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The Central Institute for Brain Research in Amsterdam and its Directors

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The Central Institute for Brain Research was founded in Amsterdam in 1908 as part of an international effort to study the nervous system with multiple institutions and various disciplines. The development of research in the past hundred years at the Brain Institute has hardly been documented. We analyze the history of this institute by means of brief portraits of its directors and their main research topics. It appears that each director introduced his own branch of neuroscience into the institute. Initially, mainly comparative neuroanatomical data were collected. Following the Second World War, the multidisciplinary approach slowly developed with research programs on systems neuroscience, neuroendocrinology, and brain disorders. Every new director introduced new approaches to the study of the brain and thus played an important role in keeping brain research in the Netherlands at the international forefront where it has been ever since its foundation in 1908.

Keywords Brain Institute, Netherlands, Brain Commission, Ariëns Kappers, Brouwer, Bok, Swaab

Introduction

In the beginning of the twentieth century, plans were made in Western Europe to create special research institutes for the study of the brain, including one in Amsterdam, which was to be named the Central Institute for Brain Research. Although this institute, now over 100 years old, has played an influential role in the study of the brain, its history has not yet been analyzed in detail and most studies have been written in Dutch. In this article, we first will give a short impression of the situation in the Netherlands before the institute was founded. We then discuss the national and international activities that resulted in the actual construction of the institute. Finally, an overview of the scientific activities is given by concentrating on the consecutive directors and their specific research interests.

Before the Institute

Before the recent advent of neuroscience research institutes within universities, there were only two institutes in the Netherlands specifically devoted to the study of the nervous system. One of these is the Rudolf Magnus Institute in Utrecht, which originally focused

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on posture and movement reflexes (Eling, 2003).The other is the Amsterdam-based Central Institute for Brain Research (*Centraal Instituut voor Hersenonderzoek* [CIH]), founded in 1908.

There was little research on brain and behavior in the Netherlands in the nineteenth century (Eling, 2008). When Schroeder van der Kolk, the founder of Dutch neurology and psychiatry (Eling, 1998), died in 1863, there was a lacuna. His successor in Utrecht, the famous physiologist Franciscus Donders was, with respect to the brain and behavior issues, particularly interested in eye movements and the production of vowels. With his doctoral student Hendrik de Jaager, he developed reaction-time procedures for measuring the speed of mental processes, but, after the development of this technique, he did not use it for additional studies on cognition and the brain. There was no chair of psychiatry in any of the Dutch universities until 1893, when Cornelis Winkler (1855–1941) was appointed Professor of Psychiatry and Neurology in Utrecht. Because of a lack of resources to develop his clinic, he moved to Amsterdam three years later, where he played an important role in the first phase of the founding of the CIH (Eling & Koehler, 2002). The Dutch lagged behind compared to the neighboring countries in this field, but the idea to construct a European network of research institutes (see below) formed an opportunity to quickly catch up.

Foundation of the Institute

Before the twentieth century, scientists were generally united into regional and national associations. At the end of the nineteenth century, there was a trend towards internationalization of these associations. It started with discussions between German and British scientific societies and resulted in the foundation of the International Association of Academies in Wiesbaden in October 1899 (Alter, 1980). In this context, the Swiss anatomist and embryologist Wilhelm His (1831–1904) developed a project with respect to the study of the brain. Since the 1900s, he had been working on a plan to develop a network of research institutes to chart the brain, both in animals and man. The assumption was that a research program for unraveling the brain would be too vast for a single institute, but it would be possible to unite efforts if each individual institute would work according to fixed rules so that data could be compared and combined. For a further elaboration of this plan, a "Central Commission for Brain Research," also referred to as the Brain Commission, was installed by the International Association of Academies in London on June 5, 1903 (Winkler, 1947; Faasse, 1999; Richter, 2000; Brakel, 2008). It was active until the outbreak of the First World War. The main brain researchers of the time participated in the committee, like, for instance, Sherrington, Cajal, von Monakow, Golgi, and Ferrier. Wilhelm His was elected as the first chairman, and, after his death in 1904, he was succeeded by the German anatomist Heinrich Wilhelm Waldeyer (1836–1921). Cornelius Ubbo Ariëns Kappers was the only Dutch member. According to the resolution of the Brain Commission, authorized by the International Association of Academies in May 1904, the National Academies and Societies should address the governments of their respective countries "to found special Institutes for Research into the Nervous System, abbreviated to Brain Research Institutes" (Richter, 2000, p. 447). Several institutes owe their existence to the efforts of the Brain Commission: the Psychoneurological Institute of Vladimir Bekhterev in St. Petersburg, Russia; the Brain Histological Institute of Karoly Schaffer in Budapest, Hungary; the Central Brain Institute of Cornelius Ubbo Ariëns-Kappers in Amsterdam, The Netherlands; and Oskar Vogt's Institute for Brain Research in Berlin, Germany (Richter, 2000).

In the Netherlands, a committee of the Royal Netherlands Academy of Arts and Sciences (KNAW), including Winkler and the neuroanatomist Louis Bolk (1866–1930), developed a proposal for such a Brain Research Institute. The committee proposed that the Institute would be organized within the Royal Academy. The Royal Academy, located in Amsterdam, was an obvious choice because the committee followed the ruling of the Brain Commission that the foundation of the Institute could not properly be supported by any of the medical faculties of the Dutch Universities. Amsterdam was also chosen as the site of the Institute because of the availability of animals for research from the Zoo located there. The University of Leiden voiced disapproval probably because Gerbrandus Jelgersma (1859–1942) was Professor of Psychiatry in the Department of Psychiatry there and he was an excellent neuroanatomist, who worked for many years on an atlas on the human brain, which was published in 1934. In the July meeting of 1905, the committee proposal was accepted by the Royal Academy and presented to the Dutch government (Winkler, 1934). In 1908, the proposal for the CIH was approved and on Tuesday, June 8, 1909, the opening ceremony was attended by many internationally renowned researchers. Cornelius Ubbo Ariëns Kappers, a student of Winkler, became its first director, a position he held until his death.

The Institute was situated in a wing of the new anatomy laboratory of Professor Louis Bolk, located on the Mauritskade 61, the place where the former Eastern cemetery had been situated (see also Baljet, 1992; Figure 1). Organizationally, the Institute fell under the Royal Academy that paid the salaries. This later caused a problem when it was attempted to create a university chair for the director: The minister wanted to appoint only a professor if he was attached to a university.

In order to get some insight into the research activities of the Institute we have searched for annual reports and jubilee books but without success. Therefore, we have decided

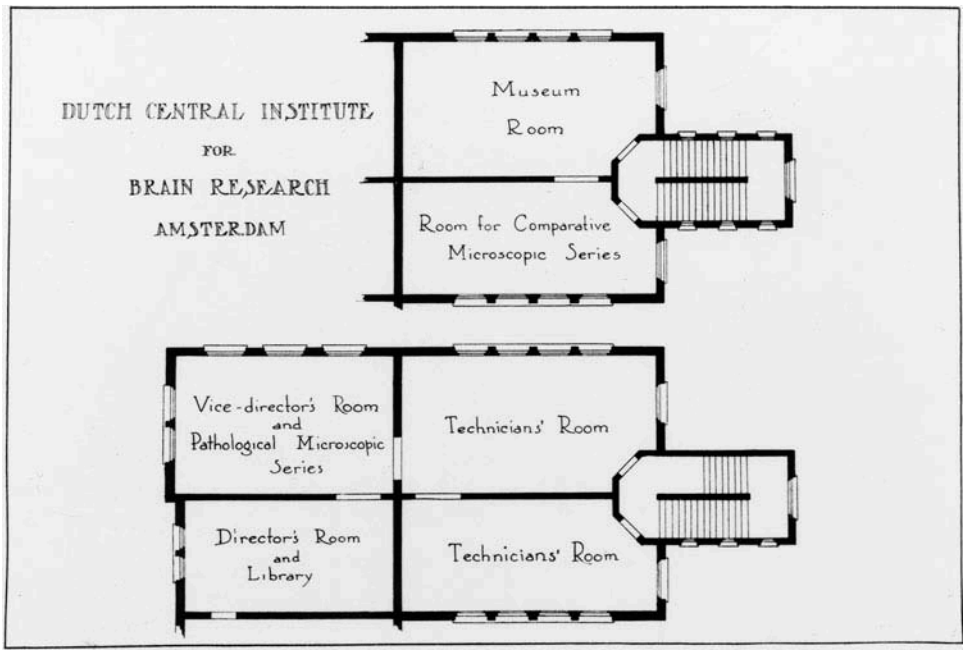

Figure 1. Plan of the Central Institute for Brain Research in 1909.

to focus on the directors of the Institute and their scientific interests rather than on all the research themes of the Institute. For the first period, this more or less coincides with the activities of the Brain Institute. In later years, the CIH consisted of several units and, therefore, our strategy only provides a limited but nevertheless interesting insight into the development of neuroscience research at the Brain Institute.

C. U. Ariëns Kappers

Cornelius Ubbo Ariëns Kappers (informally called Cor and in papers usually referred to as Ariëns Kappers rather than Kappers, which was the official last name) was born in 1877 in Groningen (Brouwer, 1946; see Figure 2). In 1896, he began to study medicine in Amsterdam, where his principal teachers were the neuroanatomist Louis Bolk and the neuropsychiatrist Cornelis Winkler. Following the latter's advice, he participated in a contest on the development of the nerve sheath, which he won shortly before finishing his studies at the university in 1901. With a scholarship thereafter, he went to the then popular Zoological Station in Naples for several months and, in 1903, he became general physician,

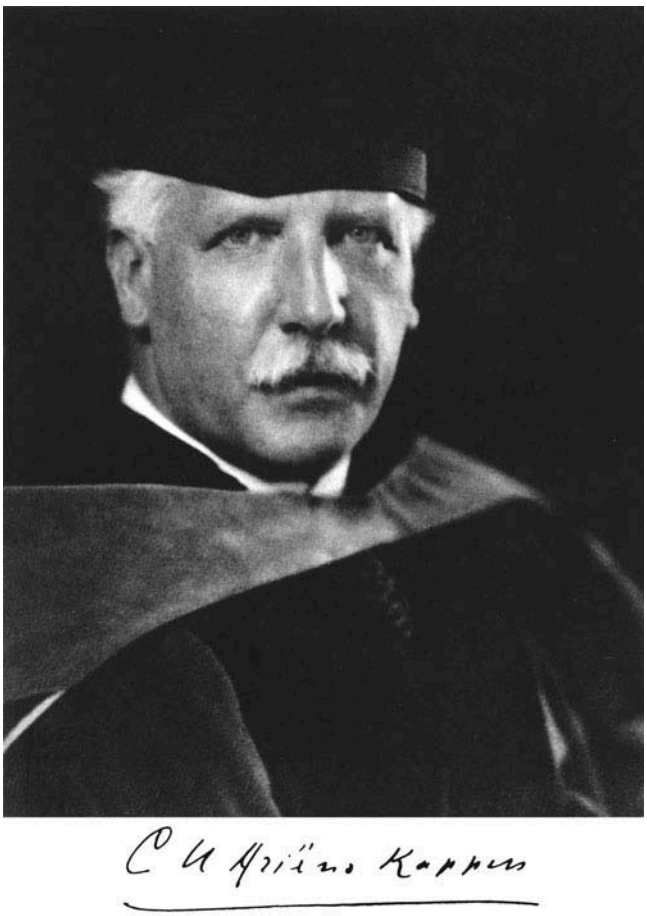

Figure 2. Portrait of Cornelius Ubbo Ariëns Kappers.

although he never practiced as a physician. He graduated cum laude in 1904 on materials collected in Naples. After brief periods in Naples and Amsterdam, he was appointed *Abteilungsvorsteher* (i.e., head of the department) at the *Senkenbergisch-Neurlogischees Institut*, the laboratory of the anatomist and neurologist Ludwig Edinger (1855–1918) in Frankfurt. In 1908, C. U. Ariëns Kappers was appointed director of the newly founded CIH and was the only senior investigator. He had four assistants. On the last day of his life, July 28, 1946, he was still at work at the Institute and he died suddenly in the afternoon.

Ariëns Kappers had many international contacts and visited many countries all over the world. International cooperation was a specific goal of the Brain Commission. The appreciation of his work is demonstrated by many honorary degrees, among which are Honorary Doctorates from Yale University and the Universities of Glasgow, Dublin, and Chicago. Although he was offered a chair at other universities several times, he preferred to stay at the CIH. In 1929, he was appointed as associate professor in comparative anatomy of the nervous system at the University of Amsterdam.

Ariëns Kappers was particularly interested in the comparative anatomy of the nervous system, a common topic for neuroscientists at the time. Annual reports from the Institute include overviews of his publications and accounts of his macroscopic and microscopic brain tissue collection, which still exists (Hofman & Johnson, 2011). In 1921, his *Die vergleichende Anatomie des Nervensystems der Wirbeltiere und des Menschen* [The Comparative Anatomy of the Nervous System of Vertebrates, including Man] appeared. It became a standard work, with an American edition in 1936 and a French edition in 1947. Ariëns Kappers (1921) is particularly known for his theory of neurobiotaxis, stating that during their development neurons migrate to areas where they receive maximum stimulation. This theory played a role in attempts to understand the phylogenetic development of the nervous system. In later years, Ariëns Kappers became interested in the cerebral cortex. He, with the physician and physical anthropologist Arie de Froe (1907–1992), also made skull measurements and helped approximately 200 Jews, during World War II, to get a declaration that they did not have Jewish anatomical features, and, thus, they were able to escape deportation. Autobiographical notes of Ariëns Kappers recently have been edited and published as a book: *C. U. Ariëns Kappers, reiziger in breinen* [C. U. Ariëns Kappers, Traveler in Brains; Kolfschoten, 2001].

In 1934, a Festschrift, a special issue of the journal *Psychiatrische en Neurologische Bladen* [Psychiatric and Neurological Journals], was offered to Ariëns Kappers on the occasion of the twenty-fifth anniversary of the CIH. The significant contribution of Ariëns Kappers is honored in the prize that bears his name since 1987 and is awarded approximately every year to an excellent neuroscientist (Swaab et al., 2005).

B. Brouwer

Bernard Brouwer (1881–1949; see Figure 3), born in Amsterdam, succeeded Ariëns Kappers as director (Biemond, 1949). He received his MD in 1906 and finished his dissertation, cum laude, in 1909, supervised by Winkler. He became assistant director of the Brain Institute in 1912, where his research focused on the occipital lobe and the cerebellum. In 1923, he became the first Professor of Neurology (without psychiatry) in the Netherlands. During the Second World War, Brouwer was rector of the University of Amsterdam and, after the war, he was dismissed by the minister, because he presumably had been amenable to the Germans, a questionable decision (see Koehler, 2006). He was then offered the position of Director of the CIH in 1946. He served in that position until his

Figure 3. Portrait of Bernard Brouwer.

death in 1949. Brouwer arranged for neuropathology to be included in the research program of the Institute.

S. T. Bok

In 1952, Siegfried Thomas Bok (1892–1964; see Figure 4), who previously held the chair of histology at the University of Leiden, was appointed director. Bok finished his dissertation in Utrecht in 1923 (Ariëns Kappers, 1963). From 1929 to 1952, he was a lecturer and later professor of histology and microscopic anatomy at the Medical Faculty of the University of Leiden. He was concerned with research into the connections of nerve fibers, reflexes, and the brain.

When Bok was asked to succeed Brouwer, he argued that the CIH should investigate the nervous system from multiple disciplines. It was originally conceived as an institute that would support the research of others by making brain slices available, so its role was more supportive. In 1959, Bok was allowed by the Dutch government to extend and organize the Institute in four units dedicated to electrophysiology, histology, comparative anatomy, and biology each with different research groups. He was one of the pioneers of the quantitative

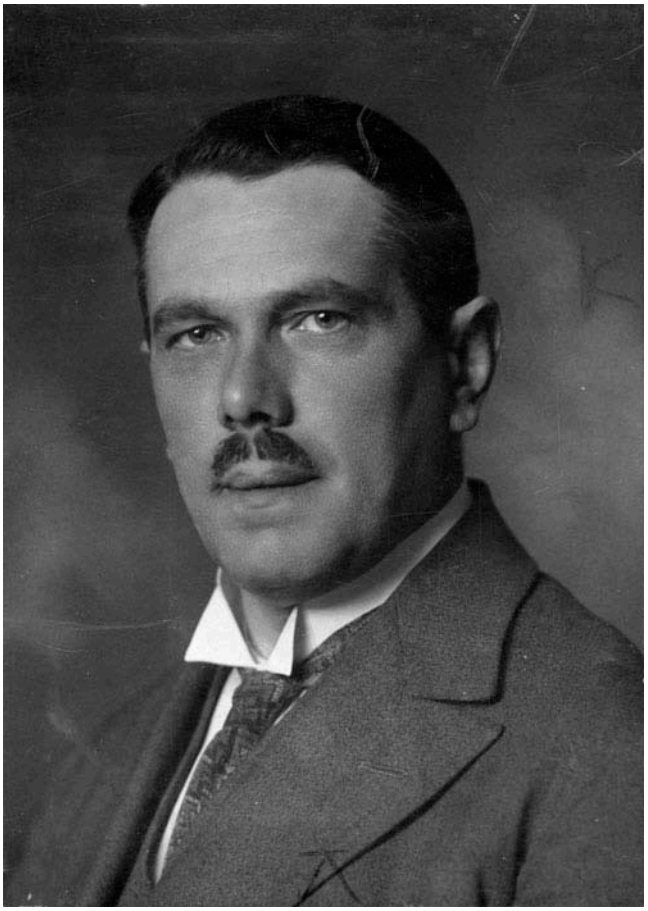

Figure 4. Portrait of Siegfried Thomas Bok.

analysis of the cerebral cortex and introduced cybernetics in the Netherlands.[1] Cybernetics focused on the study of operational systems in which feedback loops play a central role, and it had obvious applications in neurophysiology. Bok retired in 1962.

J. Ariëns Kappers

Hans Ariëns Kappers (1910–2004; see Figure 5), a nephew of Cornelius, took over as director in 1962 (Swaab, 2006). He was born and raised in Amsterdam, did his medical studies there and was soon fascinated by work going on in the Department of Anatomy and Embryology at the university, where he also had contact with staff members of the CIH. In 1946, he was appointed Professor of Anatomy and Embryology in Groningen, became particularly interested in neuroendocrinology and published studies on the pituitary and the pineal glands in the rat. When he became director, he introduced this line of research at the

[1]Norbert Wiener, in his book *Cybernetics* (1948), introduced the term cybernetics to define the study of control and communication in the animal and the machine.

Figure 5. Portrait of Hans Ariëns Kappers.

Institute where it is still pursued today. In 1962, he also became Professor at the University of Amsterdam.

The Institute expanded by adding new departments, such as neuroendocrinology, and it therefore needed a new building. In 1964, the Institute moved to "temporary" buildings at the IJdijk in Amsterdam, in which it stayed for 20 years.

Trouble brewed in 1975. Faasse (1999) notes that, although there were then many disciplines represented in the Institute, its researchers did not collaborate. They were mostly busy with their own projects. Ariëns Kappers was to retire, but, at the date of his retirement, his successor had not been decided. At the request of the government, he remained in office as temporary director. Around August 1975, the governing secretary of state, Klein, wanted to close the Institute; relatively large budget cuts had to be quickly realized. The staff resisted and on December 17, with an amendment by the House of Parliament, it was decided not to close the Institute.

D. F. Swaab

Dick Frans Swaab (b. 1944; see Figure 6) was also born in Amsterdam. Like his predecessors, he studied medicine at the University of Amsterdam until 1968. He defended his thesis in 1970, supervised by Hans Ariëns Kappers, and became general physician in 1972. In October 1975, he became the acting director and, under his supervision, the Brain Institute was reorganized. It also got a new name: Netherlands Institute for Brain Research (NIBR). He was not formally named director until 1978. In 1979, he was appointed Professor of Neurobiology at the University of Amsterdam. Under his leadership, investigators were organized in various groups, such as for neuropsychiatric disorders, sleep and cognition in the elderly, integration mechanisms of the hypothalamus, the prefrontal cortex and cognitive system, neurons and networks, neuro-regeneration, molecular reading errors, and the Netherlands Brain Bank (see below). In 1984, the Brain Institute moved to its new quarters within the complex of the Academic Medical Center of the University of Amsterdam. Swaab was and still is a very active and highly productive researcher with well over 500 publications in international journals and supervising more than 70 PhD students.

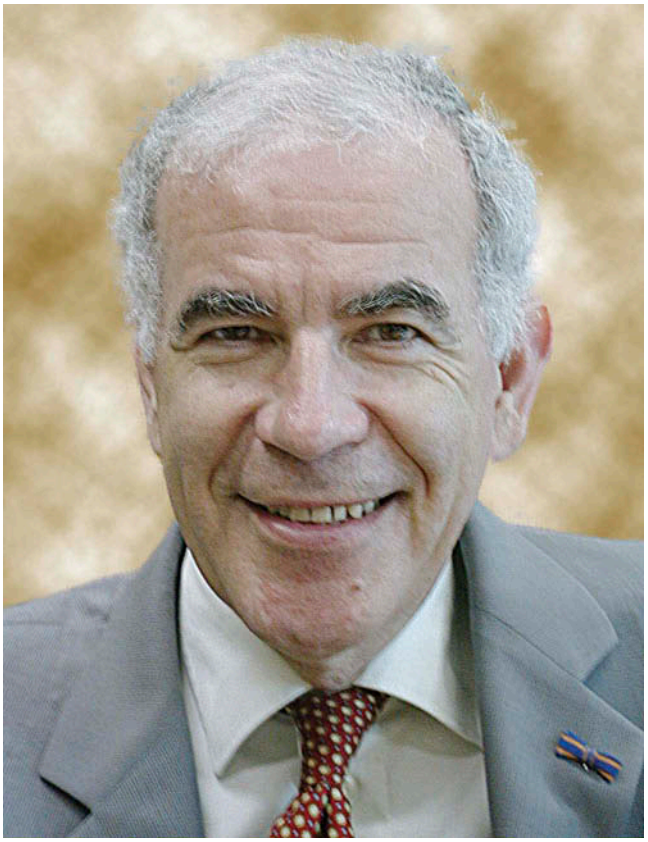

Figure 6. Portrait of Dick Swaab (color figure available online).

His research is mainly focusing on the hormonal and (bio)chemical factors affecting the development and aging of the human brain.

The sexual differentiation of the brain is another aspect of his studies. Important papers about this issue were the 1985 paper in *Science* entitled "A Sexually Dimorphic Nucleus in the Human Brain" and particularly the 1990 paper in *Brain Research* on "An Enlarged Suprachiasmatic Nucleus in Homosexual Men." These publications raised rather hectic public discussions. After his retirement as director, he published a book, summarizing the many insights drawn from his lifelong studies, under the title *We zijn ons brein* [We Are Our Brain; Swaab, 2010], which also attracted wide attention and was translated in English, German, Chinese, Italian, and other languages. The book also elicited vehement discussions, in which Swaab was accused of being a materialist and of trespassing the borders by making philosophical statements.

Netherlands Brain Bank

The Netherlands Brain Bank (NHB) was established as part of the Brain Institute in 1985 by Swaab and Frans Stam (1926–1997). The latter was professor of neuropathology at the Free University with a special interest in Alzheimer's disease. The NHB collects clinically and neuropathologically, well-documented human brain tissue and molecular genetic data

from autopsies of donors with various neurological and psychiatric disorders. In addition, about 1,200 of the more than 3,000 autopsies of donors were of people with no known neurological or psychiatric disorder. The general idea is that such a collection of brains would enable a better analysis of brain disorders.

Netherlands Institute for Neuroscience

On July 1, 2005, the Netherlands Institute for Brain Research merged with the Netherlands Ophthalmic Research Institute and together they formed the Netherlands Institute for Neuroscience (NIN). The general research objective of the NIN became the study of the brain and visual system with a focus on the interactions between the system, its genes, and outside stimuli. A major part of the research of the NIN is the fundamental research to clinical research questions, with emphasis on development, plasticity, and aging. Because high demands were placed upon the new director, finding a proper directory structure proved not to be easy. In 2007, a solution was found by appointing two directors: Pieter R. Roelfsema (b. 1965) as general and scientific director and Chris I. de Zeeuw (b. 1960) as vice director. The official opening of the new institute took place on December 9, 2008, almost a century after the opening of its predecessor the Central Institute for Brain Research.

Conclusion

The Central Institute for Brain Research was designed as a node in the international network that Wilhelm His had envisioned, an ideal that unfortunately never materialized. Every new director introduced new approaches to the study of the brain and thus played an important role in keeping brain research in the Netherlands at the international forefront where it has been ever since its foundation in 1908.

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