various invited lectures (presidential special lectures/plenary lectures) at international meetings, such as those of the Society for Neuroscience, the International Brain Research Organization, and the Federation of European Neuroscience Societies. I was particularly glad to be invited to the McGill University Brenda Milner Memorial Symposium, held in Montreal, Canada, in September 2003 to celebrate the 85th birthday of Professor Brenda Milner, whom I have highly respected for a long time. This symposium also enabled me to renew old friendships with such pioneers as Drs. John O'Keefe, Larry Squire, Trever Robbins, and Michel Petrides, all of whom I have greatly respected. It was an unforgettable symposium for me. Although I could not attend Professor Brenda Milner's 100th birthday celebration event held on July 15, 2018, because of my recent appointment as director of the RIKEN Center for Brain Science, I was glad that I could listen to her voice in a video clip uploaded to YouTube.

Beyond Memory Research: At the Rise of Functional Magnetic Resonance Imaging

In parallel with the *Local Circuits and Global Networks* project described in the previous section, in the early 1990s, I started to think about broadening the scope of my own research beyond the narrowly defined memory processes, "encoding, storage and retrieval," which have long been investigated in neuroscience. Conceptually, I wanted to look for a new research target in the field of high-level cognition, which, up to that time, had been mostly behaviorally investigated in humans. Methodologically, I wanted to introduce a new imaging technology, functional magnetic resonance imaging (fMRI), into my laboratory. This would enable me to visualize neural activity throughout the entire brain in humans.

My research interest in fMRI began just at the time of Dr. Seiji Ogawa's seminal publications reporting the discovery of blood-oxygenation-level-dependent (BOLD) imaging (Ogawa et al., 1990; Ogawa et al., 1992). At that time, however, no MR scanner was available for basic scientific research at the University of Tokyo. Although there were several clinical MR scanners at the University of Tokyo Hospital, these instruments were not able to perform echo-planar imaging (EPI), which is an essential MR pulse sequence that enables scanning at high temporal resolution. In 1992, therefore, together with Kuniyoshi Sakai, a research associate in my lab, I began work outside the University of Tokyo on a feasibility study assessing the BOLD effect. This entailed frequently traveling 30 km back and forth to the Hitachi Central Research Laboratory (HCRL) in Kokubunji-shi, where they

had an MR scanner supporting EPI sequence. In 1995, our team published two papers detailing the findings of the feasibility on the BOLD effects using the HCRL scanner (Sakai et al., 1995a, 1995b). This initial success enabled us to persuade the University of Tokyo to purchase a new 1.5 T MR scanner that was EPI-compatible and dedicated to basic research. The results of the feasibility study also convinced me of the tremendous potential of fMRI as a new, whole-brain imaging methodology to analyze higher cognitive function in both human and non-human primates.

The mid-1990s were a time of rapid growth of fMRI-related research worldwide, and my lab was no different. With a group led by Seiki Konishi, a graduate student in my lab at the time, we sought new technical and conceptual approaches to the use of fMRI. One such approach was the "event-related design" for fMRI studies, an imaging methodology we proposed in 1996 as an alternative to the then-standard "block design" (Konishi et al., 1996). Unfortunately, we were unaware that the same idea was being thoroughly developed by a group at University College London led by Drs. Richard Frackowiak and Karl Friston. Richard later became a trusted advisor to our lab on imaging studies. We wanted to demonstrate that the new event-related fMRI method could be used to rigorously analyze complex cognitive processes, something that had been difficult using conventional "block design" imaging approaches. After a series of pilot studies confirmed our approach's feasibility (Konishi et al., 1998a), we prepared to plunge headfirst into the competitive neuroimaging community with a new project targeting the functional analysis of the human frontal lobe. Our first foray (Konishi et al., 1998b) was the application of event-related fMRI to the Wisconsin Card Sorting Test (WCST), a standard neuropsychological test used to detect frontal lobe dysfunction. This was the first attempt to deconstruct the complex prefrontal neural processes enabling cognitive set-shifting into subprocesses that could be localized in different prefrontal areas. The WCST treats a subject's performance as reflective of a single mental process in neuropsychological terms; however, our research in subsequent years showed that the cognitive set-shifting in question actually emerges from the interplay of "bundles" of multiple processes within the frontal cortex (Konishi et al., 1999a, 1999b, 2002, 2003, 2005, 2006, 2008). We also demonstrated that the same basic principle applies to other domains of cognition such as "response inhibition" that can be tested with go/no-go decision tasks (i.e., the go/no-go decision actually emerges from the interplay of "bundles" of multiple processes within the cortex) (Konishi et al., 1998a; Chikazoe et al., 2007, 2009a, 2009b). Some graduate students in my lab were also interested in single-cell studies of the WCST and in testing causality with focal neuronal suppression in monkeys (Kamigaki et al., 2009, 2012).

I remained interested in all mental processes ongoing within the frontal lobe, but I simultaneously attempted to test the possibility of using fMRI to

investigate cognitive functions unique to humans. At that time, as now, the cognitive functions that were "unique to humans" brought to my mind those involved in language, especially syntax. In 1996, one year after installation of the MRI scanner in my laboratory, I launched a joint project in partnership with another group led by Professor Wayne O'Neil in the Department of Linguistics and Philosophy at the Massachusetts Institute of Technology (MIT). Domestic research funding was provided by the Japan Science and Technology Agency. This joint project yielded interesting results, demonstrating the neural basis of syntactic specialization in Broca's area (Embick et al., 2000). In addition, there were enjoyable discussions with two young, highly focused linguistics researchers at MIT, who are now working at New York University (NYU): Drs. Alec Marantz (Department of Linguistics, NYU) and David Poeppel (Department of Psychology, NYU). One of my fondest memories from the time was the "Image, Language, Brain" symposium that I held in Tokyo in November 1998, early on in our collaboration. Professor Noam Chomsky's lecture "Linguistics and Brain Science" left a deep impression on the hundreds of people in attendance. Speakers from other disciplines included Drs. Richard Frackowiak and Robert Desimone in brain science and Drs. Helen Neville, Jacques Mehler, Angela Friederici, and Willem Levelt in linguistics. An exuberant optimism was sensed on both the linguistics and neuroscience sides. All were passionate about designing new neuroscientific approaches for human language. The symposium highlights were later compiled and published as *Image, Language, Brain* in 2000 by MIT Press.

Whole Brain Metamemory Network: Monkey fMRI and Causal Evidence

I learned a lot from the joint project with MIT linguistics, and we published a lot after developing new technical tools for neuroscientific research into linguistics, including source-localization algorithms in magnetoencephalography (MEG) (Sekihara et al., 1997, 1998a, 1998b, 1999a, 1999b, 2000, 2001, 2002). Dr. Kuniyoshi Sakai, a main booster of the joint project from the Japanese side, decided to devote his scientific career to fMRI-MEG analysis of language syntax. Those were all fine. However, the causality issue bothered me. With the benefit of hindsight, I began to wonder if an fMRI-MEG approach to language syntax would face insurmountable methodological hurdles unless it was combined with human genetics. This is because research in humans cannot rely on finely targeted invasive approaches, such as lesioning or pharmacological suppression of neural activity (e.g., using muscimol) for investigation of the causal links between neural events and behavior. (Of course, I agree that neuropsychology is a powerful approach to investigating causality.) It was then that I heard about the discovery of the *FOXP2* gene. However,

I was unsure at that time whether analyses of human genetics would uncover additional syntax-related genes.

So, where to go? Since my student days, I had dreamed of reconceptualizing the philosophical thoughts of Maurice Merleau-Ponty and Edmund Husserl within the framework of natural science. Several trials and errors later, I decided on metacognition as a primary target of my subsequent research. In its long history since the time of Rene Descartes or William James, self-reflection has been recognized to be a distinguishing mental process of the human mind. Recently, it has been extensively explored in human psychology through analytical characterization of various types of metacognitive processes (Leonesio and Nelson, 1990; Nelson, 1996; Schacter, 1998). Moreover, I recognized a latent opportunity to design a realistic animal model of metacognition, the possibility of which has been discussed among behavioral scientists since the late 1990s (Shields et al., 1997; Hampton, 2001; Hampton et al., 2004; Smith, 2009).

I decided to start with human fMRI studies. There was already an abundance of psychological literature touching on metacognition via behavioral approaches. I therefore searched for a behavioral task that could withstand the strict scrutiny of neuroscientific analysis. First and foremost, the task would need to be compatible with event-related fMRI. Together with Hideyuki Kikyo, a graduate student in my lab, I successfully formalized the so-called FOK ("Feeling-Of-Knowing") task for human subjects, and published our first fMRI paper on FOK in 2002 (Kikyo et al., 2002). FOK is a form of metamemory that refers to the ability to predict the successful retrieval of information about a particular subject (Hart, 1967; Nelson, 1984; Metcalfe et al., 1993). FOK judgments do not focus on the ability to answer the question correctly, but rather on the ability to predict whether, even when one cannot recall an answer to the question, one would be able to recall the correct answer if given a hint or more time (high FOK rating if YES, and low FOK rating if NO). Using a parametric design of fMRI experiments, we identified several FOK-related areas, all of which were located in the prefrontal cortex. Interestingly, activation patterns in these regions did not necessarily depend on the difficulty of memory retrieval, recall effort, or response time. Moreover, the activation patterns in some regions correlated with whether the retrieval succeeded or failed, as typically has been seen in the parietal cortex, but activation patterns in other regions did not. All the lines of evidence suggested that these neural correlates of FOK in the prefrontal cortex play differential roles in generating FOK. [Note: We were not aware that a research group at the Department of Psychology, Harvard University, was motivated by a similar perspective (Maril et al., 2003). This fMRI research topic was far from popular at that time, and when I learned of their work I realized how much international competition and cooperation was being fostered by the evolution of fMRI research.]

I believed that clarification of the "division of roles" among the identified FOK-related areas was of great importance. I therefore sought to delve deeper into the functional architecture of the metacognition network. Notably, analysis of the causal impact exerted by each candidate area upon metacognitive behavior would be crucial to this research. This causal analysis should be done on the basis of correlational analyses (e.g., fMRI studies). Our correlational analysis of the "division of roles" went relatively straightforwardly in human subjects, but causal analysis would have been difficult using human subjects.

One potential solution was transcranial magnetic stimulation (TMS), a powerful technique capable of halting neural activity in specific targeted regions of the brain, which has been applied in human research. After serious consideration, however, I decided against its use in 2002 because of the ethical constraints on TMS usage in Japan at the time, and because of the relatively low spatial resolution for determining the border of the TMS-inactivated area. Abandoning TMS was a difficult decision, as it meant, in effect, that we would not be studying this problem in humans. To probe the biological mechanisms underpinning metamemory using a more invasive approach demanded that we develop an experimental animal model for the process, along with an fMRI methodology equally suited to human and animal research. I decided that macaque monkeys would be the optimum model animal for both purposes. And since 2002 or a bit earlier on, my laboratory has been tackling these two challenges in parallel with our continuing analysis of the global networks and local circuits involved in memory (i.e., encoding, maintenance, and retrieval), as described in earlier sections.

fMRI studies in monkeys required a more powerful scanner than the standard 1.5 T unit we had been using to date. I elected for a 4.7 T BioSpec system produced by Bruker BioSpin. The scanner had a high static field strength magnet and a high slew rate gradient field coil, enabling it to take remarkably high-resolution images as compared with the standard clinical MR models. Furthermore, I valued the high degree of freedom it provided users to design customized pulse sequences and other parameters, empowering them to find their own solutions to any artifacts—the bane of high-field MR imaging. We developed our monkey fMRI paradigm from a variety of perspectives while comparing the performance of the 1.5 T and 4.7 T scanners. This ranged from complex cognitive task paradigms, such as the WCST, to simpler eye movement paradigms, such as saccades (Nakahara et al., 2002; Koyama et al., 2004; Adachi et al., 2012; Miyamoto et al., 2013, 2014; Osada et al., 2015). Through this work, we joined an international alliance of researchers who considered MR imaging approaches in monkeys quite useful and worked hard to develop new MR technologies adapted for monkeys. In the 1990s to 2000s this included Drs. Nikos Logothesis (Max Planck Institute), Guy Orban (Katholieke Universiteit Leuven), and Wim

Vandeffel (Harvard University). Not only did I enjoy and value their friendship, these colleagues have helped me to advance and evolve my research, technically and conceptually.

The development of an experimental animal paradigm for metamemory was by no means easy. I first declared this research goal to the world in November 2005, in the Presidential Special Lecture at the 35th Society for Neuroscience Meeting held in Washington, DC. Initially, we pursued the idea of training macaques on our original FOK task that was applied to human subjects in our previous projects (Kikyo et al., 2002). However, training a monkey, even outside a MR scanner, was difficult, and measurement inside the MR scanner was never successful. I gave up on this approach and decided to design a new task for monkeys. Finally, after spending nearly a decade on wrong turns and redesigning, we finalized our "metamemory confidence task for monkeys," which is a two-stage metacognition task with a postdecision wagering paradigm for macaques. In a trial of this task, the monkeys first performed a recognition memory test. They then made a wager on the expectation of their performance (or confidence) in the preceding memory decision by choosing either a high-bet or low-bet option. If they chose the high-bet option, they received a large reward after a correct memory decision, but they would have to wait a long time without receiving any reward after an incorrect memory decision. This high-bet option corresponds to the exploitation of reward while taking a risk when they believe the reward is a sure thing. By contrast, if the monkeys chose the low-bet option, they received a small reward with no risk of a long time-out penalty, irrespective of their memory decision. The contribution of Kentaro Miyamoto, a graduate student in my lab at the time, to this metamemory project was immense, even during the design phase of the task.

The postdecision wagering paradigm was difficult for monkeys to understand; it took several months to train them even outside of the MR scanner. It then took several more months for them to perform the task in the MR scanner, where they were subjected to the loud scanner noise. Just verifying that they were truly performing the task correctly, using meta-d-prime and other behavioral metrics, also took time. Nonetheless, thanks to Kentaro's persistence and resolve, we successfully trained the monkeys to complete the task inside the MR scanner.

From whole-brain fMRI data obtained during performance of the task, we found that, during the memory test phase, before the bet, the dorsal prefrontal cortex (area 9; anterior area from the posterior supraprincipal dimple, aPSPD), the anterior supplementary eye field area (area 6; SEFa), and the frontopolar cortex (area 10; FPC) confer self-confidence on a remotely experienced event, a recently experienced event, and a nonexperienced event (Miyamoto et al., 2017, 2018). That is, activity in aPSPD was significantly positively correlated with a metacognitive behavioral index of self-confidence, Φ, for a remotely experienced event, but not on a recently

experienced event, or a nonexperienced event. The phi coefficient (Φ) is a contingency table–based statistical index of preference for optimal choice (Middlebrooks & Sommer, 2011). Similarly, activity in SEFa was significantly positively correlated with self-confidence Φ only for a recently experienced event, and activity in FPC was significantly positively correlated with self-confidence Φ only for a nonexperienced event. We also discovered that focal inactivation of neuronal activity specific to the bilateral aPSPD, SEFa, or FPC using muscimol selectively impairs metacognitive judgments about remote memory, recent memory, or nonexperienced events, respectively, without impairing recognition performance itself (Miyamoto et al., 2017, 2018). I therefore suggest that our metacognition on retrospection is actually supported by bundles of readout streams for metamemory via different prefrontal areas rather than by a single unified site devoted to metacognition in general. If I generalize it a little loosely, the result has provided evidence that our consciousness is supported, not by a single unified cortical "consciousness" site, but by bundles of "consciousness" streams via different cortical areas.

The greatest strength of this three-pronged strategy, which combines an animal model of metamemory, whole-brain fMRI, and finely targeted local inactivation of cortical activity, is that it opens avenues through which to directly probe the causal brain mechanisms governing high-level cognition, such as metamemory. A good example is that this approach enabled us to discover a novel neural correlate of metamemory in a largely uninvestigated area of the dorsal prefrontal cortex, located at the aPSPD, around the boundary of anatomically defined area 9 and 9/46d in monkeys. Neuroimaging can identify specific activation patterns and regions that appear during the performance of a task, but this evidence merely indicates a temporal correlation between brain and mental activities. The level of evidence required to answer the question, "Does this signal or region actually generate the mental activity in a causal manner?" is not achievable with fMRI alone. Describing the behavioral consequences of suppressing the function of a region or network identified in fMRI would provide the most compelling evidence of a causal link. To more broadly examine the promise of such ideas, I held an international symposium entitled "Vision, Memory, Thought: How Cognition Emerges from Neural Network" in Tokyo in December 2014. The symposium also aimed to discuss how we can link recent network analyses at microscopic (single-axon wiring), mesoscopic (cortical interlaminar connections), and macroscopic (interareal functional connectivity) levels. Among the speakers who discussed the challenges of linking these different levels of networks were: Drs. Bill Newsome, Stanislas Dehaene, Doris Tsao, Karl Deisseroth, Takao Hensch, Nikos Logothetis, and Edward Moser.

Since our first fMRI report on the visualization of human metacognition in 2002, I have spent the past 20 years or so trying to pave the way for new methodologies to explore the whole-brain network underlying

metacognition, substantiated by causal evidence. I have cleared the first step toward achieving the dream of my youth, substantiating the philosophy espoused in *The Structure of Behavior* and *Phenomenology of Perception* in the natural sciences. I am deeply grateful to all my collaborators who have traveled this road with me, especially to those I first met as graduate students in my laboratory, who are now working as principal investigators in their independent positions all over the world, including the United States, Europe, China, and Singapore.

Dedication to Community and RIKEN Center for Brain Science

My life as a researcher has spanned more than 40 years, and I am keenly aware of all the support and help I have received from both the Japanese and international scientific communities at every step along the way. One of my missions, I believed, was to devote myself to the development of the scientific community at both the national and international levels, for example, in my membership on the Board of Reviewing Editors of *Science* and my long-standing involvement in the Japan Neuroscience Society and the Society for Neuroscience. However, I continue to feel that these purely scholarly activities lack something: a deeper connection to the public. Society would reap the benefits of our research more broadly and deeply if our activities were synchronized and unified across the many relevant clinical organizations. In 2012, while President of the Japan Neuroscience Society, I founded the Union of Brain Science Associations in Japan (UBSAJ). This is a consortium of academic organizations engaged not only in particular kinds of neuroscience (e.g., neuroscience, neurochemistry, and neural networks, etc.) but also in clinical research (e.g., neurology, psychiatry, neurosurgery, rehabilitation, and magnetic resonance in medicine, etc.) and brain-related basic research (e.g., anatomy, physiology, pharmacology, psychology, and neuropsychology). The UBSAJ has grown in both strength and scope, making waves affecting not only academia but also social policy. It has influenced, for example, the Japanese government more than the Japan Neuroscience Society—or any single organization—could alone.

In April 2018, I succeeded Dr. Susumu Tonegawa as director of the RIKEN Center for Brain Science (CBS), Japan's largest neuroscience institute. Dr. Masao Ito was the first director when the center was known as the RIKEN Brain Science Institute (BSI). The advanced level and thematic breadth of the research carried out at this institute, along with the diversity of its membership, have earned it an excellent reputation and global visibility. Unfortunately, RIKEN BSI's budget has experienced heavy cuts in the years leading up to 2017, presenting BSI with the problem of stagnant PI recruitment. Since taking office, I have overseen dramatic reforms at the center, shoring up our funding sources and starting to recruit new faculty

members from the international neuroscience community. This series of reforms, I hope, will revitalize and rejuvenate the RIKEN CBS, enabling us to freshly contribute to the Japanese and international scientific communities in the coming years.

Interim Review and the Next

My research began from two starting points. One was mathematics and physics, which I first encountered in George Gamow's books, *Mr. Tompkins in Wonderland* and *One Two Three . . . Infinity*. I am indebted to George Gamow for fostering in me an interest in special relativity theory and infinite set theory, ultimately leading me to an appreciation of the mathematical beauty of the world. The other starting point was a reading club with my friends where we read the books of Merleau-Ponty and Husserl during junior high and high school. These books imprinted on me the mysteries of the human mind, particularly the enigma of self-reflection that interacts with the subconscious mind in unfathomable ways. Of course, the road to realization of the dream of my youth, to integrate these two starting points into one, was long and tough and still incomplete. *Wissenschaft als Beruf* (*Science as a Vocation*) by Max Weber taught me to cool my head by warning me not to be carried away by naïve ideas and literary rhetoric and not to ignore facts about the brain. I am heavily indebted to my academic role models, including Dr. Masao Ito, who developed the cerebellar learning theory and its experimental support; Dr. David Marr, who set out the idea of computational vision; and Dr. Susumu Tonegawa, who always demanded causal evidence. Although I was tested by these academic role models, the dream of my youth survived. And a part of that dream, which was nurtured by *Phenomenology of Perception* and *The Logic of Scientific Discovery*, is coming true in the world of neuroscience. This has been a long journey that has entailed the discovery of memory neurons and the top-down signal for memory retrieval from the prefrontal cortex, as well as the identification and elucidation of cortical global networks and local circuits for memory retrieval [reviewed in Miyashita (2019)]. This has further developed into the identification and causal analysis of the metamemory center within the prefrontal cortex. I have lived a happy life as a researcher. I would like to express my deep gratitude to my collaborators, including the graduate students in my laboratory, who worked with me on difficult projects. I would also thank my colleagues who not only deepened my research but also encouraged me through discussions at academic meetings and healthy critical reviews of my papers.

That being said, my investigations of brain metacognition circuits have just begun. The whole-brain network of metamemory will be scrutinized through various viewpoints with monkey fMRI, since a single cognitive-subtraction approach often misses an important activation due to the

problem of statistical stringency. This sounds promising to me as I will be able to test the causal roles of candidate fMRI-activation areas by focal inactivation tests and by determining their impact on metacognitive behavior. Furthermore, I will be applying all the cutting-edge neurobiological methods that I have used in my studies of memory in monkeys in the past 30 years, from now on to analyze metacognition, that is, to analyze "local circuits and global networks of metacognition." These neurobiological methods will include simultaneous recording of the activity of a large number of neurons with electrode arrays, spike-spike time series correlation analysis and their Granger-causality analysis to determine the flow of signals among neurons, structural MRI- or CSD-based anatomy-function analysis of cortical layers, and optogenetic interventions with excitatory and inhibitory opsins combined with effectively engineered promotors and tracer molecules. I am very excited about this work.

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