Josef Klingler's Models of White Matter Tracts: Influences on Neuroanatomy, Neurosurgery, and Neuroimaging

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During the 1930s, white matter tracts began to assume relevance for neurosurgery, especially after Cajal's work. In many reviews of white matter neurobiology, the seminal contributions of Josef Klingler (1888-1963) and their neurological applications have been overlooked. In 1934 at the University of Basel under Eugen Ludwig, Klingler developed a new method of dissection based on a freezing technique for brain tissue that eloquently revealed the white matter tracts. Klingler worked with anatomists, surgeons, and other scientists, and his models and dissections of white matter tracts remain arguably the most elegant ever created. He stressed 3-dimensional anatomic relationships and laid the foundation for defining mesial temporal, limbic, insular, and thalamic fiber and functional relationships and contributed to the potential of stereotactic neurosurgery. Around 1947, Klingler was part of a Swiss-German group that independently performed the first stereotactic thalamotomies, basing their targeting and logic on Klingler's white matter studies, describing various applications of stereotaxy and showing Klingler's work integrated into a craniocerebral topographic system for targeting with external localization of eloquent brain structures and stimulation of deep thalamic nuclei. Klingler's work has received renewed interest because it is applicable for correlating the results of the fiber-mapping paradigms from diffusion tensor imaging to actual anatomic evidence. Although others have described white matter tracts, none have had as much practical impact on neuroscience as Klinger's work. More importantly, Josef Klingler was an encouraging mentor, influencing neurosurgeons, neuroscientists, and brain imaging for more than three quarters of a century.

KEY WORDS: Diffusion tensor imaging, Functional neurosurgery, History of neurosurgery, Josef Klingler, Neuroanatomy, University of Basel, White matter tracts

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Mentem et manum adhibere was Vesalius' maxim; mind and hand are important for the work, not the instruments.
Josef Klingler, *Atlas Cerebri Humani*, 1956

Nearly 80 years ago, Josef Klingler developed advanced methods for the preservation, gross dissection, and 3-dimensional (3D) modeling of cortical white matter that have not been surpassed.[1-12] His articles and atlases analyzing the white matter tracts of the brain contain clinical and functional correlations. Klingler's work became the basis for the anatomic maps underpinning stereotactic neurosurgery and profoundly influenced the correlation of neurological function and anatomy to neurosurgery.

EVOLUTION OF WHITE MATTER TRACT DISSECTIONS

Perhaps because its fibrous structure could be grossly identified and traced, the white matter has received particular attention throughout the history of brain dissection. Galen first described the corpus callosum and fornix in animals. Andreas Vesalius, in Book VII of his 1543 *Fabrica*, named many parts of the white matter, including the corpus callosum, which he described as "arising not from the surface of the substance of the cerebrum, which is softer and yellowish, but from the deeper substance, which is firmer and white." Along with his observations that there was white matter in the "dorsal marrow" (brainstem), which connected to the cerebellum, he also suggested that there were convenient opportunities to capitalize for learning anatomy: "But the very beginning of the dorsal marrow, under the cerebellum, is very white, as is also its origin... You may gain acquaintance with this substance at the [dinner] table at any time from brains of calves, hares, or birds."

Vesalius observed that there were differences in color and consistency in the brain: "The substance of the brain is not all white, but near the convolutions it is yellowish or grey for a distance equal to the depth from the surface of the convolution... Any part of the brain which is not thus [ash] colored is white and shining."

Vesalius, whose advanced dissection technique for the brain was largely made possible by following the white matter tracts, described the associations of other white matter regions to the corpus callosum and devoted a detailed chapter "on that structure in the brain which experts in dissection have compared to a 'tortoise' or a vault [fornix]."[13-15]

After these initial efforts, there were many notable descriptive dissections of the white matter. During the same century, Arcangelo Piccolomini (1526-1586)[16,17] completed the first discriminative dissection of white matter from gray matter, and Volcher Coiter (1533-1576)[18,19] distinguished the gray and white matter of the spinal cord. In the next century, Thomas Willis (1621-1675), with drawings by Christopher Wren, set new standards by identifying accurately the anatomy of inner white matter structures in his 1664 *Cerebri Anatome*.[20] In 1669, Marcello Malpighi (1628-1694)[21] demonstrated that white matter was composed of fibers, whereas in 1671, Niels Stensen (1638-1686) studied the white matter tracts by following "nerve threads" through the substance of the brain to determine where they led.[14,22]

The scraping method for dissecting cerebral white matter, as suggested by Stensen, was performed by Willis and Lower in 1672. Scraping enabled them to identify in greater detail the branching of the cranial, spinal, and autonomic nerves; structures such as the fornix, corpus callosum, and anterior commissure; and structures such as the subcortical fiber tracts passing through the striatum. Fiber tracts are well depicted in Willis's *De Anima Brutorum* of 1672.[23] Their findings were based on the method of fixation by injection of alcoholic spirits into the carotid artery. This scraping method was then followed successfully by Vieussens[24] in 1685. In 1786, Vicq d'Azyr[25] identified the mammillothalamic tract and described the anterior and posterior commissures. In 1809, Reil soaked the brain in alcohol and obtained excellent gross preservation and dissection of the human brain. He also coined the term *corona radiata*.[26-28] In 1810, Gall and Spurzheim[29] differentiated the important features of gray and white matter, whereas Burdach worked extensively (1820s) on fiber bundles and identified intricate structures in his three-volume work *vom Baue und Leben des Gehirns*.[30,31] The work of Herbert Mayo (1827), Friedrich Arnold (1838), Louis-Pierre Gratiolait (1839), and Achille-Louis Foville (1844)[4,32-35] further improved brain preservation and fiber dissection techniques.

FIGURE 1. *Josef Klingler as "Basels neuer Ehrendoktor," published in National-Zeitung Basel on November 25, 1946. This is one of few existing photographs available of Klingler. With permission from Präsidialdepartement des Kantons Basel-Stadt.*

In the early 20th century, H.J.H. Hoeve (1909),[36] E.B. Jamieson (1908),[37] and J.B. Johnston (1908),[38] attempted to delineate association fiber systems using what were then considered to be enhanced techniques of gross or blunt white matter bundle dissection. During the 1920s, the white matter tracts began to assume relevance for neurosurgery, especially with the neural interconnectivity and circuitry eloquently proposed by Santiago Ramon y Cajal.[14,39-42] New tissue preservation techniques and methods of dissection and illustration were at the forefront of these applied investigations. During this period, Josef Klingler began his anatomic investigations.

"LAB TECHNICIAN" AT BASEL INSTITUT DER ANATOMIE

Josef Klingler (Figure 1) was born in 1888 in Basel. After attending a Catholic boarding school in Einsiedeln and Schwyz, he studied medicine for a few years, probably between 1925 and

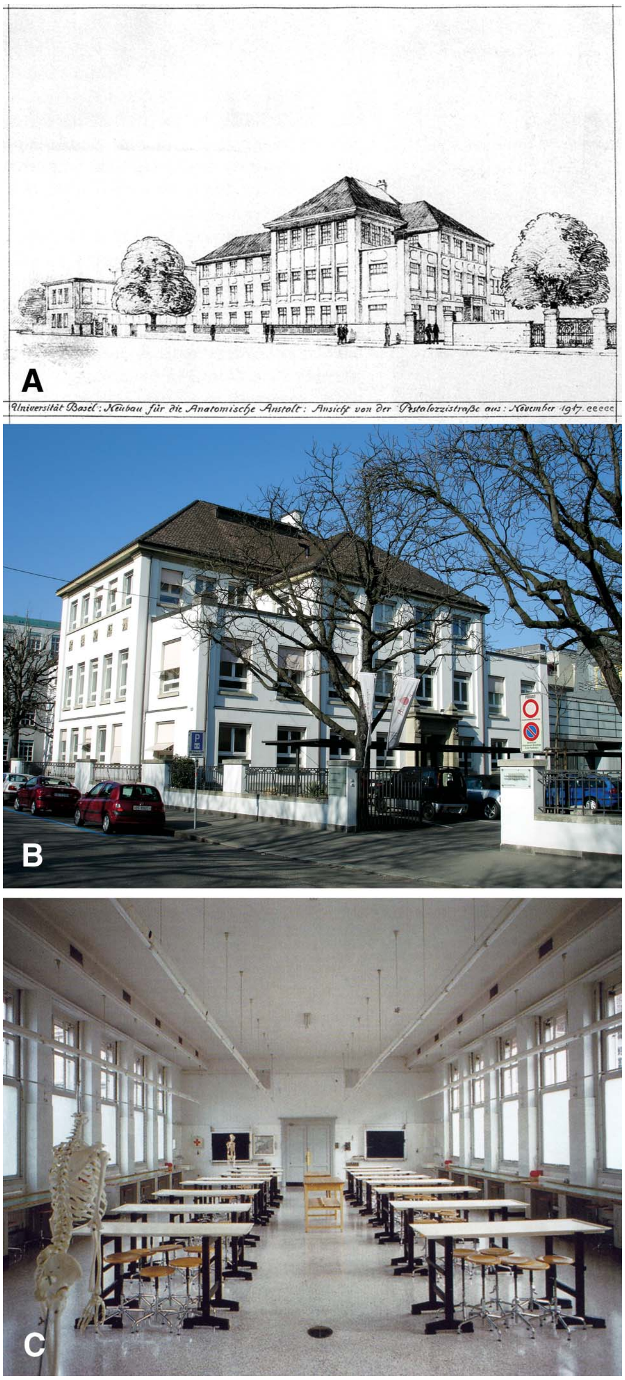


FIGURE 2. **A**, *architectural elevation of the Institute of Anatomy of Basel from 1917, along with a recent photograph of the institute* (**B**). **C**, *dissection hall at the Institute where Klingler spent years teaching and carving out the white matter tracts. With permission from the Institute of Anatomy, University of Basel, Switzerland.*

1929 at Freiburg and then at the University of Basel. However, he never finished his studies. In 1929, Eugen Ludwig (newly appointed director of the Institute of Anatomy at Basel) requested that Klingler be appointed a "lab technician" and "preparator" at the Anatomy Institute, a post that he held until 1956. Apparently, he began a fascination with real brains; knowledge from books and theories held little interest for Klingler who only completed his first medical examination.[43] Ludwig wrote that Klingler would have liked to have graduated as a medical doctor and from time to time considered reviving his medical school plans, but he was unable to finish his dissertation on the hair growth pattern of homozygotic twins and was unable to finish a grant that Ludwig had secured for him on lung development.[44] It appears that Ludwig would be an important motivating force throughout Klingler's career.

Interested in new methods of conservation and dissection, Klingler began to work on brain dissections and displayed the distinctive artistic talent that contributed to his early inclination toward anatomic preparations and illustrations, which were prominently displayed in his later atlases. He followed the long tradition of excellence in neuroanatomy at the University of Basel (Figure 2), most recently as set by Emil Villiger, a medical doctor who studied and taught neuroanatomy in Basel from 1913 to 1929.[45] In 1908, Villiger opened one of the first special neurology clinics in Switzerland and was noted for his excellent 1905 neuroanatomic monograph *Gehirn ünd Rückenmark: Leitfaden für das Studium der Morphologie und des Faserverlaufs*, which especially addressed the fiber tracts of the brain and spinal cord.[46] Villiger's text would be published through 14 editions.[47,48]

It appears that Villiger had considerable influence on Ludwig and Klingler, who immersed himself in the study of brain anatomy. However, Villiger's early editions contained only diagrammatic illustrations, a common feature of many anatomy works at the time, whereas Klingler seems to have been motivated to produce images of real brain tissue. Seeking techniques to improve the "quality" of the tissue specimens, Klingler visited Ferdinand Hochstetter to learn the preservation methods and systems of anatomy then in use at the Institute of Anatomy in Vienna and acclaimed as the best in the world.[49] The exposure to Hochstetter, who concentrated in brain anatomy and neuroscience, appears to have a profoundly influenced Klingler.[49] Klingler also studied with Lèon Laruelle in Brussels and with Henry Rouvière in Paris to learn other methods of anatomic preservation before developing his own method of dissection based on freezing brain tissue in 1934.[2,9-12,50]

In charge of brain preservation at the Basel anatomy institute, Klingler stressed the freshness of brain tissue, preservation of the architecture, and the color difference between the gray and white matter. He described in detail the cadaver position and technique of extracting the brain from the cranium and devised a formaldehyde-based fixation fluid that would preserve the brain. Klingler's description of the method of freezing the brain that permitted white matter fiber tracts to be defined involved hours of arduous effort directed at achieving optimal tissue preparation:

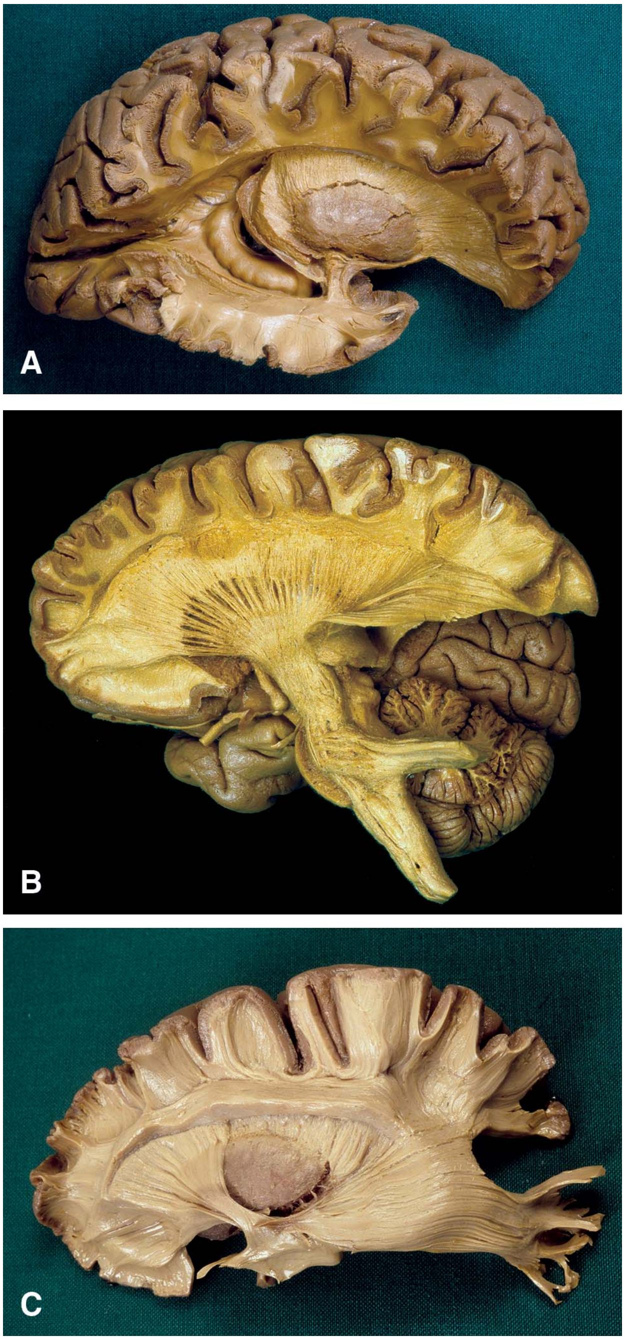


FIGURE 3. *Photographs of Klingler's specimens depicting the exquisite preservation technique based on freezing tissue and the dissection showing fiber pathways of the deep white matter.* **A**, *limbic and mesial temporal structures and tracts;* **B**, *cerebellar peduncle, brainstem, and midbrain tracts;* **C**, *deep white matter hemispheric tracts. Reprinted with permission from the Institute of Anatomy, University of Basel, Switzerland.*

> For fiber dissection studies of the human brain it is important that all parts, including the deepest structures are well fixed. Fixation in the customary 10% formalin is inadequate, for it fixes rapidly and well the external parts close to the surface, but penetration of the formalin into the deeper parts is slow and insufficient and thus results in their inadequate fixation. In brains so fixed fiber dissection studies cannot be carried out in a satisfactory way. It is, therefore, necessary to fix the brain in 5% formalin (commercial formol 5%, water 95%), which penetrates quickly and well into the deepest parts and thus gives an even fixation. The brain should be kept in this solution for at least 2 to 3 months, longer fixation times are even better. Congested brains are better than anemic ones, since they show a better contrast between gray and white matter... For the freezing process the brain is put on a plate and placed in a refrigerator. It should remain there for 8 to 10 days at a temperature of −10 to 15°C. Afterwards it is removed from the refrigerator and allowed to thaw in water at room temperature. It can then be kept indefinitely in 5% formalin. The effect of the freezing is to loosen up the otherwise quite compact structure of the brain. The mechanism whereby this happens is probably as follows: The aqueous formalin solution penetrates little or not at all into the myelinated fibers. It remains between the fibers. Consequently, when the brain is frozen, the ice forms between the fibers. Since the volume of water increases by about 10% when it solidifies into ice, the fibers are thus separated from each other. This loosening up of the brain substance facilitates dissection. Certain fiber systems can only be dissected if the brain is thus prepared by freezing. The form and consistency of the brain is not affected by the freezing.[50]

Klingler's method facilitated meticulous dissections and made it possible to delineate fiber bundles (Figure 3). Klingler used few instruments to carve out the white matter pathways:

> Dissection is mainly carried out with fine watchmaker forceps with tips made of first class steel. With this instrument the gray matter of the cortex can be removed in little bits and minute fiber bundles can be peeled off. Often this can be done in continuity from one end of the tract to the other, a very valuable criterion indicating that one is dealing with a continuous fiber system. Thus tracts and nuclei of even small dimensions can be dissected without producing artifacts these being easily recognized by the presence of broken fiber stumps and the absence of the appearance of smooth continuous tracts along which small bundles can be peeled off in continuity from one end to the other. For very fine dissections watchmaker forceps may be too coarse. We then peel the fibers off with snipe feathers, fine, wet hair pencils or with the pointed end of a small, wet piece of cotton wool. It is thus possible to avoid injury to small fiber tracts and yet they may be freed from adherent pieces of gray matter or from fibers crossing over them. When performing such fine dissections it may be necessary to work with magnifying spectacles and with a perforated head mirror such as is used by otolaryngologists.[50]

WHITE MATTER TRACT MODELING

In the autumn of 1935, Eduard Pernkopf, Hochstetter's pupil, invited Klingler to the Institute of Anatomy in Vienna to participate in studies on modeling the white matter[51] (Figure 4, A and B).

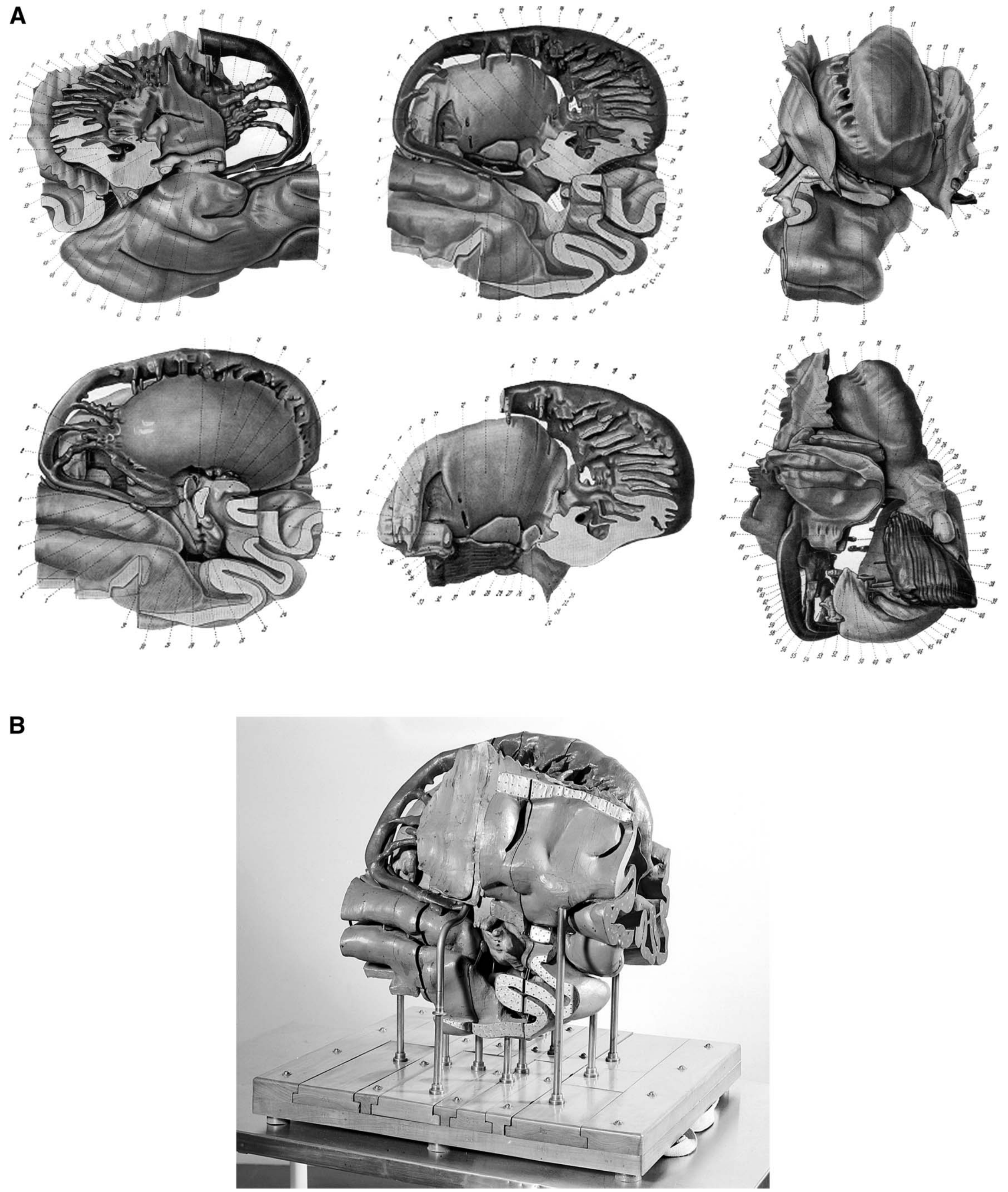


FIGURE 4. **A**, *illustration of Klingler's brain dissections when he was in Vienna working with Eduard Pernkopf and Friedrich Ehmann. Klingler modeled the dissections in wax and plaster casts. He published these illustrations in 1942*[2] *and again in 1946. These models were used for teaching purposes and communicate understanding of the deeper brain anatomy to students.* **B**, *Klingler's wood and metal brain model was constructed from 20 interdigitating sections and simulated central areas of the brain, which were then enlarged eightfold for demonstrations. He sought to provide students a thorough understanding of the white matter tracts and nuclei with macroscopic dimensions of the brain for which he had earlier developed 3-dimensional plasticized models for teaching based on the method of E. Poller*[91] *(1931). These models showed minute anatomic details and were practically indestructible. He believed that these models relieved students of the mental labor of reconstructing structures after observing numerous sections, a task at which he believed students were often unsuccessful. Klingler published this model in 1942*[2] *and later brought such models to the Montreal Neurological Institute. Courtesy of Neurophotography Archives of the Montreal Neurological Institute, McGill University.*

Klingler's visits to the Vienna institute appear to have been purely professional. There is no evidence that he became embroiled in the Nazi organization of the Anatomy Institute of the University of Vienna, which occurred a few years later under Pernkopf in 1938. It is unlikely that Klingler's visits to Vienna lasted for more than a few weeks because during this period, he remained tied to his duties in Basel, including teaching medical students, and was responsible for the large number of preparations used for teaching and in publications. Klingler only mentions Pernkopf once in his papers, that being in his 1942 paper on brain modeling in context to explain that he could not spend a protracted time in Vienna, and thus Pernkopf agreed to the construction of the brain models by Klingler in Basel.[2] Illustrations from Klingler's white matter dissections and brain models are notable in Pernkopf's epic volume on head and neck anatomy first published in 1957,[52,53] (Figure 5), although Pernkopf is not mentioned or cited in the Ludwig Klingler–edited 1940 and 1946 editions of Villiger's *Gehirn und Rückenmark*[47,48] or in Klingler's 1948 paper.[4] In addition, there is no mention of Pernkopf in any announcements about Klingler or in his obituaries. Although the white matter dissections illustrated in the Pernkopf atlas are attributed to Klingler,[52,53] the tissues that Klingler used for his models originated in Basel. He did not have involvement with Pernkopf during the period when the Vienna anatomy department was receiving bodies of executed prisoners from the Gestapo and from Vienna's assize court, which became systematized in 1938. Although there is no record of any political activity on the part of Klingler, Ludwig, in his memoirs, wrote critically about people who became associated with the Nazis.[44] Given his close relationship with Ludwig as well as being Swiss, Klingler likely held similar beliefs.

By the late 1930s, Klingler's work was becoming widely known, and his preparations and dissections received special commendation at the International Congress of Anatomy in 1936 in Milan. In 1938, he published an atlas *Noyaux et faisceaux du cerveau humain*.[11] Unfortunately, the outbreak of World War II in 1939 dampened the impact of his atlas, which soon went out of print. However, even during the war, he continued to explore the brain with subsequent publications.[2,3] A 1939 anatomy exposition in Basel attracted scientists from across Europe to view Klingler's work.[54] In the 13th and 14th editions of Villiger's *Gehirn und Rückenmark* published in 1940 and 1946, respectively, with active authorship by Ludwig after Villiger's

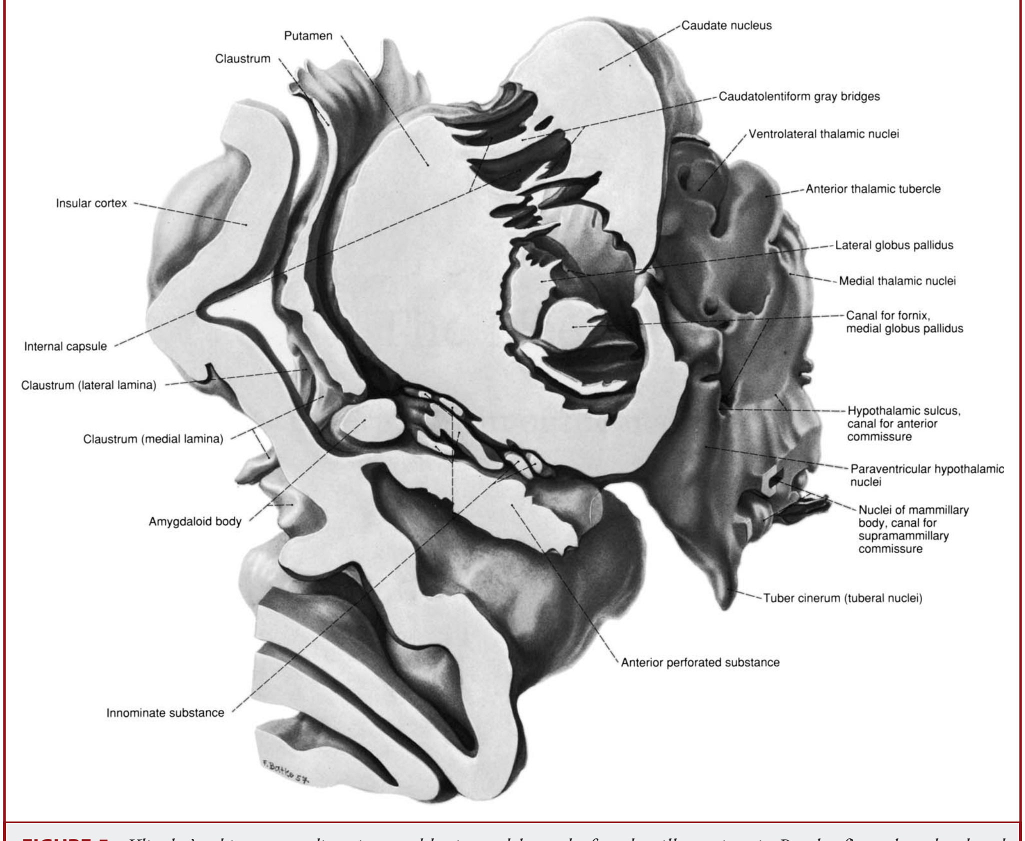


FIGURE 5. *Klingler's white matter dissections and brain models can be found as illustrations in Pernkopf's work on head and neck anatomy, such as this illustration that reflects Klingler's interest in the telencephalic and mesencephalic nuclei. Reprinted from Pernkopf E. Topographische und stratigraphische Anatomie des Kopfes: Topographische Anatomie des Menschen: Lehrbuch und Atlas der regionär-stratigraphischen Präparation. München [u.a]: Urban & Schwarzenberg; 1957.*[52]

death in 1931,[47,48] dissection and brain models created by Klingler detailed the intricacies of mesial temporal lobe structures, thalamic nuclei, and basal ganglia. In fact, Klingler created more than 70 preparations alone for the 13th edition of 1940.[47]

After the war, Klingler (1946) was awarded a PhD *honoris causa* from the Faculty of Medicine of the University of Basel, and in the late 1940s, his contributions were beginning to garner significant recognition. Nonetheless, Klingler's efforts had not necessarily translated into financial earnings or professional advancement. Because of his undefined and unusual professional situation, Klingler was concerned about his status as a preparator (at age 59 he had been working in this same position without advancement for 30 years) and his salary at the institution, likely because he lacked a standard medical degree. It appears that up until this time, Ludwig, a recognized anatomist and scientist in his own right, who was only 1-1/2 years older than Klingler, had been the guide and outlet for Klingler's academic efforts. Klingler had been recognized as only more or less a technician, but now he was beginning to achieve notoriety on his own. Klingler wrote a lengthy letter recounting his activities and successes to Ludwig, requesting a promotion with a raise of salary.[55]

> Basel, Sept 8th 1948
> To
> The Director of the Anatomical Institute
> *Prof. Dr. E. Ludwig*
> With the kind request to forward this to
> The head of the Department for Education
> *Minister Dr. C. Miville*
> Basel, Münsterplatz 2
> Dear Professor,
>
> The undersigned herewith poses the request to promote him to the position of a "Custos" [custodian] in view of his longstanding scientific activity in the Anatomical Institute.
>
> For justification he would like to allude to the following points:
>
> The undersigned is employed at the Anatomical Institute since April 1st, 1936 as a preparator and he draws since some time the maximum salary of the 6. salary class amounting to Fr. 7250. In this salary class are allocated in the administrational offices the assistants of 2nd class, ie the lower administrational clerks who are not required to have an academic education. Also according to §3 of the office regulation from the preparator of the Anatomical Institute is only required the "production of demonstration and collection objects with high technical standards". He also can "be allocated to technical work which has shown to be necessary in the course of scientific studies". – The preparator thus is not designated for making scientific publications and teaching the students.
>
> Nevertheless the undersigned can call himself, without arrogance, an especially qualified person. He is cand. med., has visited all lectures, courses and clinics which are required for the medical state examination and he has received in 1946 for his scientific achievements the honorary doctor of the University of Basel.
>
> In the laudation... it is pointed out that the undersigned "invented a highly ingenious method which like no other is suited to macroscopically visualize nuclei and fiber tracts in the human brain", that he "himself discovered a new important way for the anatomical demonstration of brain structure" that he "furthermore created with the help of his new method numerous very instructive anatomical preparations and herewith augmented substantially the reputation of the Anatomical Collection of the University of Basel and improved the quality and success of the teaching of anatomy". In addition the laudation mentions that the undersigned "has earned a lot of credit by introducing diligently numerous students and researchers both of domestic and international provenance in his as well as in all other anatomical methods and in addition by the fact that, with the help of his method, he enhanced substantially with his own studies our knowledge of the organization of the human brain..."

Klingler recounted his many teaching assignments and their impact on medical students and quoted the Director of the Anatomical Institute in Leuven (G. van der Schueren) as having stated that Klingler's anatomic preparations of the nervous system were the most beautiful he had ever seen in Europe or America. Klingler stressed that his position was not even equivalent to a custodian position such as at other institutions in Basel.

> However, according to the Personnel-Directory of the University of Basel there is also a "custos" position at the Botanical Institute. For the Anatomical Institute only a prosector is mentioned, further as the lowest level the preparator. ...[T]hus, according to my opinion; a promotion to the position of a "custos" should be possible. Therefore, I would like to ask you to approve this request. As an active member of the "Association des Anatomists" and the "Freien Vereingung der Anatomen an Schweizerischen Hochschulen" [Free Union of the Anatomists at Swiss Universities] I believe I am entitled to this demand.[55]

Klingler's request was successful. In 1948, Klingler published his dissected specimens and brain models in the atlas *Die makroskopische Anatomie der Ammonsformation* (Figure 6) and also his work on the relationships of the amygdala and cingulum.[4,5] Because of his intense interest in the limbic system and its application for the study of the anatomic and functional basis of epilepsy, Klingler was invited in 1949 to bring his 3D white matter tract model to the Montreal Neurological Institute where he worked with Wilder Penfield and Pierre Gloor (Figure 7, A and B).[56] Being Swiss and having received his advanced degree as well from the University of Basel, Gloor was familiar with Klingler's pioneering work. Anatomic studies on the mesial temporal structures and thalamus that Klingler published in 1949 and 1952 were confirmed experimentally for functional physiological competency by Gloor (personal communication, 1954; foreword in Ludwig and Klingler).[50] While in Montreal, Klingler also taught neuroanatomy.

Expanding his studies of the limbic system, Klingler worked with Wilhelm Pfuhl on the thalamus, cingulate bundle, hippocampus, uncus, and dentate gyrus in 1952. Pfuhl, a professor of anatomy in Frankfurt, Greifswald, and Regensburg from the mid1930s through the 1950s, was noted for his work on the cingulum.[57,58] During this period, Klingler's work contains

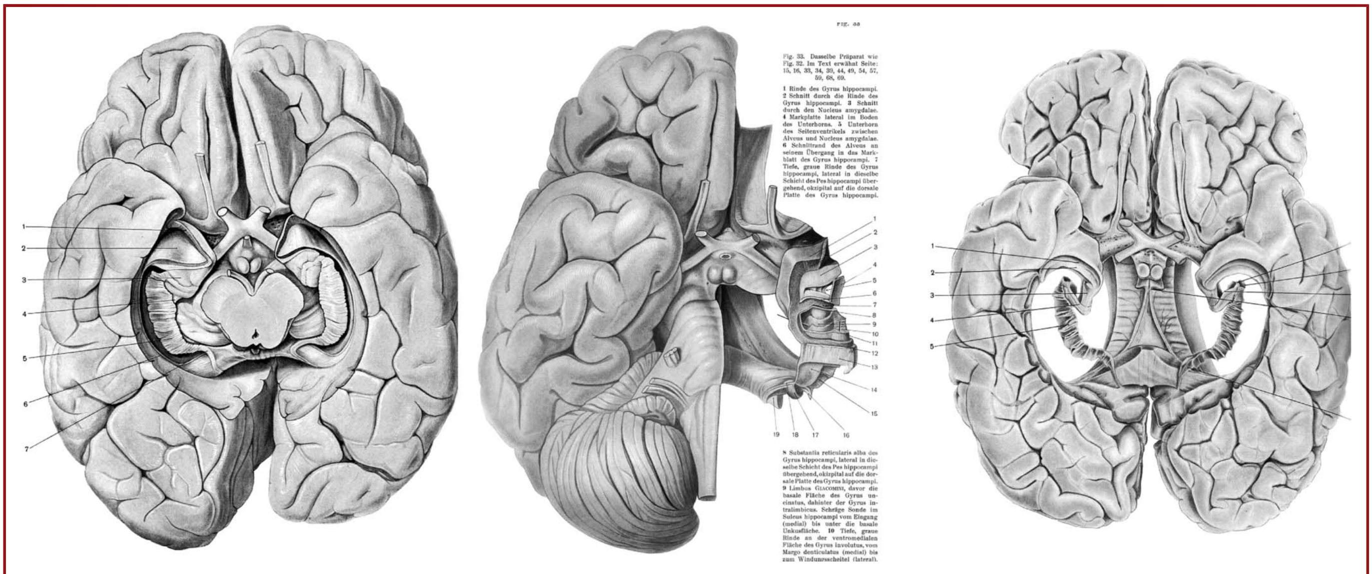


FIGURE 6. *Illustrations of mesial temporal lobe dissections from Klingler's Die makroskopische Anatomie der Ammonsformation (1948).[4] The illustrations beautifully depict mesial temporal structures along with the 3-dimensional relationships among hippocampus, amygdala, limbic system, and uncinate gyri.*

beautiful descriptions about the external localization of eloquent brain structures and stimulation of deep thalamic nuclei, along with neuroanatomic studies of the medullopontine tract.[8,59-61]

EXQUISITE, ARTISTIC DISSECTIONS

In 1955 at the International Congress of Anatomy in Paris, Klingler demonstrated his large collection of anatomic specimens.[8,59,62-64] The considerable interest among neurologists and neurosurgeons propelled compilation of Klingler's collection into a landmark work, *Atlas Cerebri Humani,* in 1956 (Figure 8, A and B).[50] The work shows that no longer was Klingler relegated to an acknowledgment in a foreword, but now shared dual authorship with Ludwig. In fact, the anatomic preparation method is highlighted in a section of the atlas titled *The Preparation Method of Klingler*.[50]

On July 30, 1955, the International Congress of Anatomy passed a resolution in Paris to follow the *Parisiensia Nomina Anatomica*. With some reservation, and a few exceptions, Ludwig and Klingler adopted this nomenclature in *Atlas Cerebri Humani*. Klingler also contributed his own nomenclature, which was published in 1957.[65] The nomenclature suggested in *Atlas Cerebri Humani* was based on the concept of Klingler's dissections with clear explanations, with the hope that it would find acceptance in the official international nomenclature. He even suggested the correct spellings of various structures, which were dropped in the *Parisiensia Nomina Anatomic*, with the result that the international nomenclature commission adopted Klingler's spellings. He was against mixing Latin and Greek names with modern English nomenclature, believing that doing so led to absurdities and confusion. A considerable portion of his nomenclature is still used for the structures that he described. The use of Latin for titles and names of structures in his most notable work lend an authority and sure link to past grand neuroanatomic works.

IMPACT ON MODERN NEUROSURGERY

The foreword to *Atlas Cerebri Humani* details the many novel contributions applicable to neurological disease and procedure made by the neuroanatomic studies of Klingler and Ludwig: "In recent years our preparations have won the attention of neurologists and neurosurgeons, but have also resulted in what may be considered as definite advances in the study of the inner topography of the brain."[50]

Klingler had a special affinity for teaching anatomy to students and he had considerable material. His preparation method was so successful that hundreds of sections lasted 20 years or more. In similar style to Vesalius, Klingler wrote advice for those wishing to learn neuroanatomy:

> "In order to prevent disappointments, it must be emphasized that the production of a true and instructive brain preparation is not an occupation for beginners. An indispensable requirement is a good knowledge of the gross anatomy of the brain to the extent indicated by the atlas of [Edward] Flatau (1895), and by the work of [Gustaf] Retzius (1896, 1898). The second requirement is practised hands, trained on dissections easier to accomplish; the third is patience and perseverance. The instruments are of secondary importance [sic]."[50,66-68]

As a medical student in Basel in 1949, and through Ludwig, M. Gazi Yaşargil came under the direct guidance and supervision of Klingler.[51,69] Klingler introduced Yaşargil to his preservation and dissection techniques. During this period, Yaşargil spent

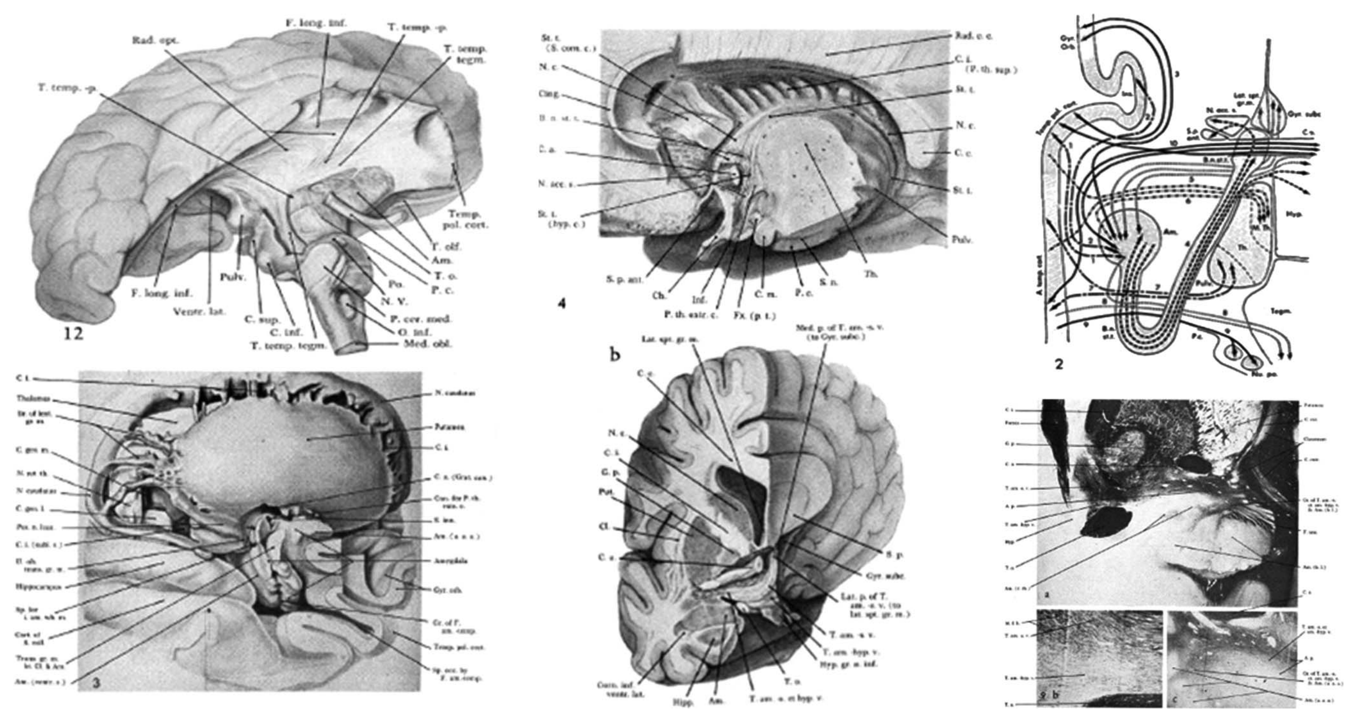


FIGURE 7. *In several extensive investigations with Gloor, Klingler used his fiber dissection technique, aided by his wax model techniques to define the connections of the mesial temporal lobe structures and insula, the relationships between the amygdala and the anterior temporal lobe structures, thalamic pathways, pontine fiber tracts, stria terminalis, lamina terminalis, and other long and association tracts of the brain.*[50,56,71] *Courtesy of Springer.*

many hours studying 3D brain anatomy using Klingler's models. After 3 months of study, Yaşargil was so profoundly influenced by Klingler that he seriously considered becoming a neuroanatomist. Ultimately, however, Yaşargil decided to apply the principles that he had learned from Klingler to a career in neurosurgery. He took a few formalin-fixed Klingler brains with him during his neurosurgical residency and often traveled to Basel to show his anatomic dissections to the encouraging Klingler. Impressed by Klingler's broad knowledge, his meticulous white matter dissection skills, and his enthusiasm for the hippocampus, Yaşargil partially attributes his success in neurosurgery to his training under Klingler.[51]

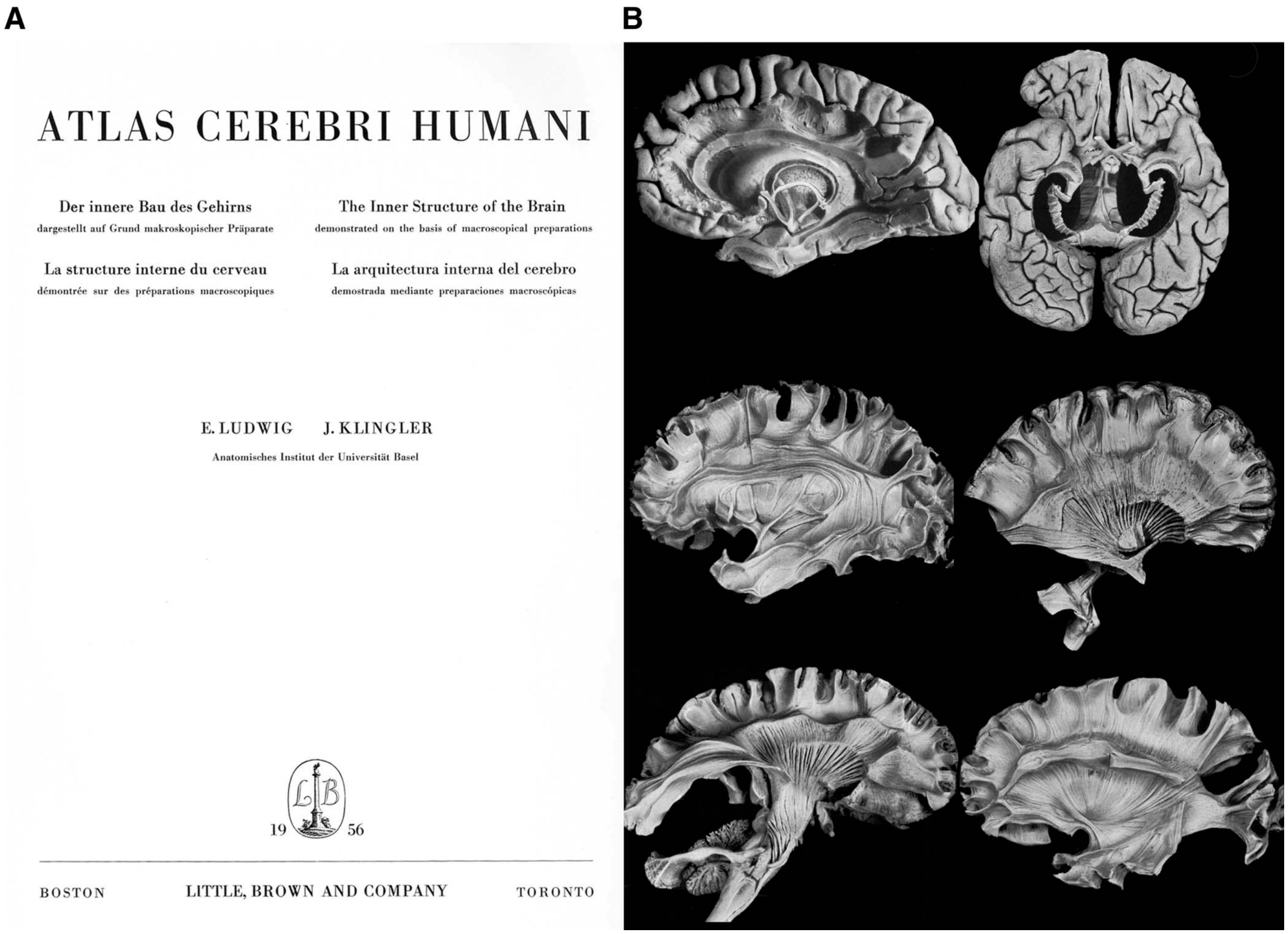
In his memoirs, Ludwig wrote:

> In principle we should have appointed him also as a lecturer because during his many years he taught a course highly appreciated by the medical students on the subject of 'Preparatory Practice of the Brain for Advanced Students.'...he was invited on suggestion of Prof. Pierre Gloor to McGill University in Montreal for giving his course there and giving additional demonstrations. There he was so successful... .[44]

Klingler wanted his anatomic work to have practical applications and was intensely interested in the interconnections of human brain anatomy, physiology, pathology, and neurosurgery. He aided Gloor as an editor,[70] and in a paper with Gloor in 1960, he wrote:

> In recent years the functions of the temporal lobe have been of prime interest to experimental and clinical workers in the field of neurology. Much of this interest has been stimulated by the intriguing problems raised by the clinical symptomatology of temporal lobe epilepsy and by the many observations made in the course of surgical treatment of this form of epilepsy by anterior and mesial temporal lobe excisions including the amygdala. Electroencephalographic observations, the responses induced by electrical stimulation of temporal lobe structures during operation and the results of careful pre- and postoperative psychological testing of the patients undergoing these neurosurgical operations have considerably advanced our knowledge of the functional significance of the temporal lobe in man. Thus the physiology of this area has become increasingly a human physiology and, as such, it obviously should rest upon firm first-hand knowledge of the human anatomy of this region. However, a great deal of our knowledge of the human anatomy of this area rests upon inferences drawn by analogy from studies carried out in subhuman mammalian species. Therefore, it seemed to us timely to restudy the anatomy of this region in the human brain itself, especially since with the rapid development of stereotaxic neurosurgery a precise knowledge of the specifically human anatomy of this and other areas of the brain will assume more and more practical importance.[71]

The results of the fiber dissections by Klingler and Gloor were directly related by Gloor and Feindel[72] in their discussions of the connections of mesial temporal structures engaged in the visceral and affective features of temporal lobe epilepsy.[56]



ATLAS CEREBRI HUMANI

Der innere Bau des Gehirns
dargestellt auf Grund makroskopischer Präparate

The Inner Structure of the Brain
demonstrated on the basis of macroscopical preparations

La structure interne du cerveau
démontrée sur des préparations macroscopiques

La arquitectura interna del cerebro
demostrada mediante preparaciones macroscópicas

E. LUDWIG J. KLINGLER
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FIGURE 8. A, *Klingler compiled his famed Atlas Cerebri Humani with the collaboration of Eugen Ludwig, Armin Wolf (one of the preparators at the Basel institute), publisher Heinz Karger, photographer Rolf Musbach, and artist Ernst Bernard, who recreated exquisite illustrations of the dissections.* **B**, *Klingler, always concerned about the artistic and aesthetic presentation of his work, illustrated detailed macroscopic preparations of the inner structures of the brain. From Atlas Cerebri Humani, 1956, originally published by Little, Brown, and Co.*

Although Spiegel and Wycis[73,74] are usually credited with performing the first stereotactic thalamic surgeries that began in 1947, it seems that Klingler independently was part of a group in Basel and Freiburg (Figure 9) that also performed stereotactic thalamic surgeries beginning around the same time. Their targeting and logic were based on Klingler's anatomic work that had delineated thalamic white matter and nucleus subregions.[75] The basal ganglia and thalamus/midbrain models that Klingler constructed were enlarged 4 times normal size at the Montreal Neurological Institute in an attempt to better delineate thalamic-frontal and thalamic-temporal fiber tracts. However, Penfield made best use of Klingler's methods to freeze and preserve the brain for use in intricate dissections with Klingler to identify tracts and nuclei that they believed might be suitable targets for deep brain surgery.[75]

Anatomic Basis for Diffusion Tensor Imaging Mapping

Recently, Klingler's work has received renewed interest, being eminently applicable for correlating the results of diffusion tensor imaging fiber mapping to actual anatomic evidence. Various recent neurosurgical anatomic studies have used Klingler dissection preparations in delineating, for example, the precise anatomic course of the inferior fronto-occipital fasciculus, combining diffusion tensor imaging with electrostimulation studies, combining fiber dissection with diffusion tensor imaging to define the functional implications of the claustrocortical system, and tracking fibers of the uncinate fasciculus. Klingler's dissection technique has been developed as an interactive tool to efficiently select fiber bundles in the brain and to visualize the embedded naturally curved anatomic structures parallel to the resultant imaged fiber bundles. Recently developed spline surface

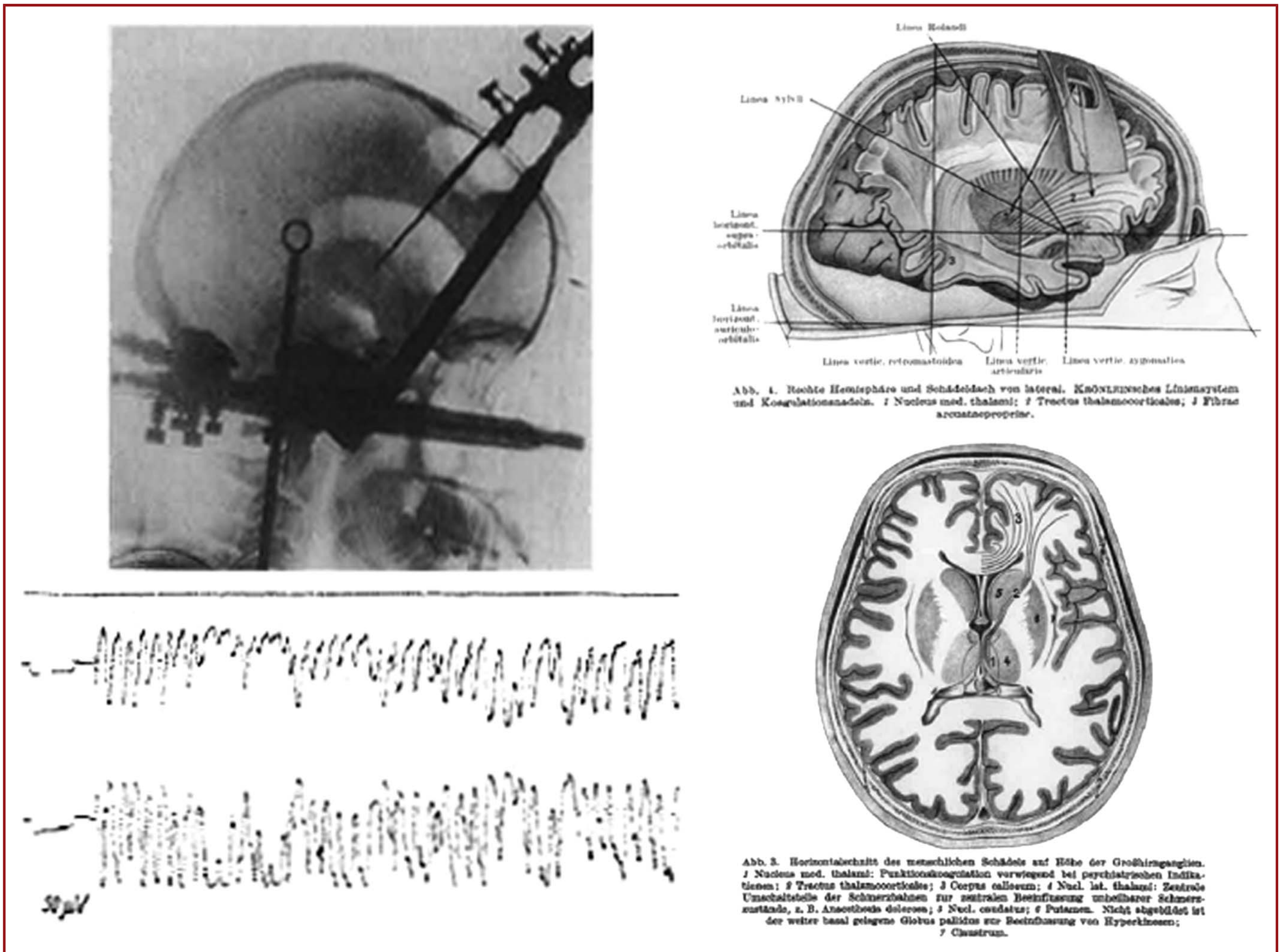

FIGURE 9. *In the most well-documented and forward-looking article published during the early 1950s ("Kraniocerebrale Korrelationstopographie thalamofrontaler Bahnen und gezielte Hirnoperationen"), Henschen and Klingler et al described various applications of stereotaxy, including intraoperative thalamic recordings, applications to motor disease, epilepsy, psychoses, intracerebral hemorrhage, neuralgias and chronic pain, and gliomas and an integrated craniocerebral topographic system for targeting, all based on Klingler's work. From Henschen C, Klingler J, Riechert T. Kraniocerebrale Korrelationstopographie thalamofrontaler bahnen und gezielte hirnoperationen. Langenbecks Arch Klin Chir Ver Dtsch Z Chir, 1952-1953;273:548-5653.*[75]

implementation allows interactive optimization of the dissection planes. The addition of diffusion texturing on these surfaces using the local fiber orientation resulting from the Klingler technique opens a novel view on the complex fiber configurations in the brain and, importantly, can be extended to examine fiber crossings (Figure 10).[76-79]

Common to all these studies[80-87] is the yield of information from the unsurpassed exquisite tissue preparation and white matter dissection technique of Klingler:

> [T]he value of the fiber dissection technique for neuroanatomy and neurosciences, especially concerning research in the field of brain connectivity, may have been underestimated. Indeed, if a detailed dissection is performed, it provides a unique opportunity to study the exact cortical terminations of the main white matter bundles.[71]

FINAL YEARS

On retirement at 65 years old, Klingler was granted permission by the University of Basel to continue his duties and remain in office for 3 more years during which he pursued his work with his usual vigor. After his retirement in 1956, he worked for the University of Montreal, maintained collaborations at McGill's Montreal Neurological Institute, and was a Visiting Lecturer at Harvard University until 1961. He received numerous invitations to share his extensive knowledge with students and colleagues at

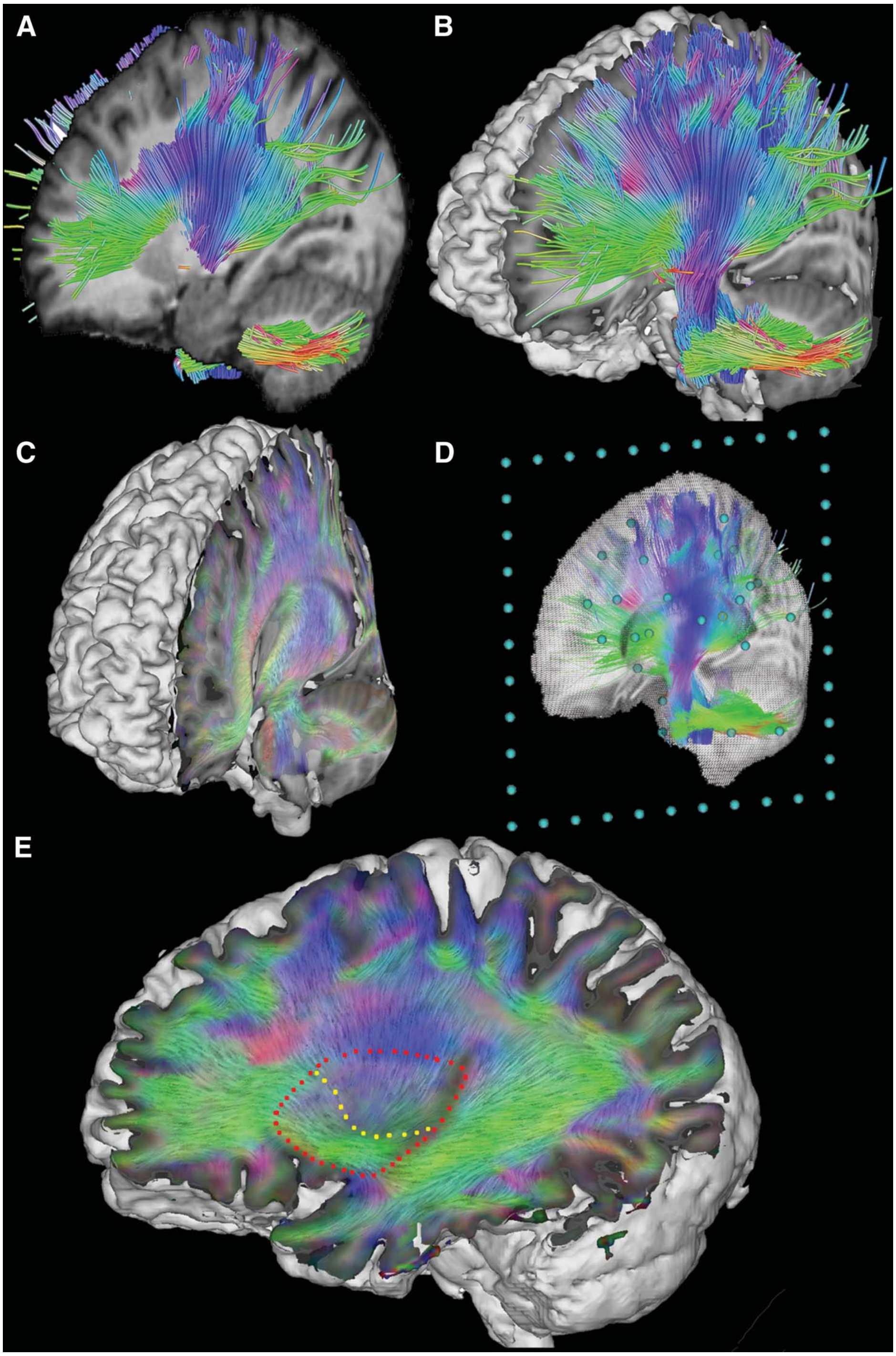

FIGURE 10. *Three-dimensional diffusion tensor imaging studies specifically based on the evidence of a "virtual" Klingler dissection have recently been used to reveal complex tract relationships between the optic radiations and the temporal horn, the spread of malignant tumors within the frontal and temporal lobe, and other anatomic imaging features to determine the exact location of fiber tracts (illustration from http://public.kitware.com/ImageVote/images/27/; based on the work found in White Matter Imaging with Virtual Klingler Dissection by Alfred Anwander et al, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany). Courtesy of Max Planck Institute for Human Cognitive and Brain Sciences.*

many institutions. So admired for his teaching, when Klingler decided to return to Switzerland in 1961, the institutions on the west side of the Atlantic expressed their profound sadness. Josef Klingler died in Basel on June 13, 1963.

Ludwig and Klingler

Ludwig and Klingler shared a unique association. Although Ludwig was the recognized scientist and academician, Klingler achieved success and notoriety through his alternate path and his perseverance in pursuing anatomy and research; it is his techniques, his gift for teaching, and his concern for students that have achieved posterity. However, we believe that Klingler's professional accomplishments owe much to the efforts of Ludwig. He wrote that Klingler was a masterful teacher who connected on a wonderful basis to students and visiting scientists and was greatly concerned that they learn on the most exquisitely preserved tissue.[43] He earnestly believed it was his special calling to improve their anatomic understanding.[54,88] Klingler was able to make things visible that had previously been hidden and significantly contributed to the history and value of the Basel tradition in anatomy.[88] Arguably, Klingler's dissections of the white matter tracts are the best ever produced (photographs and illustrations of his white matter bundle dissections and models are recognizable in many atlases from other authors). He believed in careful study of past techniques, which could be used to identify and refine valuable information.

> Before the advent of the microtome, fiber dissection of the brain was the only method whereby its inner structure could be analyzed. Many of the well known larger fiber tracts of the brain were thus discovered by the older anatomists (Burdach, Arnold, Reil and others). With the advent of histological techniques based on microtome sections, the more time consuming fiber dissection method was largely abandoned. Some anatomists, however, still practised it, among them Hultkrantz (1929) in Sweden and Curran (1909) and Rasmussen (personal communication) in the United States. When one of us (Klingler, 1935) developed the freezing method, new possibilities were opened and it became feasible to attack even small fiber tracts. We consider this method as valid as any histological technique. This view was also held by Curran (1909) who states that he never had been forced to abandon as an artifact a tract identified by this technique. We believe that for the study of the human brain this method has definite advantages, in view of the obvious obstacles to the application of the finer histological techniques based upon degeneration methods with which one is faced in human neuroanatomy. This is partly due to the fortuitous location and delineation of pathological lesions of the human brain, to their frequent multiplicity, their ill defined limits and, in part, to the frequent impossibility of applying the most precise histological methods (eg, the Nauta Gygax stain). In these circumstances fiber dissections often prove more advantageous than the classical histological methods [sic].[71]

What we know about Klingler's personality and family must be extrapolated and perhaps this is the irony of Klingler's life, a life we know from its noteworthy contributions, yet relatively unknown for paucity of public personal information. Ludwig wrote several moving statements in obituaries that provide a view of the Klingler he knew: "To work with Klingler was a pleasure. He often quoted Thomas Aquinas, or told of his beloved Uri, the homeland of his maternal ancestors [and the legendary Swiss figure Wilhelm Tell] . . . His philosophical approach to life and death was illuminated by a humble, deeply Christian religious conviction." [49,70]

CONCLUSION

Klingler's contributions to neuroanatomy and neuroscience and hence to neurosurgery are important. An extensive search of his personal and professional life (Swiss Economic Archive, Archive of the State, University of Basel Institute of Anatomy, and Swiss Department of Education) yielded only a few short newspaper articles about him. Unfortunately, it seems that most of his specimens, which were initially preserved in the anatomy museum in Basel, have been discarded as they have deteriorated over the years.

Klingler stressed 3D anatomic relationships, and his work laid the foundation for defining mesial temporal, limbic, insular, and thalamic fiber and functional relationships that had a direct impact on surgery of the mesial temporal structures for epilepsy and on the potential of stereotactic neurosurgery, especially of the thalamus. Remarkably, Klingler's work is still relevant. It now serves as the best basis for comparison of gross white matter tract morphology with advanced imaging techniques and is being used some 80 years after the technique was introduced.

Perhaps most importantly, Josef Klingler was an encouraging mentor, influencing neuroscientists, including anatomists, neurosurgeons, and brain imagers for more than three quarters of a century. His accomplishments assume parity with those of earlier great brain anatomists, and he rightly belongs in their pantheon. It is no accident that Klingler's work was accomplished in Basel, Vesalius having come to the city to supervise the publication of his epochal anatomic work. Fortunately, like the arms dissected by Vesalius and preserved by Rembrandt,[89,90] a few of Klingler's dissected brain specimens still survive in Basel, treasures that commemorate their creator.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

As a preparator at the Institute of Anatomy in Basel, Joseph Klingler refined the method of white matter dissection, which enabled him to develop new 3-dimensional models of white matter tracts and to define fiber relations. With his technique and models, Klingler gave new insight in white matter biology and had great influence on following generations of neuroscientists. In contrast, little is published about Klingler himself and his contributions to white matter anatomy. Now, Agrawal et al arranged a comprehensive review about Joseph Klingler and his work. After a detailed introduction about history of white matter anatomy until the 1930s, the authors describe Klingler's background, his training of anatomic preparation with his effort to achieve excellent white matter dissections and his development of new 3-dimensional models of white matter anatomy. In this context, the authors discuss also Klinglerś visit of Eduard Pernkopf at the Anatomical Institute of Vienna in 1935. Pernkopf became an active member of the Nazi party in 1933 and of the Hitler's storm division (Sturmabteilung) in 1934 (long before the annexation of Austria to the German Reich in 1938) and was mired in the Nazi system.[1,2] In this context, Pernkopf's anatomical institute in Vienna received at least 1377 cadavers of executed persons.[3] However, Agrawal et al found no clues that Klingler became embroiled in the Nazi organization of the Anatomy Institute of the University of Vienna or sympathized with the Nazi regime and that Klinglerś involvement with Pernkopf extended "during the period when the Vienna anatomy department was receiving bodies of executed prisoners from the Gestapo and from Vienna's assize court which became systematized in 1938." Therefore, Klinglerś visits to Vienna's Institute of Anatomy "appear to have been purely professional." Further, the authors exemplarily document Klingler's influence on neuroscientists like M.G. Yaşargil or W. Feindel and on development of new surgical techniques like stereotactic functional surgeries. Therefore, it is the authors merit to give the neurosurgical community new insights in life and work of Joseph Klingler.

The life and person of Joseph Klingler also reveal some basics: He never finished studies and he was less interested in complex theories; Klingler is a prototype of a practical scientist who focused his work on the development of 1 method, in his case, white matter dissection. With his continuing refinements, he tried to gain perfection. Indeed, Agrawal et al concluded that "Klingler's dissections of the white matter tracts are the best ever produced." Even today more than 50 years after his retirement, Klinglerś method is a standard and reference method used in recent studies (eg, Martino et al, 2010, Peltier et al, 2009). Typically, these methodical advancements resulted with Klinglerś three-dimensional white matter models in important new insights. Basic scientific analyses, such as work of Klingler, may also have great clinical impact leading to clinical advances, and subsequently Klingler was a part of a group that performed one of the first stereotactic surgeries.

But as Agrawal et al point out, Klingler was also the prototype of a scientist who was an encouraging mentor and teacher and was able to impart fascination of his subject. The time M.G. Yaşargil learned brain anatomy and the method of white matter dissection from Joseph Klingler might be a fascinating example. One might speculate whether Yaşargil's later merits may in part have their background in that time. However, Klingler's influence on a generation of neuroscientists and the impact of his work further shows the imperative of a connection between the particular neuroscientific fields.

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1. Williams DJ. The history of Eduard Pernkopf's Topographische Anatomie des Menschen. *J Biocommun*. 1988;15(2):2-12.
2. Atlas MC. Ethics and access to teaching materials in the medical library: the case of the Pernkopf atlas. *Bull Med Libr Assoc*. 2001;89(1):51-58.
3. Malina P, Spann G. [Senate's project at the University of Vienna, "Studies in anatomical science in Vienna from 1938-1945"]. *Wien Klin.Wochenschr*. 1999;111(18):743-753.

This is an interesting article dedicated to the legacy of the Swiss neuroanatomist Josef Klinger (1888-1963) who is known for his dissection technique of white matter tracts. Unfortunately, the biographic data on Klinger are scarce. Why he did not finish his medical studies? Did he have a family? It is noted that Klinger was invited to the Institute of Anatomy in Vienna in 1935 by Eduard Pernkopf. The reason of this invitation was Pernkopf's work on his famous anatomic atlas, *Topographische Anatomie des Menschen* (*Atlas of Topographical and Applied Human Anatomy*), which started in 1933 when a contract with the publisher (Urban & Schwarzenberg, then based in Vienna) was signed. Pernkopf was a fervent believer in National Socialism. He joined the Nationalsozialistische Deutsche Arbeiterpartei (National Socialist German Worker's Party, NSDAP, or Nazi Party) in 1933 and the Sturmabteilung, SA, or Brown Shirts, a year later. According to Michael Hubenstorf, "In fact, Pernkopf's institute was a focal point of Nazi activity even before the annexation of Austria to the German Reich in 1938 [Anschluss]. Under professors Carl Toldt, Ferdinand Hochstetter, and Pernkopf, the University of Vienna's second department of anatomy had a continuous history of pan-Germanism, anti-Semitism, and political extremism among students and academic staff that dated back at least to the 1890s. By contrast, the first department, under Emil Zuckerkandl and Julius Tandler, was populated by Jewish, liberal, socialist, and foreign students. Political differences were paralleled by variations in scientific orientation, with narrow morphological and systematic anatomy prevailing at the second department (Pernkopf), and topographical, clinical, and physiological approaches at the first. It was not merely Eduard Pernkopf who joined the Nazi party in 1933, but a whole set of his assistants, technicians, and anatomy painters."[1] One of Pernkopf's technicians was Josef Klinger.

After the Anschluss, Pernkopf was instated as dean of the medical school. One of his first acts as dean was to purge the medical school faculty of Jews and other "undesirable members." The University of Vienna, once among the premier medical schools of Europe, lost 153 of its 197 faculty members, including 3 Nobel laureates. Pernkopf remained dean until 1943, when he became Rektor Magnificus (president) of the University of Vienna (until May 1945). Although never charged with war crimes, Pernkopf spent 3 years in an Allied prison camp near Salzburg.[2]

Presumably, Klinger helped Pernkopf in preparation of his famous Atlas, which has been hailed as one of the most important anatomic atlases since the work of Vesalius. However, the issue of the sources of the cadavers received by the University of Vienna, and from which the illustrations in Pernkopf's *Topographische Anatomie* were drawn, became a subject of hot debate in 1990s. It is has been documented that 1377 cadavers were delivered after execution at the Vienna District Court and Gestapo execution chambers in Munich and Prague.[2] These included political dissidents who opposed the Nazi regime.

The authors write that "Klingler's visits to the Vienna institute appear to have been purely professional." Was it really so? It would be interesting to undertake further research on their relationship.

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1. Hubenstorf M. Anatomical science in Vienna, 1938-45. *Lancet*. 2000;355 (9213):1385-1386.
2. Williams DJ. The history of Eduard Pernkopf's Topographische *Anatomie des Menschen*. *J Biocommun*. 1988;15(2):2-12.

I found this a charming historical study, relevant to current practice because of the connection with Dr Yaşargil, and, even more importantly, the renewed interest in fiber tract mapping with diffusion tensor imaging (DTI) tractography. Indeed, because DTI techniques can be performed on postmortem tissue, a very exciting experimental exploration of Klingler's technique could be contemplated, studying some actual specimens with both techniques.

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This well-written and interesting article leads me to think about the history of white matter studies in historical epochs, defined by available technologies. From this point of view, there have been 3 overlapping eras in such studies: (1) blunt dissection, (2) chemical staining, and (3) in vivo imaging. It appears that Klinger's work represents the apogee of dissection. For his work, the only requirements from modern technology were refrigeration and microscopy. As the authors' historical review shows, for most of the long history of the dissection technique, even those 2 technologies were not always needed, right into the 20th century. For practical purposes, staining technology began in the second half of the nineteenth century.[1] It was an offshoot of the textile industry, especially in Germany. Staining, of course, requires good microscopy, which began to appear in the middle of the 19th century. For following long fiber tracts, large and precise microtomes were needed.[2]

Most of the research by staining involved following long tracts in adult brains with myelin stains. However, another way to investigate long tracts is to use myelin stains to see the developmental patterns of tracts in fetuses of different ages (myelogenesis). This was the special province of Paul Flechsig (1847-1929),[3] whose theoretical conclusions from his studies became part of the supporting data for Norman Geschwind's (1926-1984) paradigm-changing conceptions of modern connectionism as the basis for behavioral neurology in the later 20th century.[4] Now, in the early 21st century, computer-based imaging is a powerful new tool to study functional connections in the living human brain. Over several centuries past, the white matter of the brain seems to have been the neglected stepchild of neuroanatomy, but the existing anatomic knowledge derived from blunt dissection techniques and chemical staining is the necessary starting point for interpreting the results of computer-based imaging.

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3. Flechsig P. Developmental (myelogenetic) localisation of the cerebral cortex in the human subject. *Lancet*. 1901;2:1027-1029.
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