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Constantin von Monakow (1853–1930): A pioneer in interdisciplinary brain research and a humanist

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Abstract

Constantin von Monakow (1853–1930), director of the Brain Anatomy Institute in Zurich, was a pioneer in the early history of interdisciplinary brain sciences. The elucidation of connectivity in sensory and motor pathways was richly illustrated in two landmark monographs: *Pathologie du cerveau* (1897) and *La localisation de l'encephale et la dégradation fonctionelle par des lésions circonscrites du cortex cérébral* (1914). His special merit was to conceptualize his accumulating results. As to his term 'diaschisis': (1) neurological lesion are rarely restricted to a histologically defined neural structure; (2) any brain focus is interconnected with remote structures – thus, dependent structures are deafferented from the lesioned territory (= '*diaschisis*') –; (3) dependent structures, however, gradually regain some autonomy, as reflected in partial behavioral recovery. His term 'chronogenic localization' was used for the brain's fundamental organization in time-dependent network constellations. Monakow attracted many researchers, particularly from Japan. He was an engaged member of the International Brain Commission until its dissolution during World War I. ***To cite this article: M. Wiesendanger, C. R. Biologies 329 (2006).***

Résumé

Constantin von Monakow (1853–1930) : un pionnier de la recherche interdisciplinaire du cerveau et un humaniste. Constantin von Monakow (1853–1930) fut directeur de l'Institut d'anatomie cérébrale de Zürich et, à cet égard, un pionnier des sciences interdisciplinaires du cerveau. La connectivité dans les voies sensorielles et motrices cérébrales fut élucidée et richement illustrée par l'auteur dans deux monographies qui ont marqué leur temps, *Gehirnpathologie* , en 1897, et *Die Lokalisation im Grosshirn und der Abbau der Funktion durch kortikale Herde* en 1914. Le mérite de Monakow fut d'avoir su conceptualiser les résultats qu'il accumulait. Par *diaschisis*, un des termes qu'il a souvent utilisés, il a voulu exprimer : (1) que les lésions neurologiques sont rarement limitées à une structure nerveuse histologiquement bien délimitée ; (2) que tout foyer cérébral est lié à des structures plus éloignées, qui pourront de la sorte être « désafférentées » de la zone lésée (*diaschisis*) ; (3) que ces structures regagneront progressivement une certaine autonomie, d'où une restauration comportementale, au moins partielle. Le terme de localisation chronogène fut créé pour établir une analogie entre cette organisation cérébrale et les constellations liées au temps. Monakow a attiré de nombreux chercheurs, en particulier japonais, vers son domaine. Il fut un membre très actif de la Commission internationale du cerveau, jusqu'à sa dissolution pendant la première guerre mondiale. ***Pour citer cet article : M. Wiesendanger, C. R. Biologies 329 (2006).***

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1. A short overview of Constantin von Monakow's career (1853–1930)

At the age of 10, Constantin left Russia with his family. They first settled in Dresden, three years later in Zurich, where Constantin lived for most of his life. After his retirement, he wrote about his scientific life, *Vita mea*, which was edited and published 40 years after his death [1] (see also [2] and Fig. 1).

1.1. Early formative years

Already during his medical education at the University of Zurich, he established a personal contact with the professor of psychiatry at the Burghölzli Clinic, Eduard Hitzig (1838–1927), who, together with Gustav Theodor Fritsch (1838–1907), had discovered the 'excitable cortex' by means of low galvanic stimulations in a discrete area of the frontal cortex [3,4]. Monakow was determined to pursue a scientific career in the field of brain research. Hitzig, recognizing his talent, invited him to take over an assistant position for a limited period and granted him a small salary. This first contact with psychiatric patients was a decisive period, as he was confronted with the question of a link between behavioural and brain pathology; Monakow knew about Wilhelm Griesinger (1817–1868) who, as Professor of internal medicine in Zurich, pioneered the concept that *psychiatric diseases are brain diseases* [5]. As discussed later, Monakow was convinced of the biological foundation of psychiatry. At the end of Monakow's period at the Burghölzli, Hitzig sent him to Munich for a short visit of Bernhard von Gudden (1824–1886). Like Hitzig, Gudden had also been, for a short period, professor of psychiatry in Zurich, but he was also much interested in brain anatomy and pathology. The encounter of the student Monakow with Gudden lasted only two days, but had important consequences for Monakow's future research. Hitzig demonstrated to him how to make histological sections, including brain sections of deceased patients. The large microtome, developed by Gudden, became the gold standard in this early period of brain studies and was later intensively used by Monakow. He learned also about the mechanism of retrograde degeneration that played a crucial tool in establishing the neural connectivity of brain systems, such as the visual pathway from the retina to the cerebral cortex [6]. Monakow also took over the staining method from Gudden (carmine red) that he used all along his experimental career. These early contacts had certainly beneficial consequences for Monakow's scientific career. After having passed his final medical examination, Monakow was unable to obtain a paid assistantship and finally decided to engage as a ship doctor, travelling for one year from Hamburg to Brazil and Argentina.

Fig. 1. Portrait of Constantin von Monakow (date not provided), published in [1].

1.2. First research besides medical duties in a remote neuropsychiatric clinic

On his return in 1878, he managed to obtain an assistant position at the Asylum of St. Pirminsberg in the mountains above Bad Ragaz (Saint Gall), far from a university environment, where he stayed for seven years [7]. Although the conditions were rather poor, he truly made the best of it. The director left most of the clinical work to Monakow who, in addition, had to function as a practitioner of the village. It was an incredible luck that put him on his success track: by chance he discovered in a small never-used room a never-used 'Gudden-microtome'. He quickly managed, with the help of a skilled workman, to organize a small laboratory. Soon he made his first experiments in rabbits and – indeed – he reproduced the mechanism of retrograde degeneration as initiated during his stay with Gudden! He vividly tells the story in *Vita mea* [1]. Full of joy, he was now planning his long-term research during walks and he was to follow it most successfully! One of his discoveries in that period was the elucidation of the architecture of the visual pathway, from the eye to the lateral geniculate body that he identified for the first time as a relay projecting to the visual cortex in the occipital lobe. His research plan was laid down.

1.3. Back in Zurich (1885)

Monakow's work on the visual pathway (done in St. Pirminsberg) consisted of three consecutive parts that he had published in the German *Archiv für Psychiatrie und Nervenkrankheiten*, and that he assembled for a 'habilitation' thesis [8–10]. The medical faculty in Zurich accepted the thesis – he was now a University 'Privatdozent', lecturing to a few interested students. However, he had to face new, economical difficulties: he had no salary, no room, or any financial support from the University! Not without difficulties, he opened a private neurological and general practice, but as it turned out with minimal revenue. He could only afford a small and modest private laboratory. In 1886, still alone and in a difficult financial situation, a young American, Henry Robert Donaldson (1857–1938) came to Monakow, asking for work under his guidance. Thanks to his optimism and persistence, Donaldson and Monakow succeeded to obtain a small empty room in the Pathology Department (for a monthly rent!). Donaldson worked hard during his stay of less than a year in Zurich. His task was to prepare histological sections of a dog's brain which had been operated by Hermann Munk (1839–1912) in Berlin [11]; Munk was famous for having localized the visual cortex by means of the lesion technique and behavioural tests. Donaldson, after having visited other laboratories in Europe (Forel in Zurich, Gudden in Munich, Meynert in Vienna, and Golgi in Pavia), returned to the USA, where he was trained as a clinical neurologist. He also made a PhD thesis under Stanley G. Hall at the Johns Hopkins University. Later on, at the Clark University, he made a thorough investigation on a blind deaf mute patient "whose brain was investigated after her death, probably the most thorough study of a single human brain that has been carried out". After a further stay in Chicago, Donaldson was elected as professor of neurology and director of research at the famous and still existing Wistar Institute in Philadelphia [12]. The Swiss physiologist Jean M. Posternak (1913–2005) worked for a few years at the above Institution in Philadelphia, together with Schmidt, Bronk and Larrabee. In 1951, Posternak returned to Switzerland to occupy the chair of Physiology in Geneva until his retirement in 1980 [13].

In 1894, Monakow received an offer as full professor of psychiatry at the University of Innsbruck: a lucky incidence that was to improve Monakow's situation. It shows that Monakow had acquired visibility in Europe; yet he preferred to stay in Zurich with his family. Monakow was then nominated as associate (not full) professor for brain anatomy and head of the (previously private) neurological policlinic. Ironically, the medical faculty had voted against Monakow's election, but that vote was wisely overruled by the Zurich government! At least his research laboratory and the neurological policlinic received now a university status (the first in Switzerland!), together with a salary for a regular assistant, Mieczyslaw Minkowski (1884–1972).

Minkowski, born in Russian-ruled Warsaw, was excluded from medical studies. He continued his study in Munich and Breslau. After his final examination in Kasan, he worked in the laboratory of Ivan Petrovitch Pavlov (1849–1936) in St Petersburg. Further short studies followed in Munich with Alois Alzheimer (1864–1915), in Berlin with the physiologist Rothmann (1868–1915) who studied deficits in pyramidotomized monkeys.

1.4. The success story of the Brain Institute

The 'Hirnanatomie Institut' now gradually increased its research and was on a good path to become a world-known centre of brain research. The initial one-man show was amplified by young Swiss collaborators: Minkowski was joined by Nägeli, Veraguth, Tramer, Brun, Katzenstein, Frey (who later also had academic positions). Over the years, a series of visitors from Japan came to work at the Brain Institute. It had a considerable impact on the accomplished work, as recently reported by Akert and Yonekawa [14]: Tsuchida (monograph on the oculomotor system); Masuda (pontine nuclei – a link from the cerebral cortex to the pontine grey and cerebellum); Gennosuke Fuse (1880–1946), assistant of the University in Zurich from 1907 to 1911 and again from 1914 to 1916; his opus magnum was an atlas of the lower brainstem; Hisakiyo Uemura working on long-term retrograde degeneration after cerebellar lesion; Tsunesuke Fukuda on thalamo-frontal projections in neuropathological cases (the discovery of the dorsomedial relay nucleus to the prefrontal cortex); Itsuki Nagino (auditory pathway); Sakuemon Kodama (1895–1970), a pupil of Fuse, stayed five years in Zurich. Finally, in 1928/29, Ko Hirasawa (1900–1989) studied the basal ganglia. He made a brilliant career in Japan with a series of outstanding pupils. The Japanese were hard-working scientists, adding considerably to the prestige of the Institute.

The scientific languages included English, French and German, but the large majority of Institute's publications were in German, a few in French and probably none or only a few short ones in English. Monakow travelled intensively to meetings in Europe, mostly in Germany, and presented his richly illustrated work. The talks were often distributed in printed form, either as a résumé or as long full papers. He had already accumulated anatomical results about the visual and auditory pathways. Less known are also investigations of the pyramidal and rubrospinal tracts (the *Monakow Bundle* [15–17], see also Fig. 2). Monakow's primary aim was to elucidate functional systems, rather than single neurons.

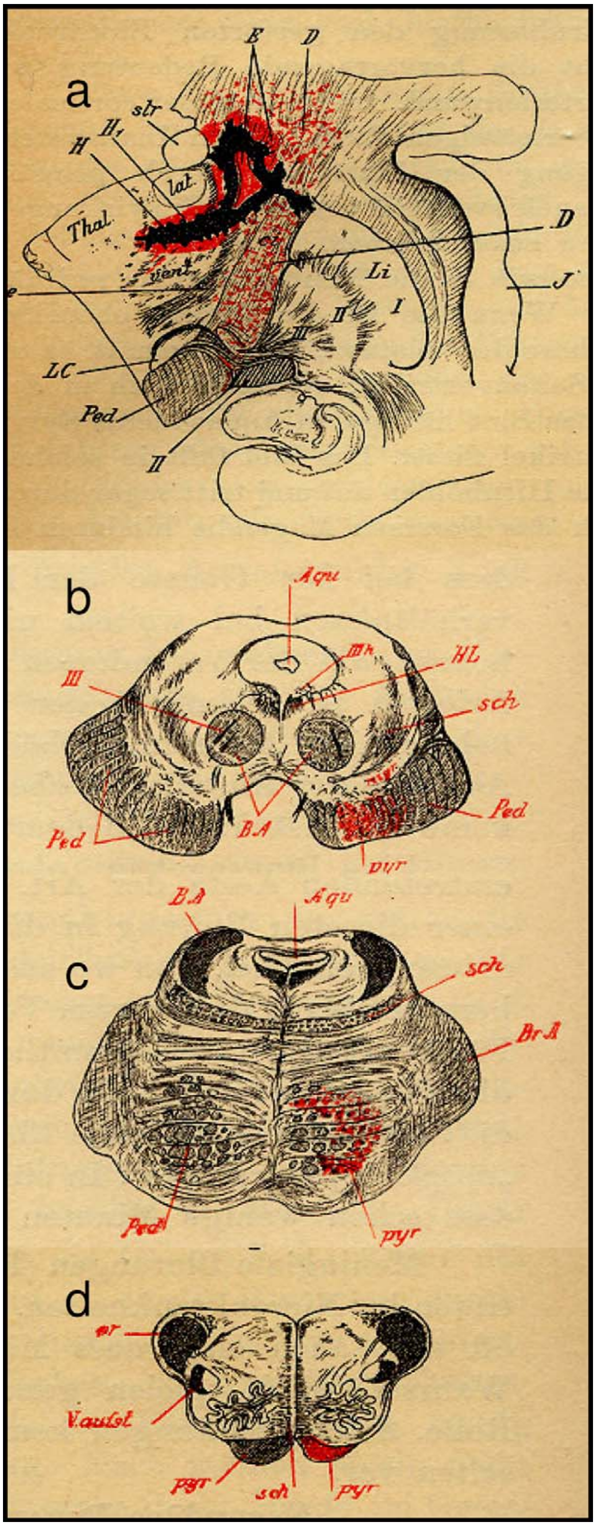

Fig. 2. The course of degenerated pyramidal tract fibres revealed by Marchi degeneration (marked red points in the transverse sections b, c and d). Reproduced from Monakow [22 (p. 722, figs. 171–174)]. At the time, this was the typical technique for establishing the connectivity of the motor and sensory pathway. Brain sections from a patient who suffered from a haemorrhagic insult (exitus six months later). (**a**) The focus of the bleeding is indicated in black at upper midbrain level. A massive interruption of descending fibres in the capsula interna entering the peduncle (quasi-horizontal section) led to their anterograde degeneration, as viewed with the Marchi procedure. (**b**) Transverse section at the midbrain level shows the degenerated fibres in the middle segment of the peduncle. (**c**) At the pontine level, descending degenerating fibres in a crescent-shaped order between islands of pontine neurons (neurons not visible with the Marchi staining). (**d**) Pyramid totally filled with degenerated fibres directed to the spinal cord. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

An interesting paper is about the construction and localization of movements in Humans [18] that he presented at the 4th international 'Kongress für experimentelle Psychologie in Innsbruck' (Austria). He discussed the various forms of movements, like reflexes, rhythmic automatisms, respiration, mastication, sucking, swallowing, orienting movements (eyes, neck, trunk), finger pointing, hand dexterity, expressive movements; also the principle of division of labour, synergy as a manifold of cooperative muscles required for postural support of aimed skilful movements. He emphasizes the time factor, i.e. the kinematics ('kinetische Melodie') versus the static view in anatomy. He then proceeds with the neural organization of movements and the results of brain lesions. The first brain map of the Human cortex, obtained with electrical stimulation by the neurosurgeon Krause (1857–1937), is also reproduced in this paper. Neural structures fulfilling such tasks are likely to be distributed as networks occupying an ensemble of several cortical and subcortical structures. Finally, he suggests that higher brain structures generate mental projects of voluntary actions (*Bewegungsentwurf*). This talk must have had an impact because it provided an unusually rich insight on the behavioural organization of volitional movements. It was precisely the time when neurologists, such as Hugo Liepmann (1863–1925), began to differentiate paretic and apraxic deficits in neurology [19].

In addition to many German colleagues, Monakow had also strong links with Dutch neuroscientists, such as Cornelis Winkler (1865–1941, the first professor of neurology and psychiatry in Holland), Brouwer and De Vries (from Jagella and Koehler; see: http://www.onderzoekinformatie.nl/en/oi/nod/oderzoek/OND1260170). Monakow had only few contacts with England (e.g., at the Brain Commission, see below). In 1895, he went to Paris for a few weeks, visiting the famous neurological centres, first of all at the 'Salpêtrière' hospital. He visited Jules Joseph Déjérine (1849–1917) and his wife Augusta Déjerine-Klumpke (1859–1937), an American doctor from San Francisco. She was the first women doctor to pass the 'interne' examination in neurology in Paris; accordingly she was appointed as 'chef de clinique'. Monakow was well received and was amazed how freely and alone he could visit all the neurological collections. He was amazed about the large number of technical staff, as compared with his own minimal technical support. On the other hand, he considered his own private collection to be equally rich and also more diverse. Monakow was particularly impressed by Mme Déjerine-Klumpke – in the words of Monakow "the soul of the laboratory". She had much contributed to the collection of anatomical and pathological preparations. Before returning to Zurich, Monakow also visited other neuro-centres of Paris, but remarked that "*in hirnanatomischer Hinsicht (war) für mich relativ wenig zu holen*"![1] But 28 years later, when he was celebrating his 70th birthday, Monakow thanked the colleagues from Paris for the friendship he had received during his stay and how much he had been enriched by the famous Neurology schools (p. 274 in [1]).

As far as we know, Monakow never returned to his country of origin that became the Soviet Union. However, he had contacts with the neurologist–psychiatrist Vladimir Michailovitch Bechterev (1857–1927) in Petrograd, since he and Monakow were members of the international Brain Commission (see below). Bechterev, as a University Professor of clinical Neurology and Psychiatry and as director of the Psycho-Neurological Institute of the Russian Academy, was a pioneer in studies on brain localization (see also Meyer [20]). In 1923, Bechterev was invited to contribute to the Festschrift for Monakow's 70th anniversary; his presentation (in German) was printed in *Schweizer Archiv für Neurologie und Psychiatrie* [21]. This was the year of Monakow's retirement. The medical Faculty opted for another nobility to follow Constantin von Monakow: the Neurologist and Neuroscientist Constantin von Economo (1876–1931) who was famous for his studies on the pandemic Encephalitis lethargica in the 1920s, and also for his cytoarchitectonic work on the human brain. For reasons unknown to me, this succession did not come true. Monakow was now a honorary professor and as such continued to be director of the Brain Institute and to keep the chair of neurology until 1927. The idea of the authority was to keep the options open for an external candidate. In 1928 Minkowski then took over as director of the Brain Institute and the chair of neurology until 1954. The neurology clinic, under the new head of Fritz Lüthy (1895–1988), then moved to the new University Hospital. It was only in 1961 that a new Brain Research Institute was created by Konrad Akert (born 1919), as a succession of Monakow's Brain Anatomy Institute.

An important factor for the dissemination of Monakow's work was the early publication in 1897 of the 'Gehirnpathologie' [22], a massive tome, which was soon followed by a much updated second edition in 1905. Already in 1899, the French scientist Jules Soury [23], director of studies on current doctrines of physiological psychology at the Sorbonne in Paris, wrote an extensive review on the accumulating German publications of Monakow. In the last updated reception of Monakow's work [24], Soury's surprisingly early and detailed evaluation of Monakow's research is not men-

[1] "In terms of brain anatomy, there was little to gain for me!"

tioned. Another tome of Monakow, *Die Lokalisation im Grosshirn und der Abbau der Funktion durch kortikale Herde* [25], was apparently less distributed than the 'Gehirnpathologie', although it was in this monograph that the concepts of 'chronogenic localization' and 'diaschisis' are presented (Section 3 of this article). The book was a compilation of three long reviews, vols. 1, 3 and 6 of *Ergebnisse der Physiologie*, republished in 1914 as a monograph. Monakow dedicated the book to the Faculty of Medicine at the inauguration of the new University building in 1914 – perhaps his 'revenge' for not having been well treated by the Medical Faculty at the occasion of his appointment as Associate Professor! A third book was published together with Mourgue [26]. It provides a broad picture on brain matters, including also psychological, sociological, philosophical, ethical and religious issues. It was written in the last period of Monakow. The historical heritage of Monakow's work has not been much discussed in English. Some punctual anatomical discoveries of Monakow have been considered by Meyer's *Historical aspects of cerebral anatomy* [27].

The tragedy of World War 1 had clearly affected Monakow's previous enthusiasm. He was still active in expressing his views in articles and conferences and guided experimental work, but diminished his clinical-neurological activity. International collaborations were broken, particularly in the framework of the established Brain Commission in which Monakow had been much involved. In the following, I attempt to discuss three central issues of Monakow's work: (a) the international and interdisciplinary Brain Commission; (b) the issue of functional localization and plasticity; and (c) views on the biological foundations of psychiatry.

2. Monakow and the International Brain Commission

2.1. Beginnings

In the last third of the 19th century, there was an extraordinary impetus for anatomical-physiological research and discoveries, as well as for clinical-neurological issues. Some centres emerged in Europe that were particularly involved in neuroscience research, among them Monakow's Institute of Brain Anatomy and the Neurology outpatient clinic in Zurich. Wilhelm His (1831–1904), Professor of Anatomy in Basel and later in Leipzig, was crucial in propagating the creation of interdisciplinary institutions for brain research [13]. In 1901, the International Association of Scientific Academies commissioned an *ad hoc* committee in Paris to take stock of existing collections of material based on brain research. The aim was (a) to widen the knowledge about the organization of the brain, (b) to investigate how the existing material can be made available to the brain research community, (c) to encourage international collaboration. In view of the complexities of the brain and considering also its relevance for clinical neurologists, brain surgeons, psychologists, educationists and lawyers, it was deemed necessary to make a concerted effort in specialized institutes to make the new insights available to a broad audience.

Already in 1904, an *ad hoc* commission received the mandate from the International Association of Academies to work out details of how such a commission should be functioning [28,29]. The Brain Commission was established in 1906 and consisted of eight institutions: (1) the Wistar Institute in Philadelphia, USA (Henry Donaldson, the only member outside Europe, who had been Monakow's first visitor in the laboratory); (2) the Anatomy Institute in Madrid (Santiago Ramon y Cajal); (3) the Brain Anatomy Institute in Zurich (Constantin von Monakow); (4) the Neurological Institute in Frankfurt a.M. (Ludwig Edinger); (5) the Neurological Institute in Vienna (Heinrich Obersteiner); (6) the Neurological and Psychiatric Clinic in Leipzig (Paul Flechsig); (7) the Neurological-Physiological Laboratory in St Petersburg (Vladimir Michailovitch Bechterev); (8) the Central Brain Research Institute in Amsterdam (Cornelis Winkler).

The idea was in the first place to develop further the exchange of information, in terms of publications and also of a transfer of novel methods and technical devices; specialized libraries should be open to the Institutes; coordinated collaborations on common large projects, like the production of brain atlases, were to be implemented. Moreover, shorter visits in laboratories were encouraged. An additional aspect was also to foster better ties among basic scientists and clinical neurologists and psychiatrists. Interestingly, a topic that has now lost its interest, was also considered to be important: to investigate brains of deceased famous people in order to capture the specifics of a genial brain [30]. As an example of many others, the brain of Monakow was also analysed in 1935 by Anthony [31]. All the above recommendations had been accepted by the International Association of Scientific Academies.

2.2. The Brain Commission and 'Internationalized' Brain Research in Zurich

In the 1912 paper, i.e. a few years after its foundation, Monakow [29] presented the actual situation of the Brain Commission and its importance to the Swiss Neurological Society. Of course, Monakow gave a positive picture of the development of the international commission, consisting of 30 official members. He was motivated to fulfil all the recommendations from the international Brain Commission and wanted also to see progress in the Swiss Neurological Society. From the published protocol of Monakow's oral exposé on the above commission, one gets the feeling that it was well received. There was, however, one reported item that found some resistance: the traditional institutions should not lose their contribution in their teaching – a delicate issue! Was there perhaps also a fear that research on the nervous system would be an exclusive privilege of Monakow's Institute?

It is not clear whether the progressive ideas of the Brain Commission proved to be successful at the international level. According to Monakow [32], Gennosuke Fuse had come in 1907 for a limited period to work with Monakow and a more prolonged visit was reiterated (1913–1915). This time he was most involved in the project of the Brain Commission, to illustrate and comment comprehensively successive histological sections of the Human *medulla oblongata* – a beautiful atlas, printed in Zurich (Die Medulla oblongata, Orell-Füssli, 1916). The plan of the Brain Commission was to complete such work with further volumes that eventually would include the whole Human brain; unfortunately, this never happened! It is only in the present era of brain imaging that such atlases are again in demand.

In *Vita mea* [1], Monakow gives a most impressive account on the consequences of World War I. Almost all international connections were broken, many of the official members of the Commission had died (only three out of 30 survived). Travelling became increasingly difficult – in short: the Brain Commission lost its raison d'être. It was a turning point for Monakow's intellectual life, as impressively described in *Vita mea*. He continued to give talks and published his thoughts, but now concerning more psychological and philosophical issues of the Human brain (see more details in Section 4).

After World War I, Monakow made a last effort to revive the international Brain Commission [32]. In his speech to the Swiss Society of Neurologists, he repeated the arguments he had explained before the foundation of the Brain Commission. He also mentioned the intention to continue the work of a Human whole-brain atlas that was started by Fuse. But Monakow realistically also mentioned that the predominance of German delegates may have been an unfavourable factor. Apparently, the British, American and French delegates rarely attended the bi-annual conferences, even before the outbreak of World War I, perhaps also because of language problems. However, Monakow's hope was to motivate the young generation for re-creating a new international cooperation with similar aims, as in the past.

As we now know, it took a long time, including the devastating WW2, until new and this time a most successful world organization was created: the International Brain Research Organization (IBRO), founded in Paris under the auspices of UNESCO. In the *History of IBRO – A brief survey* (see IBRO on the Internet) says:

> "The International Brain Research Organization (IBRO) was founded in 1960, in response to a growing demand from scientists from many countries and different disciplines for the creation of a central organization for the better mobilization and utilization of the world's scientific resources for research on the brain. The origin of IBRO can be traced back to a meeting of electroencephalographers in London in 1947, which led to the establishment of an International Federation of EEG and Clinical Neurophysiology. At a conference of this group and others in Moscow in 1958, there was unanimous support for a resolution proposing the creation of an International Organization representing the whole of brain research. This plan was welcomed by UNESCO and in 1960 IBRO was established as an independent, non-governmental organization. In all continents there are now large 'regional' IBRO-dependent associations, particularly with the aim of a broad education of students of Brain Research in underdeveloped regions..."

There is no mention about the old *Brain Commission*, despite the fact that the goals were similar to those of IBRO. Shortly after WW2, scientific contacts among European countries were difficult, often because of the economic situation. The pre-war years of the 20th century had produced Brain Centres, similar to Monakow's Institution, in Austria, Belgium, Britain, France, Germany, Italy, The Netherlands, Scandinavia and Spain, many of them functioning poorly in the early post-war years. Recovery was slow until, in the early 1960s, a phenomenal and steady rise in Brain Research, coupled with a restored economy, made it possible to acquire modern electronic equipment, including computers, and to hire young people for research, and last not least the opportunity of frequent interactions with neuroscientists in the world! There are now several very large and attractive neuroscience societies in Europe, the USA, Canada, Japan, Australia, New Zealand, with strong emphasis on the young generation. The ways of how this happened is different from the pre-war time, but the aims, the spirit of Monakow and of many other great figures in brain research still enrich the present studies of the brain.

3. Doctrines on brain 'centres' versus Monakow's chronogenic localization, diaschisis, and plasticity

3.1. Controversies on brain localization and the factor of time

Localization has always been an issue in brain discussions: in the middle age and up to the 'phrenologists' in the early 19th century (the whereabout of *mental faculties*). The dominating idea remained that the brain is subdivided in functional *centres*, even with the birth of a more scientific, neurological approach in the 19th and 20th centuries. The discovery of a speech centre by the surgeon Pierre-Paul Broca (1824–1880) paved the way for further intensive searches in neurology and neuropathology. Broca's patient had lost his 'faculty' to speak; after the patient's death, the autopsy revealed a large lesion in the left hemisphere, from the lateral end of the Rolandic fissure extending far rostrally. The discovery of a speech centre was an enormous boost for making further discoveries in identifying other centres in the brain that may be associated with a given function (the old 'faculties'). And indeed, more or less localized 'centres' for moving, feeling, hearing, and viewing were soon established. Broca's far-reaching discovery had two consequences: (1) classification of distinctive neurological syndromes and their neuropathology, and (2) understanding the brain in terms of its functional representation, often also called centres.

However, an enormous problem was arising right from the beginning. The question is (and actually still is!): *What* is represented? Since the early 19th century, a harsh non-ending controversy arose between 'localizationists' and 'anti-localizationists'. Here is a documented example that took place at the famous Salpêtrière Hospital in Paris (reported in a recent book by Gasser [33], on the base of the C. R. Soc. Biol. Paris, 1875). The famous neurologist Jean-Martin Charcot (1823–1893) presented his thoughts about localization in the brain and ends as follows: "*Il existe certainement, dans l'encéphale, des régions dont la lésion entraîne fatalement les mêmes symptômes*."[2] However, the well-known and experienced physiologist Charles-Édouard Brown-Séquard (1817–1894) intervenes with the following remark: "*J'ai le regret d'être en complet désaccord avec M. Charcot. Je ne saurais accepter la théorie des localisations telle qu'elle est émise actuellement*." An important argument of Brown-Séquard was that a lesion is unlikely to cover the territory of a given representational unit; moreover, that a given lesioned territory loses its connection with unlesioned functional units that are then inhibited. (But at that time, the *mechanism* of inhibition was unknown and he may have conjectured that inhibition is equal to loss of excitation from the lesioned territory.)

Monakow's point was: *The clinicians identify the localization in terms of the resulting symptom (or of symptoms) instead of a function; the function is displayed in time* [26]. Already in 1905 Monakow therefore coined the key expression of 'chronogenic localization' [34].

3.2. Diaschisis

Associated with the above term of chronogenic localization, Monakow also coined the term of *diaschisis* [35]. The latter concept was discussed in more detail in Monakow's second large monograph on localization [36]. In short, *diaschisis* means: (1) an acute brain lesion is likely to affect the function of several dependent, non-lesioned representations; (2) the lesioned tissue (for example of the motor cortex) is interconnected to and from other brain regions by afferent and efferent fibre systems (e.g., disrupted thalamic ascending and descending fibres, or descending fibres to subcortical motor relays); (3) as a consequence, interruption of the connections leave the dependent, but anatomically intact regions without control; (4) thus these disconnected, distributed structures lose their normally integrated function as a coalition. Monakow used the term *Betriebsstörung*, which may be translated by malfunctioning coalition. The process of diaschisis is responsible for the initial and most severe deficit. Gradually, the non-lesioned, but previously dependent structures regain a certain autonomy. For example, subcortical motor structures may take over some control on the motor apparatus. This process of functional recovery (or *'plasticity'*) is slow and can last for months and even years. In essence *diaschisis* has the attribute of a dynamic process, starting with a sudden deep depression of functions with (a non-linear) slow recovery that only rarely ends with a full reconstitution of functions – there is almost always a remaining deficit (Monakow's *Restdefizit*). It should be clear that the above term of diaschisis has a link with *chronogene Lokalisation* described above.

[2] Focalized lesions in a given brain area produce always the same symptoms.

A recent historical paper on *diaschisis* [37] provides a broader picture on the context and the multifacetted aspects of diaschisis in terms of post-lesion recovery. Conceptually, Monakow's ideas foreshadow also present research and speculations on the dynamics of the brain (e.g., [38]).

The term *diaschisis* had only rarely been mentioned in the neurological literature. Related issues are now discussed more in terms of *plasticity* (*Anpassungsfähigkeit*), a term that is vague and descriptive, involving a number of potential mechanisms: synaptic reorganization, formation of new connections, and last, but not least, changes in strategies. Most interestingly, and to my knowledge not discussed, is Monakow's speculation in the first (1897!) edition of the *Gehirnpathologie* about potential collateral sprouting of 'internuncial neurons' (= interneurons), particularly when interneuronal activity is increased [22], verbatim: "*Auswachsen infolge gesteigerter Inanspruchnahme der Collateralen mancher Sammelzellen Neuronengruppen aus der weiteren Umgebung mit in den Bereich des Erregungsgebietes jener Zellen gelangen...*"[3] In an annotated translation of Ramon y Cajal's work [39], one can read a similar hypothesis with reference to Monakow's diaschisis concept (pp. 485–486): "...new collaterals which, on running through the damaged regions, reestablish contacts with the disconnected neurons", and "...the new-formed branches would go in search of other nerve cells [...] to give a new functional character" [39]. Both authors, but especially Cajal, emphasize also the value of training to enhance functional recovery by enhancing the transmission from neuron to neuron: "... it could be supposed that *cerebral gymnastics* (sic!) leads to a little beyond ordinary development of dendritic processes and axonal collaterals, *forcing the establishment of new and more extensive intercortical connections*" [39 (p. 81)]. But note that, at this time, neither Monakow nor Cajal had the proof of this. Monakow also conjectures that a part of functional recuperation may be achieved by means of selecting or learning new strategies – termed the principle of motor equivalence by Karl Spencer Lashley (1890–1958) [40]; similar terms were voiced by Albrecht Bethe (1872–1954) [41] and Nicolai Bernstein (1896–1966) [42]. Monakow made also a schematic sketch of the diaschisis concept [35] (Fig. 3).

At the time of Monakow, the concept of *diaschisis*, was more often discussed among neurologists (see also English translation by Pribram [43]). Another English translation (from the German version in *J. Psychol. Neurol.* 17 (1911) 185–200) on the issue of *localization of brain functions* has been published by Gerhardt von Bonin [44]. In recent years, the concept of *diaschisis* found again some support with the advent of brain imaging (e.g., [45]). It was also observed that regions outside of a lesion may first be metabolically depressed, gradually changing into a locally increased metabolism.

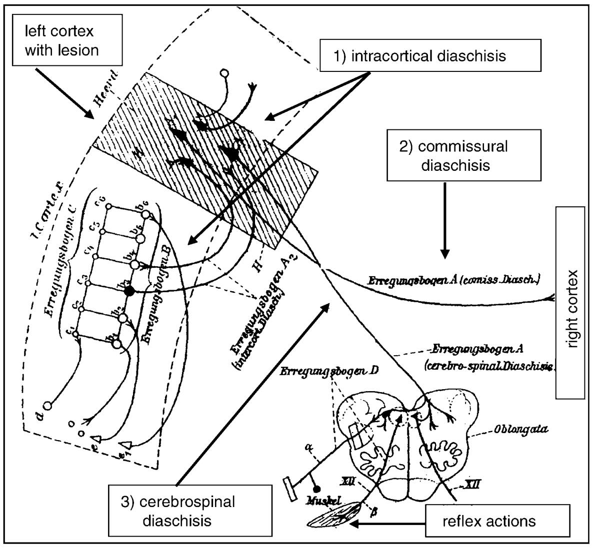

Fig. 3. Monakow's concept of *Diaschisis* (taken from [35]). Schematic drawing of left motor cortex with a lesion (filled rectangle). The black pyramid-shaped neurons lose their outgoing axonal connections, (1) to nearby and more distant cortex of the same hemisphere, (2) to contralateral cortex (commissural fibres), (3) descending fibres to brainstem nuclei and spinal cord. The lesion interrupts neural transmission to the dependent structures. This sudden loss in controlling the target structures is what Monakow means by the term *diaschisis*. As a consequence, the function of the non-lesioned dependent structures (e.g., structures in the brainstem) are initially depressed. Partial recovery is observed when the dependent structures increase again their own neural resources. Typically, a remaining deficit (caused by the cortical lesion) can be observed (Monakow's *Restdefizit*). It follows from this argument that the process is time-dependent. For that, Monakow introduced the term of *chronogenic localization*. In other words, the loss of a function (or functions) after a brain lesion is time-dependent because the initial deficit entails a number of distributed networks that are not adequately controlled (Monakow's *Betriebsstörung*).

More generally, Monakow was also interested in compensatory ('vicarious') plasticity. He illustrated this in his *Gehirnpathologie* [22 (p. 263)], in a case of an old (possibly perinatal) right-sided cortical lesion, a much reduced volume of the left cerebellar hemisphere, right pyramid and right inferior olive, whereas on the right side these structures had an increased volume (Fig. 4). Monakow was not sure what the significance of this increased volume of the right pyramid and cerebellar hemisphere might be – was it a compensatory anatomical reorganization? Since that time, similar cases have

[3] In short: Sprouting as a consequence of hyperactive interneurons.

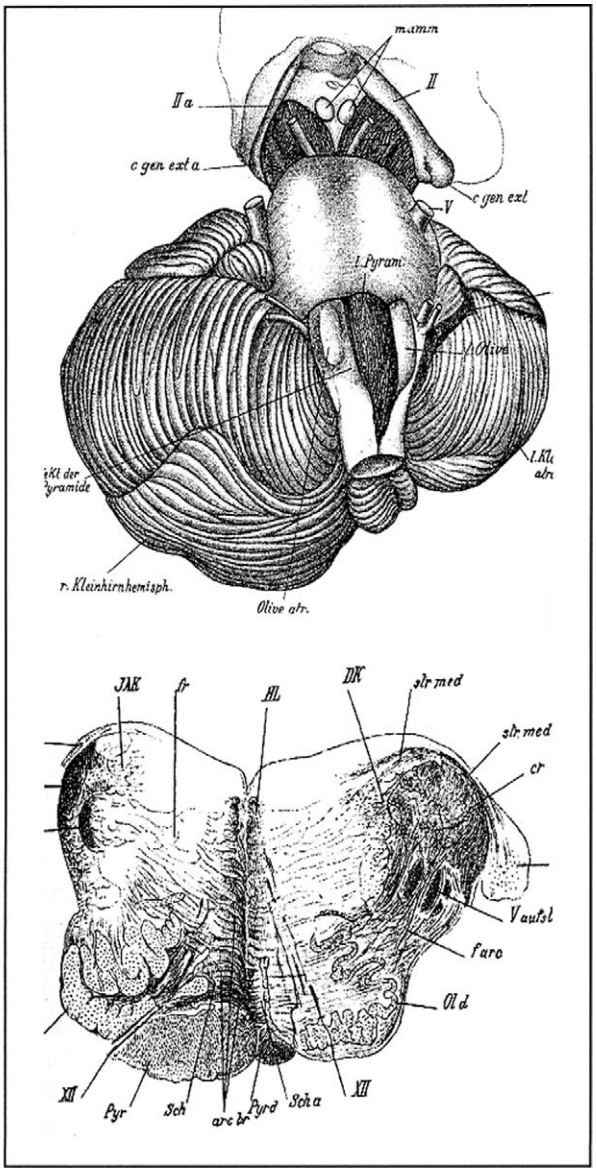

Fig. 4. A case illustrated in Monakow's Gehirnpathologie [22 (figs. 86 & 91)]: the pathology showed long-term massive asymmetries of the cortico-cerebellar and pyramidal systems probably due to multiple long-term perinatal lesions ('Porenzephalie') in the right cortical hemisphere and the left cerebellar hemisphere. The long-term reorganization of this case was remarkable. See further explanations about the plasticity issue in the text.

been reported in chronic cases with unilateral perinatal brain lesions, for example, by Schachenmayr and Friede [46] from the Institute of Neuropathology in Zurich (who mention the above case of Monakow). They found that the cause of the increased volume of the hypertrophic tract were "...increased myelin sheets that encompassed columns of glial nuclei instead of pyramidal axons...". Therefore the authors concluded: "This type of change, along with the clinical data, may indicate that the lesion originated in the perinatal period when myelin formation is in progress and is susceptible to derangement."

4. Monakow's growing interest in psychiatry, psychology and philosophy

4.1. The culmination followed by the outbreak of war and its consequences

Monakow worked and fought all his life long for the creation of a new centre of interdisciplinary brain research. In fact, brain research centres in Germany developed their Institutes at a fast pace, for example, in Berlin the 'Neurobiologische Station' of Cécile (1875–1962) and Oskar Vogt (1870–1959), and later their expansion in a newly built complex at Berlin-Buch. In this area, a number of 'Kaiser Wilhelm Institutes' were established, notably the institutions of the Vogts: Departments of Neuroanatomy, Neurophysiology, Neurochemistry, Genetics, workshops, an attached Neurology Clinic, – at that time probably the largest brain research institution.

In 1913, when the Brain Institute in Zurich was already well known among the neurology community in Europe, Japan and, to a smaller extent, also in the United States and Canada, Monakow finally had also reached a consolidation of his University status, including the 'Nervenpoliklinik' (outpatients only) and the laboratories, now all in the nice large mansion 'Belmont', situated near the newly-built University. Finally, clinical and biological neurology was under the same roof – it was the culmination of Monakow's career.

As said before, the outbreak of the war in 1914 changed Monakow's life style. He now wanted to go beyond the brain structure and to address the great questions about the human brain, including psychology, psychiatric diseases, especially schizophrenia and depression. A famous discussion club was created where many open questions on brain matters were discussed, a kind of a journal club – called the 'Monakow Kränzli'. Participants were: Monakow, the psychiatrists August Forel (1848–1931) and Eugen Bleuler (1857–1939) with his assistants Carl Gustav Jung (1875–1961), and Gustav Bally (1893–1966), the neurologist Max Cloetta (1886–1940), the professor of Forensic Medicine Heinrich Zangger (1874–1957), the physiologist Walter Rudolf Hess (1881–1973), and the ophthalmologist Adolphe Franceschetti (1890–1868).

Whereas Monakow gradually withdrew from hands-on experimentation, the number of visiting researchers and assistants increased, and they added much to the forthcoming results and publications. I can only allude to a few important publications of Monakow's oldest pupils, Minkowski (1884–1972) [47,48] and Brun (1885–1968) [49].

Since the outbreak of the war in 1914, Monakow gradually withdrew from hands-on experimentation, but took the time to discuss with his co-workers their research progress. The focus of his own interest, however, is now directed to higher brain functions. He is not happy about the division of neurology and psychiatry; in his clinical work, he saw both types of patients. His belief was that progress in understanding the underlying mechanisms and adequate treatment require an interdisciplinary, *neurobiological* approach, including psychiatry. Accordingly, Monakow now also publishes articles about his vision of an integrated and multidisciplinary neurobiology including one on biological psychiatry [50]. Another typical paper is on the emerging phenomenology of the philosopher Husserl, whose writings (and his use of language) are criticized by Monakow [51].

In 1925, Monakow initiated a new book project, together with the French psychiatrist Raoul Mourgue [26], who came to Zurich for daily discussions and for composing and arranging the notes for the intended book. The completed book (in French) consists of two parts: (*i*) *Intégration* and (*ii*) *Désintégration*. The mixed flow of observations, interpretations and suggestions makes reading somewhat difficult. The first part (four chapters) deals first with six variations of instinctive behaviour, autoregulation ('syneidesis'), motricity as an instrument of instincts, orientation, language, and the problem of causality. The four chapters of Part II are about disintegration of movements, apraxia, agnosia, aphasia, disorders of orientation (Ch. 1), neuroses (Ch. 2), schizophrenia (Ch. 3), and disorder of the blood–brain barrier (Ch. 4): indeed a formidable *tour d'horizon*!

The last chapter in Part II is of historical interest, because the authors suggest that psychoses may occur due to malfunctioning of the blood–brain barrier (BBB). The basic ideas go back to an investigation done in 1919 by Monakow and Kitabayashi [52]. The hypothesis was that schizophrenia is due to a biological disorder. In particular, Monakow conjectured that a disorder of the choroid plexus, producing the cerebrospinal fluid, may cause the psychosis.

4.2. The discovery of the blood–brain-barrier and Monakow's link with Lina Stern

A thin layer of ependyma cells cover the villi of the choroid plexus and also the 'bare' walls of the ventricles. The plexus receives a dense capillary blood supply. By and large, the concentrations in the blood compartment and in the cerebrospinal fluid compartment are similar for small molecules, but not for large protein molecules and other macromolecules, which cannot pass the barrier. The separation thus has a function of a *selective* blood–brain barrier, termed *la barrière ecto-mésodermique*. This notion was discovered by a medical doctor, Lina Stern (1878–1968), of Russian origin [53]. After her medical studies and final examination in Geneva, her goal was to do clinical research. She was accepted and started immediately her work at the Physiology Institute of Geneva. First, together with Frédéric Battelli (professor of physiology in Geneva, 1867–1941), they worked on biochemical problems. She soon was recognized as a brilliant researcher. The work was mostly published in German (Biochemische Zeitschrift) and became known also to Hans Krebs who, in his talk at the Nobel prize ceremony, mentioned Lina Stern and Frédéric Battelli as pioneers in the discovery of some metabolic cycles. Lina Stern, still in physiology, lectured biochemistry to the students and created her independent research group. She was the first women to be appointed as professor at the University of Geneva. Later, together with her co-worker R. Gautier, experiments were done that lead to the extraordinary discovery of the blood–brain barrier [13]. In 1921, Lina Stern gave a general talk to a medical audience about her work on the blood–brain barrier. This talk was then published in the *Schweizer Archiv für Neurologie und Psychiatrie* [54], a journal inaugurated by Monakow. I do not know when Lina Stern first met Monakow. In the above-mentioned publications of Monakow and Kitabayashi and Monakow and Mourgue on schizophrenia and the blood–brain barrier, Monakow is often referring to her. Unfortunately, it appears that this research provided no clear response about the role of the blood–brain barrier in schizophrenia. The authors suggested that in schizophrenic patients, permeability problems could occur that produce pathological changes to the brain. As is also described in detail in the book of Monakow and Mourgue [26], they claim to have observed a pathological histology of the choroid plexus. That claim was based on 60 brains of deceased schizophrenic patients. Monakow suggested that the observed histological alterations may change the penetration of agents, having negative effects on brain functions. However, the claimed alterations of the 12 microscopic sections of the plexus, illustrated in the book, are of poor quality of today's standard and not convincing. The work was also criticized, as admitted by Monakow in the above book chapter. Since a lot of work had been invested in this new, pioneering work, the authors must have been disappointed by the outcome. Nevertheless, the idea to approach psychiatric diseases also on biological foundations was a pioneering attempt. Although today's treatment of schizophrenia has much improved, the cause of this disease is still unsolved.

At Monakow's 70th birthday, colleagues from many countries were invited and delivered speeches (as mentioned before, also the old master in Brain Research Bechterev from Leningrad). Lina Stern was also invited, but was not able to attend. However, she contributed to the *Festschrift*. She left Geneva in 1925, being invited to contribute to the scientific development in Moscow. She kept the links with Geneva and came a few times to participate at scientific meetings in Switzerland (see [53]).

4.3. The last visits in the late 1920s

It the 1920s, when Monakow travelled several times to the French-speaking part of Switzerland, he met several colleagues, such as the psychologist Édouard Claparède (1873–1940). He visited Forel (1864–1927), who now lived in his old, somewhat neglected house in Yvorne (near the Lake of Geneva in a lovely wine-producing village in the Rhone Valley). He had been psychiatrist in Zurich and an eminent pioneer of the neuron doctrine. But long after his retirement, he had suffered from a stroke and Monakow noted some sequels, especially of his right hand and his spoken language (Forel published an interesting and extensive report on his own recovery process from the stroke [55]). Monakow found him much changed and was sad to see him, somewhat neglected in his clothing and continuously speaking about his garden, his world-famous ant collection, etc. Monakow, one year older than Forel, made this remark after the visit: "*Sic transit gloria mundi*".

In the last years of his life, Monakow continued to read and write, to discuss with his pupils and to meet friends, apparently with a still well-functioning brain (except some memory problems!). He could look back to a very successful career, although paved with obstacles, particularly during his earlier years. It certainly needed a strong will to match his goals. During his last years, Monakow put together some of his longer papers on psychological, philosophical and religious issues for a last book project. It was then completed by his successor Minkowski who added to Monakow's legacy a first bibliography of his work [56]. Monakow was indeed a great scientist and humanist.

Constantin von Monakow died peacefully in 1930, three years after Auguste Forel.

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