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## **JÁNOS SZENTÁGOTHAJ. 31 October 1912 — 8 September 1994:**

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### **Abstract**

János Szentágotthai was an eminent, creative and renowned neuroscientist, who made pioneering and seminal discoveries contributing to our current understanding of brain functions. His vision of the brain as a network of specific populations of nerve cells, each engaging in selective operations and self-organizing into modules, has provided the framework and stimulus for generations of neuroscientists. His irrepressible curiosity and enthusiasm for the beauty in the organization of the brain never faded. He had a towering intellect and was a great humanist. Szentágotthai was born in Budapest, Hungary, in 1912 and died in his native city in 1994. He was educated and worked in Hungary. During the six decades of his scientific activity, he made remarkably original and lasting contributions to the neurosciences, including the exploration of basic architectural features of many brain areas, the functional–anatomical bases of elementary brain operations such as reflex arcs, the vestibulo-ocular system, the brain control of hormonal regulation, general organizational principles of the neuraxis, the organization of the cerebellum and the modular organization of the neocortex. He left for posterity not only his discoveries, which have stood the test of time, but also a vigorous school of pupils as well as a large number of friends and admirers. Thanks to him neuroscience is one of the strongest scientific fields in Hungary today.

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### **Family background, early life and education**

János Szentágotthai was born János Schimert in Budapest on 31 October 1912 into the family of the respected doctor Gustav Schimert, as the second of six sons, Gusztáv, János, Márk, Arnd Péter, Pál and György. The family well represented the riches of the Hungarian kingdom, which was lost forever a few years later. On his paternal side the Schimerts were of Transylvanian Saxon origin and, as such, belonged to the Lutheran Church. From his maternal side he inherited Hungarian and Szekler blood. Both the paternal and maternal forefathers of Szentágotthai were physicians going back several generations. Among the first medical students of Hungary's prime university, founded by Cardinal Péter Pázmány in 1635, were both his great-great-grandfathers: Johannes Petrus Schimert and Stephanus Lumnitzer, respectively receiving the 7th and the 14th medical diplomas of the university's medical faculty. His maternal grandfather, Géza Antal, was the first professor of urology in Hungary; his great-grandfather, Sándor Lumnitzer, was a professor of surgery and head of the university's second department of surgery in Budapest. Lumnitzer's uncle, Ágost

Schöpf-Merei, was the pioneer of paediatrics in Hungary: he established the first orthopaedics clinic in Budapest in 1836, followed by the first children's hospital in 1839; he published the first Hungarian textbook of paediatrics and launched the journal of paediatrics.

Szentágothai's father was a man with inclination for introspection and religious pietism. He was an excellent physician with a crystal-clear mind, a unique sense of diagnostics and clinical practice, and a humanistic attitude towards his patients; nevertheless in his daily medical activities he often resorted to homeopathic practices, despised by the representatives of the 'official course of academic medicine'. 'He was doubly heretic: as a physician, he was a homeopath, as a religious man, he was anti-clerical and a free church leader', noted Szentágothai. His mother, Margit Antal, was a counterpart of her husband: a down-to-earth 'grand lady' with a big heart and aristocratic manners. She was rigorous, puritanical, full of irony and a deep dedication to the beauties of nature, which all her sons inherited. Of the six brothers, born between 1910 and 1918, five reached adulthood; all five became medical doctors.

After his years in the elementary school, János Szentágothai attended the German Gymnasium (Reichsdeutsche Schule) in Budapest. The gymnasium had a uniquely enlightened and tolerant atmosphere. Several teachers had arrived from Germany after the collapse of the Weimar Republic, continuing the spirit of German liberalism and regarding the school as their shelter. The students primarily came from upper-middle-class families; the language of instruction was German, but all the students had to learn Hungarian, Latin, French and English as well.

While in the gymnasium, at the age of 16 years Szentágothai received a small microscope as a Christmas present and within a few months managed to produce some hand-cut histological sections from the brain of an unfortunate mouse he caught; he stained the sections with the Golgi method, revealing individual nerve cells in all their beauty. As he put it, what he saw resulted in 'a love at first sight', and the 'imprinting experience' engaged him with the brain for a lifetime. Some of his later discoveries, particularly in the neocortex and cerebellum, were produced by the same golgi method (introduced by Camillo golgi, an Italian histologist at the end of the previous century) which is used to this day for visualizing nerve cells. The same method was used extensively by Santiago Ramón y Cajal, one of the greatest neuroscientists of all time.

After his graduation from secondary school, Szentágothai started his university studies at the Medical Faculty of the Péter Pázmány University, Budapest, in 1930, and graduated as a medical doctor in 1936. In 1938 he married Alice Biberauer; the couple had three daughters, Katalin (1939), Klára (1941) and Mária Krisztina (1951). In 1940 he changed his original family name, Schimert, to Szentágothai, as a reference to the place of origin of his father's family. The village Szentágota (Agnetheln in German, Agnita in Rumanian) belonged to the Transylvanian Saxon community and is 60 km from their former main town, Nagyszeben (Hermannstadt, Sibiu). Some of the forefathers of Szentágothai owned an estate in the village, and one of his great-uncles, Count Kálmán Lang de Szentágotha, was the landlord.

## Early years in science

After his successful first anatomy examination, Szentágothai joined the Department of Anatomy, first as a student demonstrator, later as an instructor and associate professor. The institute had an old tradition in brain research and its head at that time was Mihály Lenhossék. The Lenhosséks were eminent figures of medical sciences in Hungary and had been so since the early nineteenth century. The founder of the tradition had been Mihály Lenhossék senior, Professor of Physiology and Pathology at the universities of Pest (Budapest) and Vienna, Rector of the University of Pest, and later Hungary's 'protomedicus', the chief physician. His son, József Lenhossék, was Professor of Anatomy and Anthropology at the University of Budapest, and his interest focused on brain research. He identified and described for the first time, among others, the reticular formation (Lenhossék 1855, 1857, 1858). József's son, Mihály Lenhossék junior, was also Professor of Anatomy and Anthropology at the same university, and like his father was a noted neuroanatomist who identified various constituents of the nervous system for the first time. For example, he identified a new cell type in the central nervous system and gave them the name 'astrocyte'. But other terminologies in neuroanatomy, including tigroid and lemnoblast, are also his creations (Lenhossék 1893*a, b*). Mihály Lenhossék also discovered the growth cone, although in most textbooks the discovery is nowadays attributed to Ramón y Cajal. Mihály Lenhossék junior's nephew, Albert Szent-Györgyi, also followed the family tradition and started his career as a neurobiologist, but later he turned to biochemistry and made seminal discoveries, including that of vitamin C, which resulted in his being awarded the 1937 Nobel Prize in Physiology or Medicine.

When the young Szentágothai, still a student of medicine, joined the Institute of Anatomy, he was immediately captivated by the impressive personality of Lenhossék as well as by the flourishing scientific atmosphere of the institute. Following the instructions of his professor, he soon found himself in the midst of an international scientific dispute, the 'neuron theory versus reticular theory' (using Ramon y Cajal's terminology, 'neuronismo o reticularismo') or, in other words, the 'continuity versus contiguity' debate. Joseph von Gerlach and Camillo Golgi, the two protagonists of the reticular theory, claimed that the nervous system is basically a 'rete nervosa diffusa', a diffuse network of the nervous tissue, and that the nerve cells communicate with each other through their protoplasmic processes, with no barrier between them. On the other hand Ramon y Cajal, on the basis of his neurohistological discoveries—ironically many of which were made possible by the silver-chromate technique developed by Golgi—claimed that 'each nerve cell is a totally autonomous physiological canton' and they are 'independent elements that are never anastomosed'. Thanks to the meticulous neuroanatomical work of Ramón y Cajal and his followers, and to Charles Sherrington's formulation of the concept of the synapse as a way of communication among nerve cells, by the mid 1920s the neuron theory seemed to be settled. However, in the late 1920s and early 1930s the debate took a new turn (2)\*:

When I was 'awakening' on the scene of neurobiology in the early thirties, the neuron concept was once again under heavy barrage from the 'reticularists', then

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\* numbers in this form refer to the bibliography at the end of the text.

led by Jan Boeke at Utrecht and by Philipp Stöhr, Jr., at Bonn. My first impressions about this nineteenth-century type of scientific *Streitschrift* (debate) derived from the hopeless struggle of my revered teacher in anatomy, Michael von Lenhossék, to refute the claims of Boeke (1926) about the existence of a ‘periterminal network’ in the motor endplate, which would allegedly prove the continuity between neural and muscle substance. Von Lenhossék had too critical a mind not to realize that it was impossible then to beat Boeke with his own weapons, the sole use of neurofibrillar impregnation methods: so he refrained from publishing anything about the results of his last researches. However, I became ‘imprinted’ with a fundamental distrust of the ‘histological picture’ as a source of information about things that were not obvious in routine preparations and not visible with the mediocre resolving power of available optic systems.

The young Szentágothai started to modify the Bielschowsky silver impregnation method and initiated with it experimental secondary degeneration studies after removal of the stellate ganglion. His working hypothesis was that filamentous elements in the vegetative ground plexus, which the ‘reticularists’ claimed to be neurofibrils forming a continuous network (‘option one’), are indeed axons (as the ‘neuronists’ claimed—‘option two’), embedded in the same Schwann-cell processes (2):

However, option two would and could be proven exclusively correct if it could be shown that the filamentous elements underwent partial degeneration in the same Schwann-cell process after partial transection of the nerves feeding into the network.

His experiments clearly demonstrated that some impregnated filaments underwent degeneration, whereas others in the same Schwann cell did not (1–3). His conclusion was that these elements were nerve axons from various sources, with up to 10 or more axons embedded in the same Schwann-cell process. He presented the results at the 1937 Congress of the Anatomische Gesellschaft at Königsberg, only to meet sarcastic criticism from the ‘reticularist establishment’, led by Boeke and Stöhr, the former claiming that Szentágothai’s results were ‘to bury the neuron theory’, and the latter referring to them as ‘childish attempts of some nincompoop beginner’. Szentágothai’s evidence was proved beyond any doubt two decades later by electron microscopy, and the neuron theory gained full support by the identification and demonstration of synapses in the early 1950s (Palade 1954; Palay 1954).

The widespread application of his secondary degeneration technique to various brain nuclei resulted in other predictions and discoveries as well, the importance of which only became evident years later. For instance, he realized that after the extirpation of the ciliary ganglion only one-fifth of the cells in the Edinger–Westphal nucleus degenerate; most remain intact. This finding was in contrast with the prevailing view on the function of the Edinger–Westphal nucleus, advocated widely by Waldeyer and his followers. Realizing that only a minority of the cells degenerate (those that participate in the parasympathetic innervations of the eyes) and that the morphology of these cells is different from that of the remaining intact neurons (which reminded him of neurons in the hypothalamus), Szentágothai postulated that ‘they might have some vegetative functions, like neurons in the hypothalamus’ (4). This was a prophetic prediction, substantiated by plenty of evidence years later when the role of these

non-cholinergic cells, which secrete urocortin and calcitonin gene-related peptide, were clarified (for a review see Kozicz *et al.* 2011).

## The war years and Pécs

During the war years he continued his teaching and research activities at the Institute of Anatomy in Budapest, interrupted by a one-year postdoctoral research period in the Institute of Anatomy at the University of Basel. In 1942 he became 'privatdozent'. During the final weeks of World War II Szentágothai was drafted into the army as a member of the medical corps. He served briefly in the military field hospital Nr 559 in Bad Kissingen in Austria, but both the personnel and patients of the military field hospital became prisoners of war of the US Army. He had sepsis (which he probably contracted during an autopsy) and as a result was seriously underweight when he returned to Budapest a few months after the end of the war. In 1946 he was offered the chair of the Institute of Anatomy at the University of Pécs, in Hungary's oldest university town, 180 km south of Budapest, where Hungary's first university had been established in 1367.

Both the town and the university suffered a lot during the war, and the institute that Szentágothai took over basically had no teaching or research faculty. He reorganized teaching in a surprisingly short time using third-year and fourth-year medical students as student demonstrators, and gradually started to set up a research team from his best young collaborators. He initiated experiments in three fields close to his heart. First, he continued a field in which he already had experience from his Budapest years: the functional anatomy of synapses and elementary reflex arcs. Following on from a chance observation, he initiated research in the field of neuroendocrine regulation, and finally he entered the field of experimental neuroembryology.

## Research on the functional anatomy of reflex arcs

During Szentágothai's medical studies, as a young 'demonstrator' and researcher in the Institute of Anatomy at Budapest, associate professor Péter Mihálik had been his immediate superior. Szentágothai wrote of Mihálik: 'His figure could have given rise to main characters in novels and dramas, there were numerous stories about his peculiar behaviour. But as a scientist, he was one of the clearest minds I have ever met with.' Mihálik called Szentágothai's attention to the stereotaxic technique developed by Horsley & Clarke (1908), which in the 1930s was introduced into the routine battery of functional neuroanatomical experimentation by S. W. Ranson in Chicago (Marshall & Magoun 1990). In the early 1940s Szentágothai created his first home-made apparatuses: a polar-coordinate apparatus for cats, another one for rats built from old microscope stages, and a third, a special instrument for the spinal cord.

As a newly appointed professor at Pécs, Szentágothai initiated experiments in which he combined electrophysiological stimulation with microlesion-based experimental neurodegenerative approaches, using his home-made Horsley–Clark instrument. With the help of these combined approaches he began to explore the somatotopic representation of motor neurons supplying individual muscles. One of the first targets of these initial studies was the mesencephalic trigeminal nucleus containing primary sensory neurons. He found

both degenerating muscle spindles and degenerating terminals on motor neurons of the trigeminal nucleus. In 1946 he realized the significance of his results for the study of the stretch reflex arc. Focusing on the masseter reflex (jaw jerk reflex), his early work on the stretch reflex resulted in a pioneering publication on the anatomical basis of the monosynaptic reflex arc from the sensory muscle spindle to the central terminals of the same axon on the motor neurons (7).

He also explored the vestibulo-ocular system and the functional representation of the six eye muscles, using the microlesion-based degeneration technique. The initial results were surprising because they were contradictory to textbook view: the innervations of some muscles were ipsilateral, whereas others received their innervations from the contralateral abducens nucleus. To Szentágothai's astonishment, the results coincided with those obtained half a century earlier by a pioneer of experimental medicine in Hungary, Endre Högyes, a former professor of physiology at the University of Budapest. Högyes, on the basis of ingenious experiments that he performed in the 1870s, suggested that there is a functional correlation between eye-muscle contractions and the assumed stimulation of a semicircular canal, and he described in great detail the functional-anatomical bases of these phenomena. The pioneering works of Högyes paved the way to Róbert Bárány's Nobel Prize in 1914 on the mechanisms of the vestibular apparatus and balance. As Bárány explained in his Nobel lecture (Bárány 1916):

Högyes began by re-examining and modifying the experiments of Flourens and Breuer. He then set himself the task of establishing the site of the central mechanism governing the movements of the eyes, the nystagmus already referred to, which is set in motion by the movement of the endolymph. Here he was successful in the case of rabbits. He was able to show that the nystagmus mechanism is located in the parts of the brain between the entrance of the auditory nerve into the medulla oblongata and the corpora quadrigemina, and that the removal of other parts of the brain has no great influence on the course of this reflex. Högyes also produced the best description of the symptoms after uni- and bilateral destruction of the semi-circular canals in animals and, in particular, proof that these symptoms are at their most violent immediately after the injury and then gradually subside, furthermore that the violent symptoms caused by the destruction of one side only can be reduced to a minimum by the destruction of the other side. He proved, in fact that the semi-circular canal on the one side influences that on the other side and that during stimulation they balance one another.

(It is worth noting here that Högyes also paved the way to a Nobel Prize won by another Hungarian scientist later. In 1879 Högyes developed an electronic audiometer, based on the first telephone apparatus built by Alexander Graham Bell in 1878, and this audiometer was further modified and used by Georg von Békésy in his experimental work, leading to his Nobel Prize in Physiology or Medicine in 1961 'for his discoveries of the physical mechanism of stimulation within the cochlea'.)

Szentágothai was elated by the harmony of his own experimental data and Endre Högyes's suggestions and original observations. After several initial failures and misinterpretations,



the work led him to his widely recognized publications on the functional anatomy and physiology of the vestibulo-ocular reflex arc (5, 8) and ocular movements (9).

Through these studies he familiarized himself with the challenging problems of the functional anatomy of complex reflex arcs and with the intriguing role of inhibition in reflex activities. These initial combinations of neuroanatomical and neurophysiological approaches seemed to be highly rewarding in Szentágothai's future research activities and resulted in further seminal discoveries regarding the functional-anatomical aspects of Clarke's column (18) and those of the spinal motor nucleus (10, 11, 13, 17). The success of the dual (functional-anatomical) approach culminated in his long-time collaborative research with Sir John Eccles FRS on the neuronal circuits of the cerebellum (figure 1).

The results of these investigations had become, in an admirably short time, 'canonized' and were incorporated in basic textbooks edited by Fulton, Carpenter, Brodal and others, including *Gray's anatomy*, and most of them have survived the test of time.

## Contributions to the functional anatomy of the hypothalamo-hypophyseal system

In the early 1940s Szentágothai was already trying to trace degenerating axons with his stereotactic instruments in the hypophyseal neurosecretory pathways. Soon after his appointment in Pécs, in 1946, a young medical doctor, Miklós Halmi (Nicholas S. Halmi) approached him with his plans to apply the stereotactic approach and test the resulting effects of hypothalamic lesions in various endocrine organs. The first experiments with hypothalamic (tuberal) lesions produced spectacular changes in the endocrine organs. But Halmi soon departed for the USA, where he became a well-known researcher in the field of pituitary physiology and cytology. His initial work was taken over by some talented medical students, including Béla Flerkó, Béla Mess and Béla Halász (who, so as not to confuse them when called, were named with various diminutives of the common Hungarian forename 'Béla'). They all became professors in due course, Béla Halász founding the 2nd Department of Anatomy at the Semmelweis Medical University, Budapest. The three Bélás gradually developed their own experimental models, some of which have become widely used, even becoming 'standard' models used by neuroendocrinologists worldwide. This period was not easy for the group, because any communication with other groups in the world was severely hindered by the 'iron curtain' and no study visits were possible at all. But despite all this, Szentágothai's group in Pécs in the early 1950s became one of the cradles of neuroendocrinology. Whereas his students concentrated on various functional-anatomical aspects of the hypothalamo-hypophyseal system, Szentágothai focused on the study of the general neuroanatomy and the circulation. He applied the axonal and terminal degeneration techniques combined with various stains, including the Nauta silver stain, but the initial results were unsatisfactory. He soon resorted to the Golgi technique, which yielded marvellous results, including in 1962 the identification of the parvicellular tuberoinfundibular neurosecretory system and its terminals in the surface zone of the median eminence, a pioneering result that was later confirmed by electron microscopy.

His contribution to the discovery of the portal circulation system was not less fundamental and well demonstrates Szentágothai's never-diminishing curiosity and creativity. In the words of György Székely (Székely 2011), now Emeritus Professor of Anatomy at the University of Debrecen, who graduated at the Pécs Medical University in 1952 and joined Szentágothai:

As a novice in science, in 1952/53, I was working on neuroembryology and needed fresh frog's eggs. In order to obtain them out of season, a few hypophyses had to be grafted into the lymph-sac of a female animal. Szentágothai was interested in everything that happened in the laboratories, and he came to see what I was doing with a frog under the dissecting microscope. Due to large red cells in the frog, it was easy to follow the circulation under the power of the microscope. He intensely observed the ventrally exposed hypophysis and the basal brain, and quite inadvertently pressed the belly of the animal. After a short while he exclaimed that it was incredible to see the red cells running up from the hypophysis to the brain upon the pressure of the belly, and they streamed back after lifting the pressure. It could be clearly seen that the hypophysis received the blood supply by way of the hypothalamus. This experience was enough for Szentágothai. He entrusted the object to a young staff member, and using now dogs, they explored every little detail of the portal circulation of the hypophysis. He encouraged other members of staff to investigate the effect of hypothalamic lesions on peripheral endocrine glands. ... This little story demonstrates how Szentágothai was able to create a new trend, a very successful one, from a chance observation peripheral to his primary interest.

Even though in the early 1950s various neuroanatomists, including Spatz and collaborators, were already describing non-magnocellular neurosecreting cells in the hypothalamus (Spatz 1951), it was definitely Szentágothai who discovered the functional importance of these cells and emphasized their role in the control of the anterior pituitary. He realized the functional coherence between parvocellular neurosecretion, portal circulation and the tuberoinfundibular tract and recognized the system's importance and regulatory role. The group's results were summarized in a 1962 monograph, *Hypothalamic control of the anterior pituitary* (14), which became the foundation of neuroendocrinological research and was repeatedly updated and re-edited. One of the most surprising features of the book was characteristic of Szentágothai's unorthodox way of thinking: decades before the computer era, he realized the analogy between the operational principles of the neurosecretory system and computers, then still at an embryonic stage:

The hypothalamus proper and some of the extrahypothalamic structures can much better be envisaged as some kind of a computer, which according to a number of built-in programs elaborates the solution for each actual situation on the basis of a large wealth of information partly stored partly flowing in continuously. The results are then distributed over a number of 'print-out' channels both neural and neurohumoral. This very crude analogy might give an impression how senseless it would be to expect some rigid and monolithic 'centre-type' localization of endocrine function.



The book was indeed a revolutionary step forward in the history of neuroendocrinology because it was the first monograph dedicated to parvicellular neurosecretion. 'The anatomical reality of the Releasing Factors System as a parvicellular neurosecretory or tubero-infundibular neuron system is established beyond any doubt' (14).

Years later, in retrospection, with his usual self-deprecation he remembered this heroic discovery (29):

Looking back now on this period, I am quite conscious of many naive, romantic features in the book especially in the first edition, for which I have to assume sole responsibility. Drs. Flerkó and Halász were of more realistic disposition and tried to dissuade me from various unorthodox notions. Even so our efforts to explain the results of hypothalamic interferences by various types of hypothalamic feedback (negative, positive, short-circuit, purely neural, etc.) made a modest contribution to the understanding of these complex mechanisms.

## Budapest again

In 1963 Szentágothai was invited to take the chair of the 1st Department of Anatomy at the Medical University in Budapest. He was moving 'back home', because this institution was the cradle of his scientific career. His main objective at that time was already crystallized: to identify and describe in great detail the basic operational circuits or, as he called them, the 'higher integrative units' of centres of the central nervous system, including the spinal cord, the thalamic nuclei, the cerebellum and, last but not least, the cerebral cortex (26, 28). He soon recognized that neural centres are made up of smaller, repeating neuronal circuits, which can be regarded as functional units or 'modules', together giving rise to the brain area as an operational centre. He formulated the modular architecture concept of the nervous system as an organizational principle. In his modules the same types of neuronal element occupied stereotypical spaces and formed stereotypical synaptic connections. To explore the anatomical organization and the functional behaviour of various neural centres he applied a large battery of methodologies, including the tracing of pathways by silver impregnation degeneration techniques, the Golgi method, quantitative light and electron microscopy, electrophysiology and mathematical modelling.

As his results became known and his fame grew, he was one of the few privileged scientists allowed to travel to the West by the communist authorities, which kept a watch on every aspect of life. At conferences he could make personal contacts with colleagues worldwide, including his long-time scientific sparring partner, Sir John Eccles. It also made a change in his personal life because, like most intellectuals, he was barred from travelling to the West for quite a while after the 1956 Hungarian Revolution.

His department became a magnet for visitors from both East and West, and the different groups were once more at the forefront of international progress in neuroscience. However, with teaching, textbook writing, increasing travelling, university and national scientific administration he was not always able to follow the day-to-day scientific events and personal changes of the department. When he became President of the Hungarian Academy of Sciences, a demanding representational role, he had to relinquish the chairmanship of the

department, which lost its most spirited and formidable head ever. In a hierarchical authoritative society and academic structure, no attempt was made to search for the most suitable person to build on the scientific strengths of the department, which has lost its impact. Nevertheless, the group led by Miklós Palkovits has continued a world-class contribution to chemical neuroanatomy and systems neuroscience.

## The cerebellum as a neuronal machine

Szentágothai's long-standing engagement with the cerebellum started in the 1950s with the discovery of the source of the climbing fibres as the inferior olive (12). With Károly Rajkovits he placed small lesions in the inferior olive and traced the degenerating fibres to the molecular layer of the cerebellum, and from their shape he identified them as the climbing fibres known from Golgi impregnations by Ramon y Cajal. His finding gave considerable leverage to the application of micro-electrophysiological methods to the cerebellar cortex by Sir John Eccles and his associates. On the basis of the anatomical findings, Szentágothai speculated on how excitation might spread along the longitudinal axis of the folium via a beam of parallel fibres. He predicted that, to explain the functions of the cerebellar cortex, the basket cells should have inhibitory properties; this was soon confirmed by single-cell recording studies. When he realized that Purkinje cells are inhibited by the basket cells and that this may lead to an activity 'pattern generation' in the cerebellum, he explained the concept to his pupils: 'the cerebellum is functioning in a way as a "negative organ player" plays the organ; the player is not pressing the keys on the keyboard which open the pipes that would be heard, but the player presses the keys which silence the pipes which should not be heard.' Because the axons of the basket cells ran perpendicular to the direction of the parallel fibre beam, he envisaged that they provided lateral inhibitory bands on two sides of the Purkinje cells activated by parallel fibre excitation.

His original observations on the fine structure of the cerebellar cortex gave rise to a highly fruitful collaboration with John Eccles and Masao Ito and led to the 1967 book *The cerebellum as a neural machine* (15), a landmark in neuroscience. This book was a pioneering brave account of all knowledge about a part of the brain at the time. It formulated the concept that the complete quantitative circuit of a neuronal centre and its relationship to other brain areas need to be defined if they are to explain its role. Unfortunately, many of the tools were not yet available half a century before the current flurry of activity in connectomics, circuit research based on imaging and genetics.

Understandably, the original concept soon came under fire when researchers in the field began to apply more detailed physiological methods and found that closely neighbouring Purkinje cells may behave in very different ways in the same physiological response, something not foreseen in the original concept (Eccles *et al.* 1971a, b; Llinás *et al.* 1971). Szentágothai wrote (29):

My own peace of mind (or 'tao' in the sense of Lao-Tse) in this matter had been disturbed before by the uneasy feeling that any speculation on the possible functions of neural nets would be on extremely shaky ground unless exact numerical and metrical relations of the neuron network were known. We started, therefore, a major enterprise in stereological analysis of the cerebellar cortex. The

results (20-23) were shocking at first, because they showed that all numerical and many metrical conclusions obtained from earlier naive counts and measurements were grossly off the mark. On second thought, however, the accumulated data, and especially the total numerical transfer functions of the cerebellar neuron chain, make some sense and offer distinct possibilities for realistic modeling of the network functions by digital computer.

To explore the behaviours of the system, he first initiated computer modelling studies, an unusually bold approach in the early 1970s (24-27), followed by quantitative cytological and electron microscopic studies to clarify the exact numerical and stereological relationships between the major players of cerebellar circuitries, stellate cells, basket cells, Purkinje cells, and their axons and axon terminals (30, 31, 33, 34). These studies were forerunners of subsequent cerebellar models, and he encouraged the improvement of the model by incorporating the results of further anatomical and physiological investigations.

In all these studies his unique visual imagery played a determining role. Using two-dimensional microscopic images as a basis, he could envisage highly complex three-dimensional neuronal circuitries with ease and he produced inspirational schemas and sketches. It is no wonder that his books and papers are full of imaginative three-dimensional illustrations of his vision of the neuronal circuits (figure 2).

## The modular organization of the cerebral cortex

The success of his approach to deciphering the structure of neural centres such as the cerebellar cortex inevitably led him to the cerebral cortex. The Golgi technique was particularly informative for the characterization of single cortical neurons, and supplementing this with his degeneration methods he embarked on the investigation of the intracortical connections. A great stimulus to his efforts was provided by the discovery of functional columns by Mountcastle (1957) in the somatosensory cortex and by Hubel & Wiesel (1962) in the visual cortex (29):

My anatomical speculations did not remain confined to the cerebellar cortex. I tried to generalize this way of looking at neuron nets into a general concept of 'higher integrative units of the nervous system' (16). By this term I meant the minimum amount of neural tissue that would be able to perform the essential part of the information processing for which that piece of tissue is built.

His endeavour to understand the anatomical bases of the functional columns in the cortex required not only his imaginative mind but also the devising of experiments to explore, identify and classify the highly diverse intracortical connections. He used Golgi impregnation, which reveals the dendritic trees of single neurons in their entirety, and the tracing of axons degenerating after lesions to identify long-distance connections. The limitation of the Golgi method is that it does not reveal myelinated axons; the axons of long-distance projection neurons cannot therefore be traced, and the source of incoming afferents leaving the myelin sheet remains unknown. The silver impregnation of degenerating axons of known origin does not reveal single axons; it can only be used to study the pathway as a whole. These limitations hampered the delineation of functional units and columns in the

cortex, which remain undefined today even though complete single-cell labelling has become a widespread technique. Szentágothai envisaged the area occupied by the axons of a functionally identical single cortico-cortical projecting pyramidal cell group as the physical substrate of the cortical column (figure 3). In his time the axon of a single cortico-cortical cell could not be visualized, and neurons in a radial column of the cortex have widely different axonal projections.

Using the golgi technique, he delineated numerous types of local circuit neurons. His work yielded such discoveries as the chandelier cell. He described this cell first as part of his modular concept (26), and later documented it in detail (29). He named the cell for its unmistakable terminal axonal segments, which were arranged radially like the candles on a chandelier. One of us (P.S.) subsequently showed that these terminals only innervated the axon initial segments of pyramidal cells and inhibited them via  $\gamma$ -aminobutyric acid A (GABA<sub>A</sub>) receptors. Szentágothai predicted the inhibitory role. Because the axon initial segment generates the propagated action potential, the joint inhibition of hundreds of pyramidal cells by chandelier cells must have a profound and still unknown role, as this arrangement is unique to the cerebral cortex.

Understanding the microcircuitry of the cortex was his last scientific love affair; he kept updating his models of the modular architecture of neocortical circuits with the latest results, for example in his Ferrier Lecture (32). Although not enough knowledge was available to achieve a grand synthesis, he, as always, sought to provide a complete account of how information might flow in the cortex (29):

A more imaginative approach—even though burdened with a broad margin of error—sometimes does more for progress than the ‘correct’ inductive path to discovery. To be exact, both are needed. I might perhaps return to the example of the glomerular synapses in the lateral geniculate body, which I predicted purely on the basis of light-microscopic studies in a lecture at Atlantic City in April 1961 .... I had not seen until then a single electron micrograph of this region. This stereoscopic view was very naive indeed by our present standards, but it does demonstrate that certain essentials of some very complex reality can be predicted quite well on the basis of extremely incomplete information.

### The artist-cum-scientist

Szentágothai wrote in his retrospections in 1975, ‘Perhaps my readers will not be unduly shocked if I confess that the elegance and beauty of a concept is much more attractive to me than the dreary details of fact’ (29). And this has proven to be a key sentence for understanding his attitude towards science. He often emphasized what Keats wrote so elegantly in his poem, ‘Ode on a Grecian Urn’:

‘Beauty is truth, truth beauty,’—that is all

Ye know on earth, and all ye need to know.

He was convinced that all details of Nature bear an immense beauty in themselves and that our scientific discoveries reveal this beauty. For this reason, science is a never-ending

endeavour to reveal the beauty of Nature and, consequently, not only should the scientific facts bear beauty, but scientific theories and hypotheses also.

From his early twenties until his death, he taught human anatomy to medical students on a regular basis. His famous atlas of the human, *Atlas anatomiae corporis humani* (6), created together with his predecessor in the Chair of Anatomy at Budapest, Ferenc Kiss, has been published in more than 85 editions worldwide and has been translated into more than a dozen languages including Chinese and Slovenian. He designed and drew much of the artwork for this fundamental book. His textbook of anatomy (19) also testifies to his approach to Nature and to the human body, as a manifestation of natural beauty. He almost regarded the human body as the materialization and a vehicle of some transcendental beauty and truth when he referred to it in the introduction of his textbook (which generations of medical students have studied over the decades since) to one of his most beloved poets, Attila József:

Ah, what strange stuff is this of which I'm made,  
 that but your glance can sculpt me into shape?—  
 what kind of soul, what kind of light or shade,  
 what prodigy that I, who have long strayed  
 in my dim fog of nothingness unmade,  
 explore your fertile body's curving scape?  
 —And as the logos flowers in my brain,  
 immerse myself in its occult terrain!

(Attila József: 'Ode', translated by Zsuzsanna Ozsváth  
 and Frederick Turner; *The Hungarian Quarterly*, no.  
 148–149, 1997–98)

It is therefore no wonder that he himself made basically all the outlines of the figures of his famous anatomy atlas as well as those in all his publications. These sketches were then perfected by professional graphic artists and painters whom he closely supervised during his whole career. His lectures—be they his regular anatomy lectures at the university or scientific lectures at meetings—were famous for the fact that he continuously illustrated them with his handmade drawings on the blackboard, using both hands simultaneously. He regularly painted aquarelles, and these testify to his unique artistic talent (figure 4). In this regard he often referred to Ramon y Cajal, his idol, who illustrated his publications with his own drawings; these figures were more than illustrations of scientific papers: they were pieces of art in their own right. Furthermore, drawing illustrations on the blackboard during his lectures was a source of ideas for him (29):

My present approach to the functional anatomy of neuron nets began when I was trying to convey to my undergraduate medical students, in the usual course on neuroanatomy, an idea about how excitation may spread in a piece of cerebellar cortex. Since specific inhibitory interneurons were not yet known, I speculated at the blackboard that excitation might spread along the longitudinal axis of the

folium via the parallel fibers, thought then to be about 3 mm in length, and across the folium via the basket axons (i.e., about 1 mm to both sides of a simultaneously excited beam of parallel fibers).

## Szentágothai's public engagements

'To stay fair and righteous in historical times' was one of the maxims in Szentágothai's life. And in this context he often referred to Friedrich Christoph Oetinger's (1702–82) prayer, which was a guideline throughout his life:

Lord grant me the serenity  
to accept the things I cannot change;  
courage to change the things I can;  
and wisdom to know the difference.

He never hid his opinion, not even in difficult times of history, but he wisely recognized the limits that were tolerated by authorities. During the 1956 Hungarian uprising he served as chairman of the revolutionary committee of his university at Pécs and was in hiding for some time to avoid prosecution. Under the protection of powerful communist academics and later the politburo chief for culture, György Aczél, who respected him, he learned to live in and work with the system for the benefit of progress. As his fame grew and he was elected to the academies of the communist countries as well as to those in the West, he was allowed to travel to conferences and received visitors from all around the world. In 1977 he was elected President of the Hungarian Academy of Sciences and served in this capacity until 1985. His international reputation increased steadily and he was honoured by memberships of several learned societies as well as honorary doctorates from distinguished universities worldwide, including Oxford (figure 5).

In 1985 he became a member of the Hungarian Parliament, which served and functioned as a rubber-stamp institution for window-dressing the rule of the Communist Party. Szentágothai was not directly involved in politics and never joined any political party. As a Member of Parliament he gave a major speech in the Parliament on 7 October 1988 against the politically motivated and environmentally controversial hyper-project of diverting the Danube to Czechoslovakia and building the Gabčíkovo–Nagymaros hydropower station on the Danube. The popular movement and protests against the construction that erupted in 1988 were the first signs of civil disobedience that eventually culminated in the fall of the corrupt political system in 1989 after the collapse of the soviet Union. After the parliamentary elections in 1990, the first free elections since 1947 in Hungary, he became a member of the Parliament again for a full term, leaving in 1994. He vigorously defended the record of the Hungarian Academy of Sciences and spoke up against populist, unscientific tendencies and media campaigns that attacked science and scientists. During that period he was asked by several individuals and organizations to promote humanitarian causes. His door was open to everyone during these years and, indeed, many came to him for advice, not only on scientific matters but also on private matters. He was a meticulous letter writer: he replied at length to each and every letter he received.



Szentágothai lived through and influenced the turbulent history of a country that history has not favoured. He managed to maintain a creative contribution under the darkest of historic circumstances, not only to his country's culture and education but also to the pool of mankind's universal knowledge. In his witty biographical self-portrait, 'As a Ulysses around the brain' (35), written as a monologue and applying James Joyce's *Ulysses* and Thomas Mann's *Lotte in Weimar* to his life, he professed that the aims of his life had been 'to be a good neuroscientist, to remain cultural in the sense of the end of the 20th century, to remain an honourable man under the historic circumstances and above all, to remain a good Christian.'

He died of a heart attack in the early morning of 8 September 1994. One of us (B.G.) had visited him the evening before and had a long dialogue with him on matters of science, life, politics, philosophy and history, not to mention the usual 'survey' of his pupils: who was doing what, and where they were working. He was preparing with great enthusiasm for the forthcoming annual meeting of the Pontifical Academy of Sciences, due in late October, at which he planned to deliver a lecture on his theory of how the human brain perceives the world and constructs thoughts. He was full of plans and ideas and speculated about how to develop further his 'modular concept of the brain'. He wanted to know everything about new discoveries and methodologies in brain research. His mind was vivid as always.

With his passing away, one of the greatest *homo ludens* of his time left us. As his successor, the then president of the Hungarian Academy of Sciences, Domokos Kosáry, remembered him thus: 'He showed me that science should be sacred and at the meantime could be fun, very serious fun'.

The vitality of his mind is remembered by all his students, pupils, friends and everyone who ever met him. As a professor of anatomy, he educated and examined generations of medical doctors, thousands of physicians. As a neuroscientist, he built a uniquely large, lively and still expanding school of followers, including two of the first Brain Prize winners. Thanks to his taking over the torch from his mentors in extremely difficult political and infrastructural circumstances, Hungary today is a leader in the neurosciences. His discoveries and theories have shaped our knowledge on the brain and contributed significantly to the development of present day neurosciences. As a socially committed person, his impact on the shaping of the contemporary history of Hungary is undeniable. And as a mentor and friend, his memory will always stay with those who had the privilege of knowing him. As one of us (P.S.) wrote about him in an interview (Kittel 2012):

just as every atom in our body comes from long extinct exploded stars and forms novel combinations, thus we are all built of stardust, every thought in our brain bears the heritage from thousands of unknown human generations who came before us. Although we do not know most of the contributors to our culture, every now and then there is an individual whose personal legacy lives on in our minds. One of the bright intellectual stars of the twentieth century was János Szentágothai, whose heritage and intellectual 'stardust' lives on in our culture, natural knowledge, serving the universal scientific progress of mankind.

## Education

Elementary school of Cukor utca (Cukor Street), Budapest, 1918–22

German Gymnasium (Reichsdeutsche Schule), Budapest, 1922–30

Péter Pázmány University, Faculty of Medicine, Budapest, 1930–36; MD 1936; PhD 1942

## Positions held

1932–36 Student demonstrator

1936–46 Instructor, assistant professor, associate professor, Department of anatomy, Péter Pázmány University, Faculty of Medicine, Budapest

1946–63 Professor and Chair, Department of Anatomy, University Medical School of Pécs

1963–86 Professor, Department of Anatomy, University Medical School of Budapest

1963–77 Head, Department of Anatomy, University Medical School of Budapest

1973–77 Vice President of the Hungarian Academy of Sciences

1977–85 President of the Hungarian Academy of Sciences

1985–94 Past President and Professor Emeritus, Hungarian Academy of Sciences

## Honours and awards

### Decorations

1950 Kossuth Award, Hungary

1970 State Prize, Hungary

1985 Golden Medal of the Hungarian Academy of Sciences

1992 Order of Merit of the Hungarian Republic (Commander with Star)

### Membership of learned societies and professional bodies

Hungarian Academy of Sciences, National Academy of Sciences of the USA, Leopoldina German Academy of Naturalists, Academy of Sciences of the USSR, Royal Society, American Academy of Arts and Sciences (Boston), Finnish Academy of Sciences, Mainz Academy of Sciences, Pontifical Academy of Sciences, Royal Belgian Academy of Medicine, Royal Norwegian Academy, Royal Swedish Academy of Sciences, Serbian Academy of Sciences

### Honorary degrees

University of Oxford, University of Turku, University of Pécs

## Awards

1984 F. O. Schmitt Prize of Neuroscience

## Professional organizations

1976–78 President, European Neuroscience Association

1966–76 Member, editorial board, *Experimental Brain Research*

1972–80 Member, editorial board, *Journal of Comparative Neurology*

1966–78 Member, editorial board, *Brain Research*

1991–94 Member, advisory board, *Cerebral Cortex*

## Price lecture

1977 Ferrier Lecture, Royal Society

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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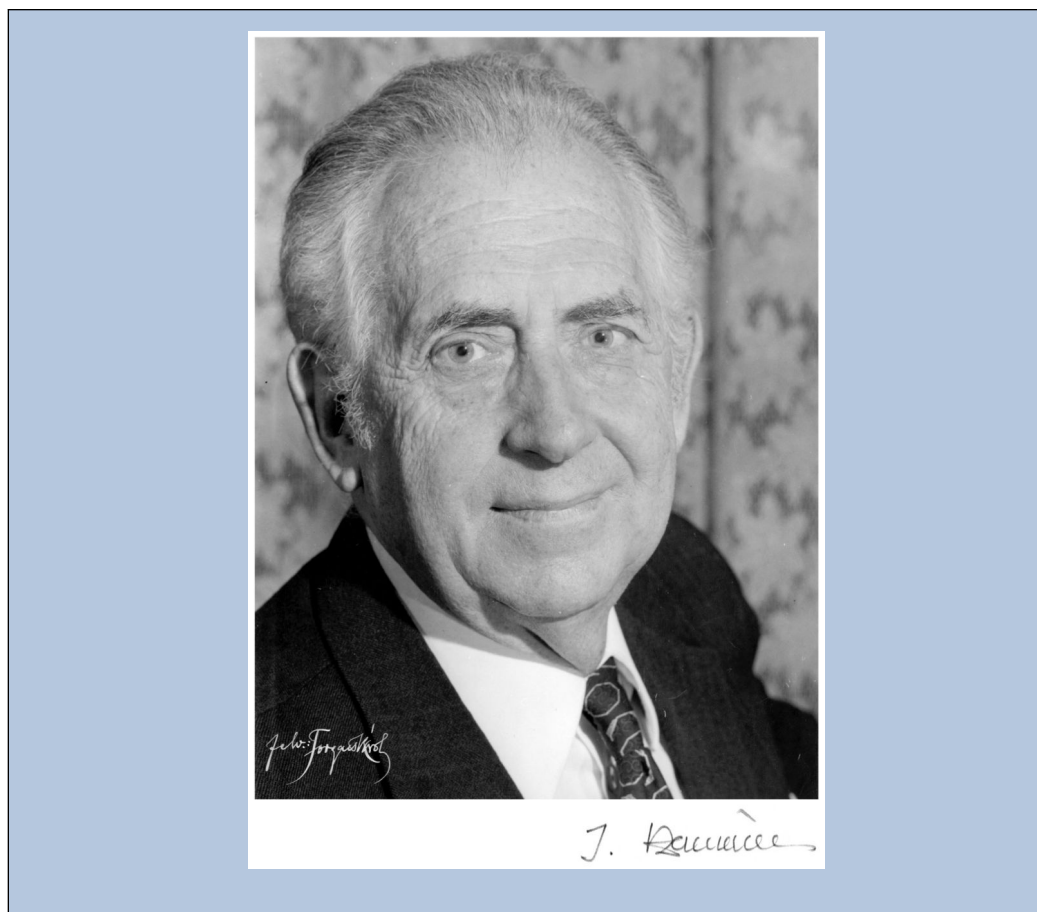
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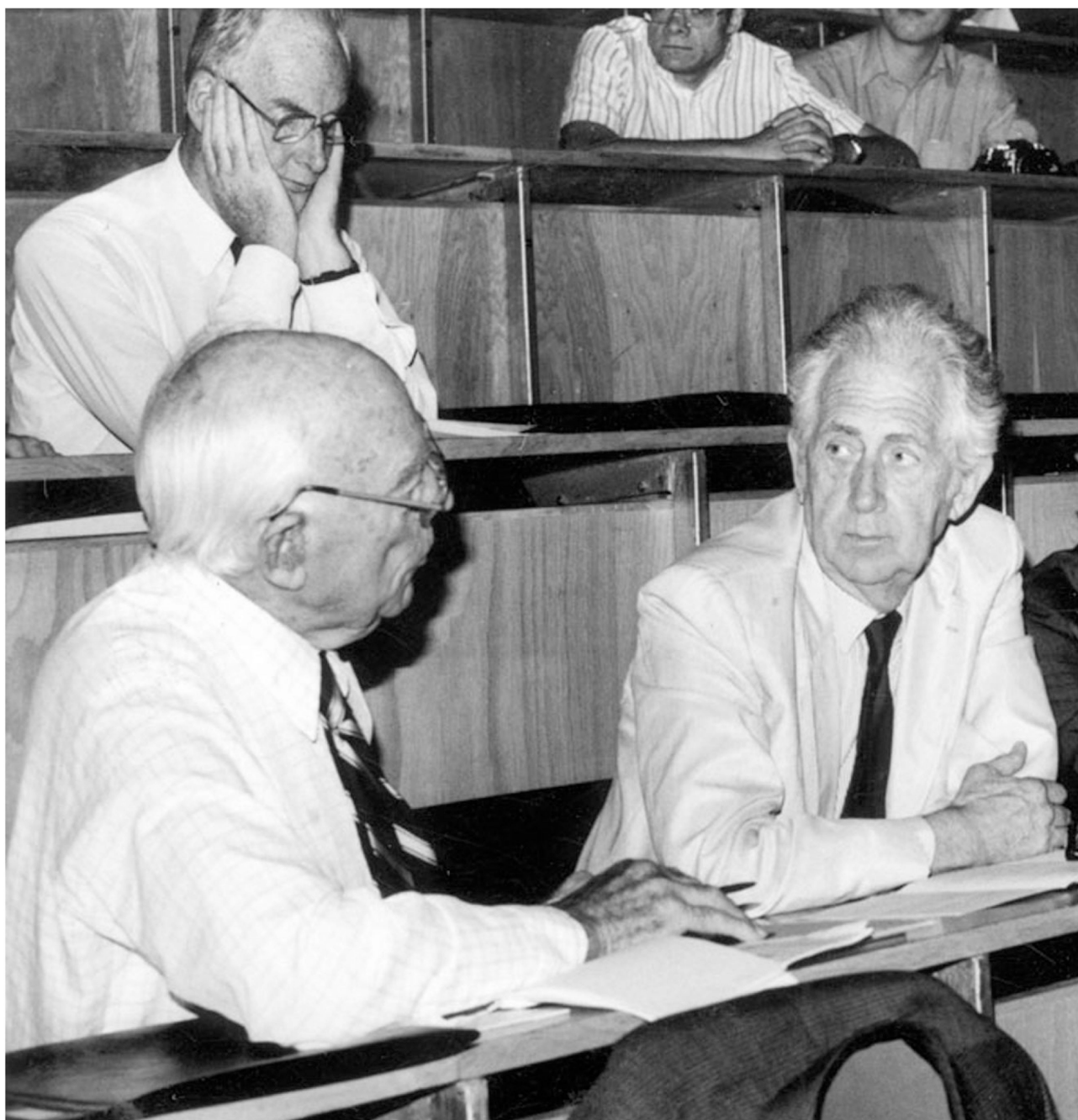
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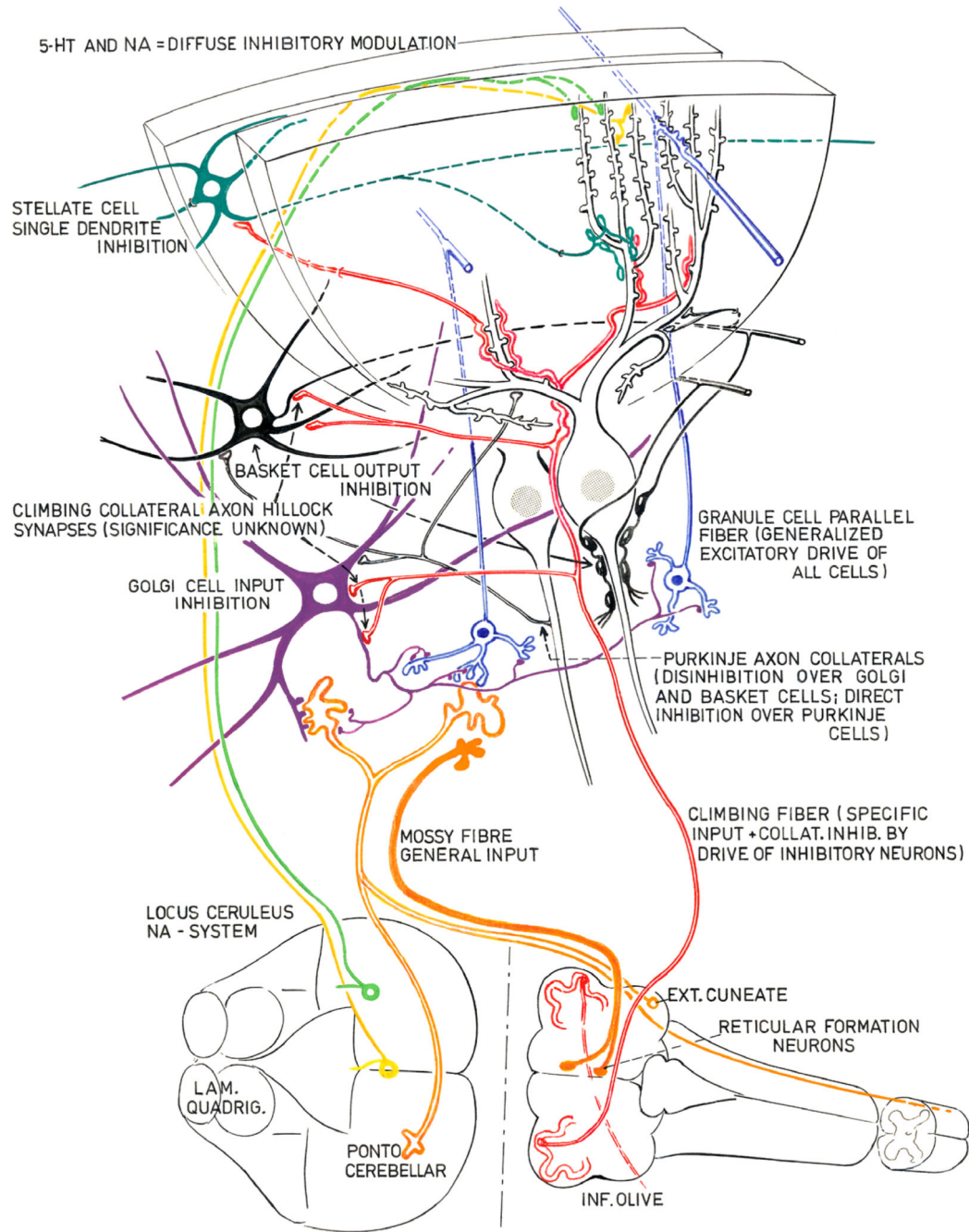
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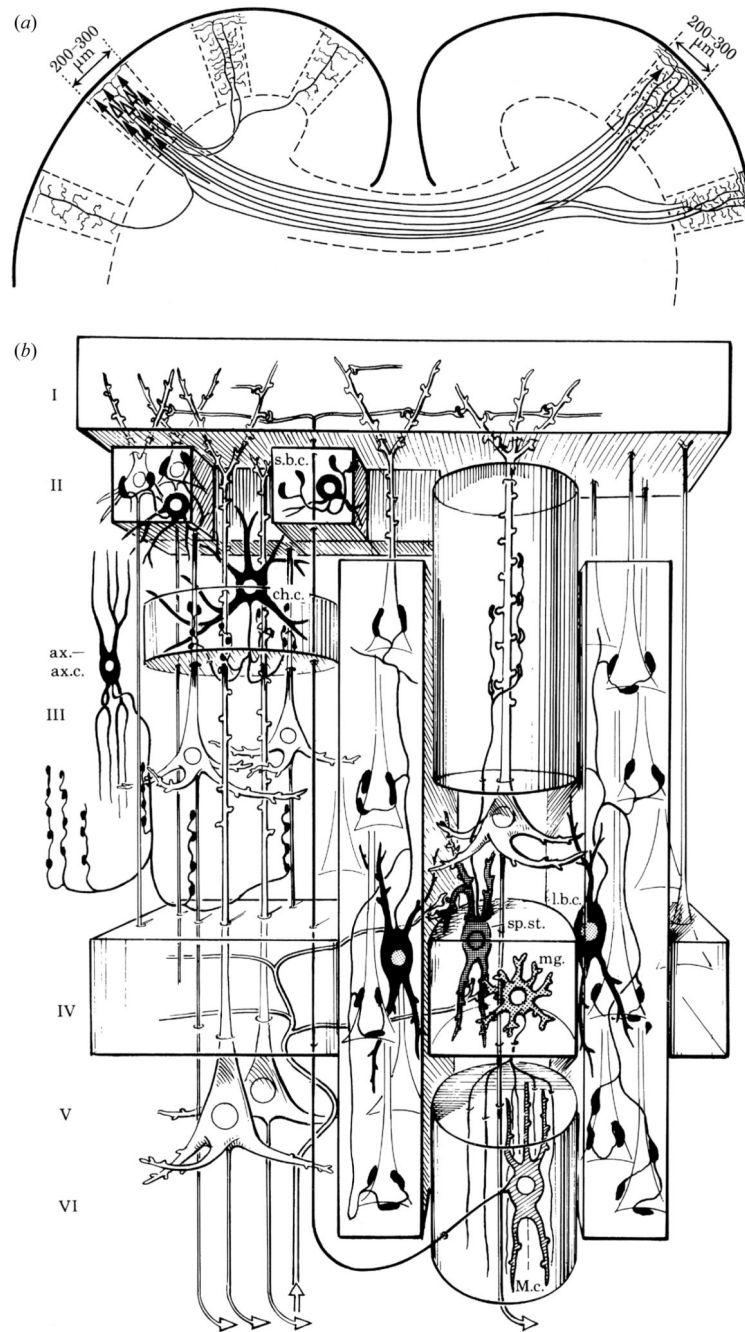


**Figure 1.**  
János Szentágothai (right) with Sir John Eccles (left) at the University of Pécs, Hungary,  
during a symposium in 1982.



**Figure 2.**

Szentágothai's scheme of the synaptic organization of the cerebellar cortex. Abbreviations: 5-HT, serotonin [5-hydroxytryptamine]; NA, noradrenalin; lam. quadrig., lamina quadrigemina; collat. inhib., collateral inhibition; ext. cuneate, exterior cuneate nucleus; inf. olive, inferior olivary nucleus. (From the collection of Miklós Palkovits; reproduced with permission.)



**Figure 3.**

Examples of Szentágothai's neocortical circuits. (a) Schematic illustration of cortico-cortical columnar connectivity. Pyramidal cell columns form highly specific ipsilateral and contralateral axonal patterns. (b) Synthetic view of modular arrangements of local neuronal connections in a column. He recognized that each cell type receives and sends synaptic connections in a characteristic volume of cortex. The scheme also shows that different cell types exert their action on different subcellular domains of the postsynaptic neurons. Pyramidal cells are empty, GABAergic neurons and their terminals are solid black or

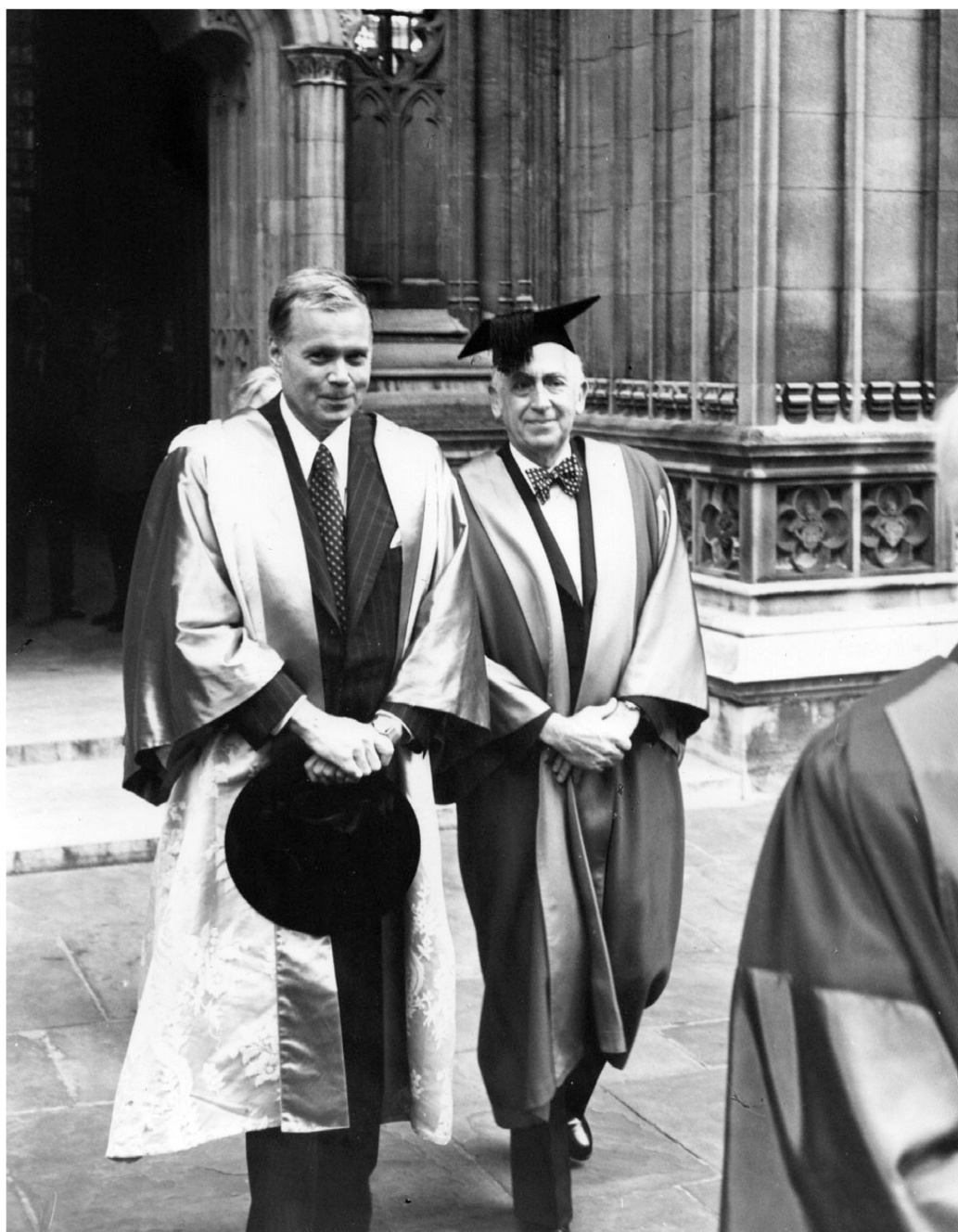
hatched, and the excitatory spiny stellate cell is cross-hatched. Abbreviations: ax-ax.c., axo-axonic cell; ch.c., chandelier cell; l.b.c., large basket cell; M.c., Martinotti cell; mg., microgliform cell; s.b.c., small basket cell; sp.st., spiny stellate cell. (Reproduced from (32); copyright © The Royal Society.)





**Figure 4.**  
One of Szentágothai's numerous aquarelles.





**Figure 5.** János Szentágothai (right) and the singer and conductor Dietrich Fischer-Dieskau (left) at the Encaenia, the Honorary Doctorate ceremony, of the University of Oxford in 1978. (Photograph by Peter Somogyi.)