The Cerebellum (2019) 18:670–672
https://doi.org/10.1007/s12311-019-01022-8

OBITUARY

Obituary: Masao Ito (1928–2018)

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Published online: 8 March 2019

> Essentially, the cerebellum is constructed of stereotyped and relatively simple neuronal arrangements which we can regard as 'neural machinery' designed to process the input information in some unique and essential manner.
>
> —Eccles, Ito, and Szentágothai (1967)

Dr. Masao Ito was a pre-eminent neuroscientist involved in research on the cerebellum for half a century, searching for the answer to the fundamental question: "How does our brain accomplish its most complex and sophisticated actions?" Dr. Ito passed away on December 18, 2018, from health complications associated with aging, just two weeks after his 90th birthday. His death is a profound personal loss to us and to many in the neuroscience community who knew him both as a steady-handed scientist and as a warm and caring mentor. Dr. Ito finished his career as Honorary Scientist and Adviser of RIKEN and Professor Emeritus of the University of Tokyo.

Dr. Ito was born in Nagoya, Japan, on December 4, 1928. He spent most of his early years under the cloud of the Sino-Japanese War until the end of World War II. Coming face-to-face with the horror of death and malnutrition, he felt compelled to study medicine. He graduated from the Faculty of Medicine, the University of Tokyo, in 1953 and obtained an M.D. in 1954. Believing from a young age that basic medical science is paramount, he pursued research in physiology in the laboratory of Dr. M. Sato in the School of Medicine, University of Kumamoto. It was at this time that he married his beloved wife, Midori. In 1957, after publishing his Ph.D. thesis on the electrical properties of the frog spinal ganglion cell membrane, he joined the laboratory of Sir John Eccles in Canberra, Australia, at the John Curtin School of Medical Research, Australian National University, as a research scholar and fellow. This was a very productive time for Dr. Ito, during which he published many seminal papers on the role of Cl^- ions in inhibitory synaptic transmission.

In 1963, Dr. Ito returned to Japan and began a new chapter in his career. He took on Associate Professorship of Physiology at the University of Tokyo, where he started his own laboratory. Soon after, he was appointed the Chairman of Physiology (1970–1989), and later became the Dean of the Faculty of Medicine (1986–1988). In 1989, Dr. Ito moved to Wako, Japan, where he embarked on a new project at RIKEN called the International Frontier Research System. He was Team Leader (1989–1992) and later the Director (1992–1997). In 1997, he founded the RIKEN Brain Science Institute (BSI). At its peak, BSI comprised more than 60 laboratories that spanned both basic and clinical neuroscience. Dr. Ito continued research on the cerebellum in his laboratory at BSI until he was 84 years old. He was the BSI Director (1997–2003) and the BSI Senior Advisor (2003–2018).

In addition to his research, Dr. Ito was a very zealous advocate for the advancement of neuroscience and contributed to increasing the awareness of policies and issues related to neuroscience research not only in Japan but also worldwide. He founded The Japan Neuroscience Association in 1974, the predecessor of Japan Neuroscience Society (JNS), and served as the President (1982–1999). He founded the official journal of JNS, *Neuroscience Research*, in 1984, and served as the editor-in-chief until 1999. He served as the President or Honorary President of several international scientific organizations, including International Brain Research Organization (IBRO, 1986–1995) and the Human Frontier Science Program (HFSP) (2000–2009). He was recognized worldwide as an exceptional scientist, and was awarded many prestigious prizes, for example, the Japan Academy Imperial Prize (1986), Japan Prize (1996), Cultural Award from the Japanese Government (1996), L'Ordre National de la Légion d' Honneur (1998), and the Peter Gruber Prize for Neuroscience (2006). He became a member of many elite

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academies, for example, the Japan Academy, the Royal Society (UK), and the National Academy of Science USA, the latter two as a foreign member.

One of the most striking functional features of the cerebellum is how much its operation is underpinned by neuronal inhibition. Dr. Ito's electrophysiological study of the cerebellum started in 1963, producing groundbreaking findings. In 1964–1968, he published two landmark papers on the nature of Purkinje cell transmission on target vestibular/cerebellar nuclear neurons. In one paper, he revealed that the Purkinje cells directly inhibit target neurons [1], and in the other, he reported that this Purkinje cell inhibition is mediated by the neurotransmitter GABA [2]. In those days, neurons with long axons were believed to be excitatory, and even Sir John Eccles did not recognize Dr. Ito's findings initially. The neural circuitry of the cerebellum was identified by Dr.Ito and many students of Dr. Eccles, which was summarized and elaborated on in their first monograph, co-authored with Szentágothai (Fig. 1 a).

Inspired by computational models of cerebellar learning at parallel fiber-Purkinje cell synapses developed by Marr [3] and Albus [4], Dr. Ito tested their hypothesis using the vestibulo-ocular reflex (VOR) and the cerebellum. VOR, a compensatory eye movement in response to head movement, is under strong learning control: training of VOR through visual manipulation (e.g., wearing magnifying lenses or left–right reversing prisms) modifies VOR dynamics. To evoke VOR, the vestibular organs send head motion signals not only to the VOR-relaying vestibular nuclear neurons but also to the cerebellar flocculus Purkinje cells through the mossy fiber–granule cell–parallel fiber pathway. Interestingly, the flocculus Purkinje cells, which directly inhibit the VOR-relaying vestibular nuclear neurons, receive visual inputs via climbing fibers. Considering these connections of flocculus Purkinje cells, Dr. Ito proposed his *flocculus hypothesis* that the flocculus adaptively modifies VOR dynamics through learning at parallel fiber–Purkinje cell synapses using visual error signals via the climbing fibers [5]. This hypothesis is explained in detail in Dr. Ito's second monograph (Fig. 1 b).

In the 1970s, synaptic plasticity underlying cerebellar learning had only been hypothesized. Dr. Ito was convinced it should be demonstrable in the cerebellar cortex, but for technical reasons, he struggled to achieve it for 10 years. Finally, he succeeded in demonstrating long-term depression (LTD) of parallel fiber-Purkinje cell synaptic transmission by conjunctive activation of parallel and climbing fibers, using decerebrated rabbit preparations [6, 7]. Marr's and Albus' models were combined with Ito's flocculus hypothesis, producing the so-called Marr–Albus–Ito hypothesis, recognized now to be a main mechanism of motor learning.

For the past 50 years, the Marr–Albus–Ito hypothesis has been supported by many lines of experimental evidence (i.e., those from studies of lesion, neuronal activity recording, pharmacological manipulation, gene manipulation in mice, or electron microscopic examination; e.g., [8, 9]). Although several controversial findings challenged the hypothesis (e.g., [10–12]), later studies supported the hypothesis [13, 14] and now the role of LTD in the early stage of cerebellum-dependent motor learning is widely accepted [9, 15].

Ito extended his cerebellar learning hypothesis to voluntary movement and cognitive functions, e.g., thought and decision-making [16, 17]. These ideas are developed fully in Dr. Ito's second and third monographs (Figs. 1 b and c). He proposed that the cerebellum learns an internal model of the cerebral cortex through a cerebro-cerebellar loop, acting as a "deputy" of the cerebral cortex. To test this idea, he started a functional MRI project to examine the brain activity of professional Japanese chess players as they solved Japanese chess problems. This project has been continued through his young colleagues.

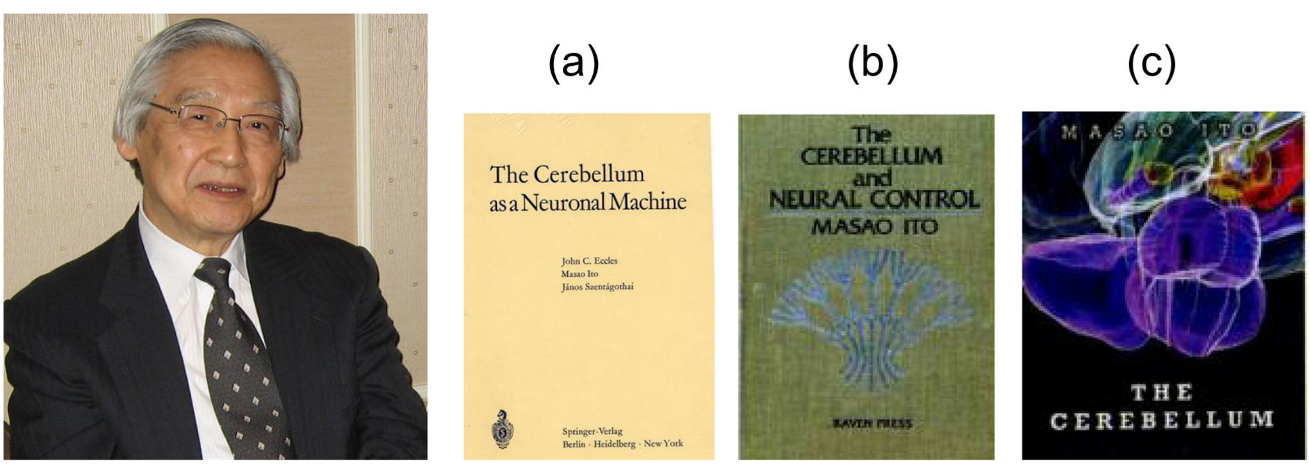

Fig. 1 A photograph of Dr. Masao Ito taken around 2007. Covers of three seminal monographs on the cerebellum written by Ito and his co-authors. **a** *The Cerebellum as a Neuronal Machine* by J.C. Eccles, M. Ito, and J. Szentágothai (1967). **b** *The Cerebellum and Neural Control* by M. Ito (1984). **c** *The Cerebellum: Brain for an Implicit Self* by M. Ito (2012)

A paper published by Dr. Ito five months before his death suggests that the human cerebellum learns the inverse and forward models of hand-reaching movements in tandem. This was investigated using the prism adaptation of the hand-reaching task [18]. The inverse model represents the motor command signals on how to move the hand to the target, and the forward model represents the prediction of the motor command signals in the sensory domain. These results are consistent with the results of several neuronal recording studies in the hand areas of the monkey cerebellum.

During his 50 years of research on the cerebellum, Dr. Ito authored three monographs on the cerebellum (Fig. 1): *The Cerebellum as a Neuronal Machine* by Eccles, Ito, and Szentágothai in 1967; *The Cerebellum and Neural Control* in 1984; and *The Cerebellum: Brain for an Implicit Self* in 2012. These monographs integrate cerebellar anatomy, physiology, neurobiology, and theory. His wish was to help young investigators not only understand the cerebellum as a whole but also find answers to as yet unanswered questions about the cerebellum. *The Cerebellum and Neural Control* will be freely available for download at the website Cerebellar Platform (https://cerebellum.neuroinf.jp) starting in 2019, a strong desire Dr. Ito had while he was alive.

Many young Japanese and international students and postdocs visited Dr. Ito's laboratory for collaboration. He always accepted them warmly. He was excited to educate and mentor young new students. Initially, he trained them how to read fundamental articles necessary for their research. Then, he repeatedly discussed with them how to plan and carry out their own experiments, until they came to an agreement. With great success, he personally taught them how to present their results at scientific meetings and in peer-reviewed articles.

In his own experiments, Dr. Ito always tried his best to obtain the data he expected from theory. However, his experiments were not always successful. For example, it took him 10 years to demonstrate cerebellar LTD. Dr. Ito's students respect him for teaching them to approach scientific research with such a sincerity to pursue the truth. Just two weeks before his death, the International Fujihara Seminar, "The Cerebellum as a CNS Hub," was held in Tokyo. Unfortunately, he could not attend the seminar, but he encouraged us with his online message (https://pf.cerebellum.neuroinf.jp/profile/75/) to continue to build a productive international network of research on the cerebellum through intense discussions with many scientists.

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