The Discovery of Encephalic Arteries—A Historical Overview

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Abstract: The knowledge of the anatomy of brain arteries developed in two main phases. The first, mainly descriptive, was the discovery of the main arteries at the base of the brain. The second was the study of the branching patterns of these arteries using more specific anatomical techniques, such as intra-arterial injection. The great anatomo-clinical work of Charles Foix (1882–1927), the first true stroke neurologist, enabled the transformation of these anatomical data into a form directly applicable to clinical practice.

1. Introduction

The names of some vessels, such as the vein of Galen and the torcular Herophili, suggest that our understanding of cerebral vascular anatomy dates back to Antiquity, but this is not, in fact, the case: for many centuries, anatomical representations of the brain completely omitted the blood vessels. Knowledge of vascular anatomy came much later, and, as in other medical specialties, did not immediately lead to any improvement in patient care.

Parenchymal cerebral anatomy and vascular anatomy were ultimately brought together by pathology. The discovery of arterial lesions (arteriosclerosis, arterial embolisms, etc.) and their role in cerebral lesions (apoplexy, softening, etc.) provided the link between the arteries and the brain.

In this chapter, we highlight the key milestones in the understanding of the cerebral circulation before the advent of neuro-imagery, from the discovery of these arteries to modern anatomo-clinical research. Many anatomical errors, both ancient, such as the concept of a human rete mirabile, and more recent, such as l'artère de la fossette latérale du bulbe (artery of the lateral medullary fossa), have hindered our understanding of the blood supply to the brain.

The knowledge of brain vessel anatomy developed in two main phases. The first, mainly descriptive, was the discovery of the main arteries at the base of the brain. The second was the study of the branching patterns of these arteries using more specific anatomical techniques, such as intra-arterial injection. The great anatomo-clinical work of Charles Foix (1882–1927), the first true stroke neurologist, enabled the transformation of these anatomical data into a form directly applicable to clinical practice.

2. The First Mentions of the Cerebral Vessels

In ancient Greece, anatomy was not a major part of medical education, which was greatly influenced by Hippocrates' humoral theory. Additionally, the Greeks considered dead bodies to be sacred, which meant that there were very few dissections of human cadavers. Some animal dissections and possibly fetal dissections were performed, but there was little interest in the brain, which was considered secondary to the heart.

In the third century BCE, the Hellenistic Alexandria established by the Ptolemaic Pharaohs became a renowned seat of learning for many well-known Greek physicians. Over a period of around fifty years, some of these physicians, particularly Herophilus of Chalcedon (ca 330–ca 250 BCE) and Erasistratus of Chios (ca 315–ca 240 BCE), dissected human cadavers. Herophilus specialized in brain anatomy. Fragments of his treatises have survived in the writings of more recent anatomists, although they have been translated multiple times in the interim [1,2]. Herophilus seems to have distinguished between arteries and veins, but his interest in the brain focused mainly on cerebral ventricles, meninges, and superficial veins. Notably, he discovered and named the confluence of dural sinuses near the internal occipital protuberance, a confluence that later bore his name—the torcular Herophili [1].

In the second century CE, the anatomical contributions of Galen (ca 129–ca 210) based on animal dissections established him as an influential figure. Galen was born in a Greek family in the city of Pergamum in Asia Minor. He undertook part of his medical training in Alexandria and subsequently moved to Rome, where he lived for most of his life. He had likely never dissected human cadavers, but his anatomical and physiological ideas based on animal models were regarded as immutable by the medieval world for centuries [3].

Galen developed the fictional concept of rete mirabile, which gained an impressive influence in the history of brain anatomy. The rete mirabile is an elaborate network of fine vessels into which the carotid arteries divide at the base of the brain. It exists only in ungulates, not in the human brain. The fragments of text attributed to the Alexandrian school of anatomy credit Herophilus of Chalcedoine with what appears to be the first description of the rete mirabile in an animal [1].

Galen transposed the rete mirabile from dissections of the ox onto the human brain [4]. The rete mirabile played a central role in the Galenic concept of physiology, which was also based on other fictional ideas. For example, food absorbed by the gut underwent "concoction" and then was transported by the blood to the liver, where it was imbued with "natural spirit". The blood then left the liver and travelled via the veins to the right ventricle of the heart, where impurities were exhaled through the lungs. It then entered the left ventricle through the pores of the inter-ventricular septum. There, the blood was imbued with a higher form of pneuma: the "vital spirits" drawn from the outside by inhalation through the lungs. This blood, along with its associated "natural spirits", travelled via the arteries to the brain and entered the rete mirabile at the base of the brain, where the blood was charged with the final and highest form of pneuma, the "animal spirits". The ventricles of the brain were the final repository of the "animal spirits", which flowed out of the brain through the nerves to the organs of the body. According to Galen, the convolutions of the rete mirabile were necessary for slowing the passage of blood, allowing the transformation of natural spirits into animal spirits [5].

The medieval times were deeply influenced by this Galenic vision and the ventricular conception of brain function, which also had a significant impact on Arabic medicine. During this period, Mondino dei Luzzi (ca 1275–1326), professor at the University of Bologna, was one of the first anatomists to have reintroduced the dissection of human cadavers to anatomy teaching. One section of his book Anathomia, written in around 1316, deals with the anatomy of the skull, brain, eyes, and ears. The description is focused on the medieval theory of the brain as cerebral chambers, without clear insight into the question of the cerebral arteries. Mondino also perpetuated the Galenic vision of the brain. The first illustrated version of Mondino's work was created by Guido da Vigevano (ca 1280–ca 1349) [6].

A rare medieval representation of the brain that dates from the mid-13th century and whose illustrator is unknown includes some cerebral and vertebral vessels and probably the rete mirabile [7] (Figure 1A). Other medieval anatomical depictions of the brain were still based on the ventricular and rete mirabile concepts. The depiction in 1501 of a human head in Antropologium de hominis dignitate (1501) by Magnus Hundt (1449–1519) of the University of Leipzig is a clear example of this [8] (Figure 1B).

A B

Figure 1. (**A**) Medieval representation of the brain including some cerebral and vertebral vessels and probably the rete mirabile (mid-13th century). Reprinted from [7], used with permission. (**B**) Depiction of a human head (1501) by Magnus Hundt (1449–1519). Reprinted from [8], used with permission.

3. The Slow Transition from the Rete Mirabile to the Cerebral Arterial Circle

The end of the 15th century marked the beginning of a new era for brain anatomy, an era that frequently challenged Galen's ideas. Initially rooted in the Italian universities, this resurgence of anatomy progressively involved scholars from across Europe and culminated with the major anatomical work of Andreas Vesalius (1514–1564). One of the debates was the existence of the rete mirabile in humans, which had rarely been questioned before then.

Among the pre-Vesalian anatomists, the Italian physician Jacobus Berengarius Carpensis (Berengario da Carpi) (ca 1460–ca 1530), a professor at the University of Bologna who introduced anatomical illustrations based on nature, was one of the first to deny the presence of the rete mirabile in humans. In his Commentaria on Mondino's Anathomia (1521) and Isagogae breves (1523), he reported that he had dissected around 100 heads but had failed to discover a rete mirabile [9,10].

The Flemish-born anatomist and physician Andreas Vesalius (Andries Wytinck van Wesel) re-established anatomy as an observational science after a long period of stagnation under the teachings of Galen. He was appointed as a professor of surgery and anatomy at Padua University, where he dissected human cadavers and relied heavily on anatomical drawings to support his teaching. In 1538, Vesalius published the Tabulae Anatomicae Sex, which included an illustration of the rete mirabile that he called "mirabilis plexus reticularis" (wonderful plexus network) [11]. At first, Vesalius still believed in the existence of a rete mirabile in humans, but comparative dissections of human and animal cadavers ultimately convinced him that Galen must have been wrong.

In 1543, Vesalius published his magnum opus, De humani corporis fabrica. Liber VII of the Fabrica, which includes a systematic dissection of the brain, illustrated with woodcut prints through 12 sequential stages. He now denied the existence of the rete mirabile in humans and castigated himself for his prior failure to recognize this error [12]. Nevertheless, the idea of the rete mirabile in humans did not disappear after Vesalius but remained part of the medico-anatomical discourse [13]. The discovery of the brain circulation by William Harvey (1578–1657) only had a small impact on the understanding of the cerebral arteries and the discussion around the rete mirabile.

From the Renaissance, the concept of the rete mirabile slowly evolved into the concept of the major anastomotic arterial system, which became one of the most famous eponymous structures of the human body: the circle of Willis. Thomas Willis (1621–1675), a physician at Oxford, demonstrated this anastomotic arterial structure with great precision, which is in fact an arterial heptagon [14].

Before Willis' accurate description and illustration, some other anatomists had evoked such a structure [15]. Gabriele Fallopius (Fallopio) (1523–1562), professor of anatomy at Padua University, described the arterial circle in Observationes anatomicae (1561), but his description was incomplete and he underestimated this anastomotic system [16]. An anatomical plate from Tabulae anatomicae by Giulio Casserio (Casserius) (1545–1605) provided an incomplete illustration of the arteries of the basal brain that also included a rete mirabile branching out from the carotid artery. Casserius' Tabulae anatomicae were incorporated into De humani corporis fabrica (1627) by Adrianus Spigelius (van der Spieghel) (1567–1625) after the death of both anatomists [17]. The German anatomist Johann Vesling (Veslingus, Wesling) (1595–1649), also a professor of anatomy in Padua, provided, in his second edition of the Syntagma (1647), an incomplete description and illustration of the anastomotic arteries. In his description, some branches that did not come from the carotid artery and that spread out on the basal face of the brain corresponded to the presumed rete mirabile [18] (Figure 2A).

Johann Jakob Wepfer (1620–1695), a Swiss physician from Schaffhausen, is usually regarded as the true discoverer of the arterial circle. Six years before Willis' publication, Wepfer published his Observationes anatomicae ex cadaveribus eorum, quos sustulit apoplexia cum exercitatione de ejus loco affecto (1658) [19]. In this work, Wepfer clearly described this anastomotic system, demonstrating that he knew the arterial organization of the base of the brain in detail. Unfortunately, he did not provide an illustration of the arterial circle but referred to one in Vestling's Syntagma.

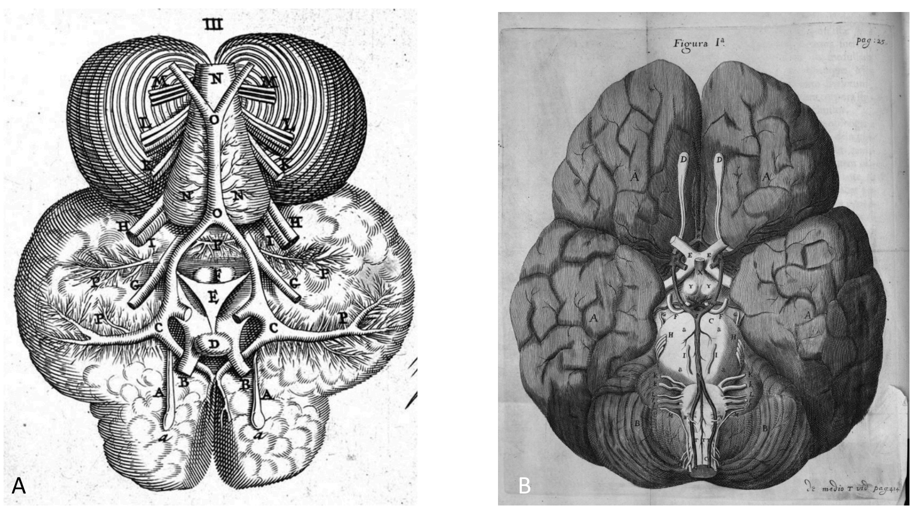

Figure 2. (**A**) Representation of the arteries of the base of the brain by Johann Vesling (1595–1649). Some arterial branches (P) correspond to the presumed rete mirabile. Reprinted from [18], used with permission. (**B**) First illustration of the arterial circle of the base of the brain in 1664 by Thomas Willis (1621–1675) Reprinted from [14], used with permission.

Thomas Willis—assisted by Richard Lower (1631–1691) and the architect Christopher Wren (1632–1723), who provided the drawings—added little new information to Wepfer's description, despite using new dissection techniques on human cadavers. However, he gave the first complete illustration of the circle in both man and sheep in 1664 (Figure 2B). The pictorial representations of these share certain inaccuracies, but his illustration highlighting the relationships between nerves and vessels is superior to those of his predecessors. As a physician, Willis also tried to understand the functional role of the anastomotic system [14].

Throughout the following century, the question of the existence of the rete mirabile in man continued to parasitize the anatomical perspective of the basal brain [20]. The French anatomist Raymond de Vieussens (ca 1541–1715) in his Neurographia universalis (1684) and the English physician Humphrey Ridley (1653–1708) in his Anatomy of the brain (1695), among others, continued to defend the idea of the existence of a rete mirabile in humans, despite knowledge of the circle [21,22]. The idea was more firmly ruled out from the mid-18th century.

4. The Time of Injection Studies

At the end of 18th century, Félix Vicq d'Azyr (1748–1794) elegantly illustrated the arteries of the base of the brain [23] (Figure 3). Nevertheless, brain and artery anatomy were still considered independently, as reflected in Samuel Thomas Soemmering's (1755–1830) anatomical book Vom Baue des menschlichen Körpers, which treated the angiology and anatomy of the brain in two separate volumes [24]. In the first quarter of the 19th century, brain anatomy was still focused on parenchymal anatomy, with numerous controversies concerning the craniology and phrenology described by Franz-Joseph Gall (1758–1828) and Johann Gaspar Spurzheim (1776–1832).

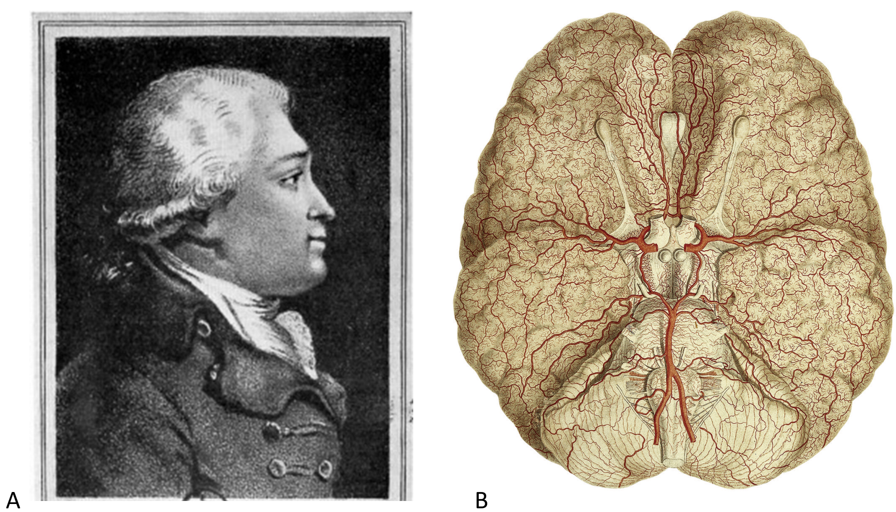

Figure 3. (**A**) Félix Vicq d'Azyr (1748–1794) (Public domain). (**B**) Illustration of the arteries of the base of the brain by Vicq d'Azyr. Reprinted from [23], used with permission.

Although slow, the emergence of arterial pathological concepts eventually brought to light the close relationships between arterial abnormalities and brain lesions. The seminal works of Jean André Rochoux (1787–1852) and Léon Rostan (1790–1866) introduced the concept of brain softening as an entity distinct from apoplexy, which is now regarded as a hemorrhagic phenomenon [25,26]. In 1829, Jean-Frédéric Lobstein (1777–1835) used the term "arteriosclerosis" to define abnormal deposits on the arterial wall [27]. A few years later, the German pathologist Rudolf Virchow (1821–1902) clarified the terms “thrombosis” and “embolism”, and coined the term “ischemia” to describe the consequences of a lack of arterial flow to an organ [28].

In this new pathological context, some anatomists decided to study the branching patterns of the main cerebral arteries coming from the arterial circle at the base of the brain or from the vertebro-basilar system. They used more sophisticated anatomical procedures, such as intra-arterial injections using syringes and liquor dyed with ink, a technique that had been used by Thomas Willis and the Oxford group two centuries earlier.

In 1872, the German physician Otto Heubner (1843–1926) was likely the first to investigate the distribution of the branches of the cerebral arteries, in an injection study performed on 30 brains. He injected each artery with a colored liquor and noted the structures supplied. He defined the cortical and central territories of brain arteries and demonstrated that the posterior communicating artery supplies the anterior part of thalamus and the anterior choroidal artery supplies the posterior limb of the internal capsule. He also described a small artery arising close to the anterior communicating artery that provides blood to the head of the corpus striatum. This artery was later named the recurrent branch of anterior cerebral artery but nowadays bears his name: the recurrent artery of Heuber [29].

Henri Duret (1849–1921), a pupil of Jean-Martin Charcot and later a professor of surgery in Lille, also conducted impressive anatomical work [30]. In 1873–1874, Duret, using an injection technique that he did not record and an unspecified number of brains, classified encephalic arteries using a morphogenetic approach. He also published diagrams describing the different distributions of the anterior, middle, and posterior cerebral arteries [31,32] (Figure 4A). He presented the first study on the distribution of the arteries supplying the medulla oblongata [33].

Duret also focused on the arterial vascularization of the deep grey nuclei of the brain, introducing the concept of the lenticulo-optic arteries (pédicule lenticulo-optique) whose existence would be highly debated in the following years [31]. Jean Martin Charcot (1825–1893), the great French neurologist, had little interest in stroke [34], but he nevertheless defended and diffused the work of Duret in his published Leçons. He presented the lenticulo-optic arteries and emphasized the role of another lenticulo-striate artery mainly involved in brain hemorrhage, later sometimes called Charcot’s artery [35] (Figure 4B).

In 1891, the Austrian anatomist Alexander Kolisko (1857–1918) performed an injection study of the anterior choroidal artery in 17 brains. He described both its cortical and deep territories and confirmed Heubner’s results concerning its involvement in the vascularization of the posterior limb of the internal capsule [36].

The years 1907–1910 were very fruitful for the understanding of brain vascularization. In 1907, the Boston physician James Bourne Ayer (1882–1963) and Hamlet Frederick Aitken (1872–1939), artist at the Massachusetts hospital, published a first detailed report on the arteries of the corpus striatum. They confirmed Heubner's views on the participation of the anterior cerebral artery in the corpus striatum supply [37]. A few months later, Hamlet Frederick Aitken made drawings from fresh dissections of numerous brains and confirmed the participation of the anterior choroidal artery in the vascularization of the corpus striatum. They denied the existence of the so-called Charcot's artery and Duret's lenticulo-optic arteries [38]. Duret replied to Aitken in a paper published in 1910 and accepted the development of some new arterial concepts but maintained his view on the anterior cerebral artery and lenticulo-optic arteries [39].

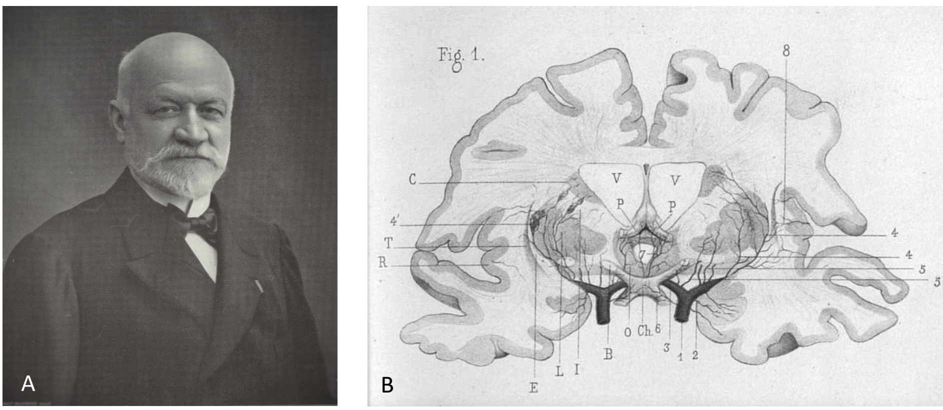

Figure 4. (**A**) Henri Duret (1849–1921) (Public domain). (**B**) Frontal section of the brain from Duret's work showing the lenticulo-striate arteries including Charcot's artery (4). Reprinted from [31], used with permission.

In the same period, the British anatomist Charles Edward Beevor (1854–1908) presented the results of seven years of arterial brain injection studies [40] (Figure 5A). Beevor injected nearly 100 brains using a different technique to that used by Duret and Heubner. Beevor used colored gelatin to inject the main brain arteries individually, including the posterior communicating and anterior choroidal arteries, following a strict and ingenious methodology [41]. His detailed results were presented in an attractive and colorful way. Beevor published the first type of brain mapping, displaying both the anatomical structures and the arterial territories in horizontal, frontal and sagittal brain sections [42] (Figure 5B).

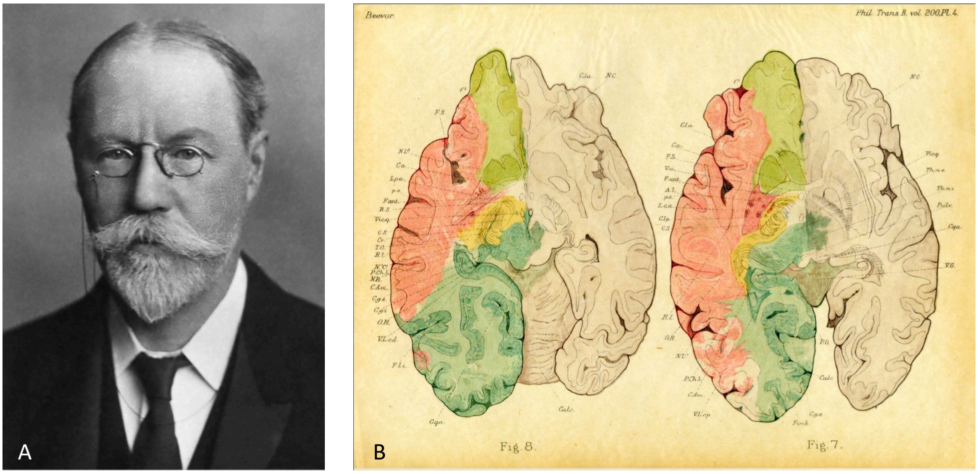

Figure 5. (**A**) Charles E. Beevor (1854–1908) (Public domain). (**B**) Horizontal brain section from Beevor's arterial brain mapping. Reprinted from [42], used with permission.

Initial works using arterial injection raised the question of the variability of the cortical artery territories and the existence of anastomoses. In his initial papers and in his 1910 article, Duret stated that there was little to no variation and that the anastomoses between the territories were too small to be of significance [31,39]. Beevor was the first to suggest a clear variability in the cortical territories of the main cerebral arteries [41].

5. Charles Foix and the Modern Era of Neurovascular Anatomy

Charles Foix (1882–1927) began his career at the Paris school of clinical anatomy, where he was a student of Pierre Marie (1853–1940). His career was interrupted by World War One, which he spent on the front in the Balkans. After qualifying as a doctor after the war, he became a professor at the Paris medical school in 1923, and he took the post of Head of Department at the Hospice des incurables d'Ivry the following year. Foix was an accomplished poet and lyricist. His death in 1927 from a perforated gastric ulcer prematurely ended his career [43] (Figure 6A).

From 1923 to 1927, Foix focused his research on the cerebral blood supply, using anatomical injection techniques—sometimes paired with the use of X-rays—anatomo-pathological studies, and anatomo-clinical correlations. He re-examined Duret's work, which was by this time somewhat outdated and of little practical use. Foix published multiple articles that became the foundations of a new discipline, of which he was the first true proponent—vascular neurology. His work was performed with the help of his interns, notably his primary collaborator, Pierre Hillemand (1895–1979).

Charles Foix made rapid progress, but these advancements occured in stages. The first step was the individualization of the vascular territory of the posterior cerebral artery [44]. Foix and Hillemand then defined Duret's thalamic vascularization pedicles: premamillary, thalamoperforating, thalamogeniculate, choroidal and lenticulo-optic. The participation of the choroidal artery in the vascularization of the thalamus had already been recorded in a summary diagram [45] (Figure 6B).

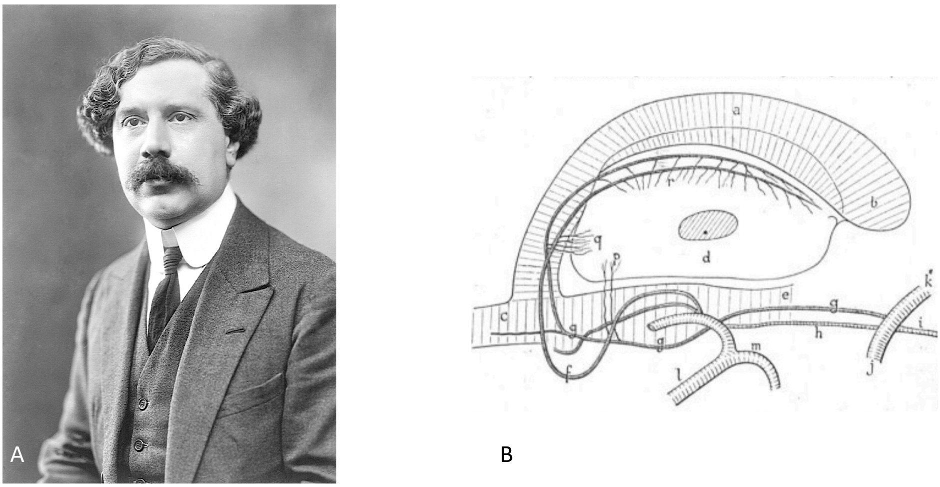

Figure 6. (**A**) Charles Foix (1882–1927) (public domain). (**B**) Arterial vascularization of the human thalamus from Foix and Hillemand's work. Arterial participation of the anterior choroidal artery in the thalamus vascularization is already mentioned here (p). Reprinted from [45], used with permission.

The next stage was the study of the blood supply to the brain stem. Before this, there had been few studies addressing this question, although Duret had studied the vascularization of the medulla oblongata and its cranial nerves in 1873, and John Sebastian Bach Stopford (1888–1961) had studied the vascularization of the medulla oblongata and the pons [33,46,47].

Foix and Hillemand proposed an extraparenchymal classification of the arteries as paramedian, short circumferential, and long circumferential, which correspond to the three sections of the brain stem [48,49].

Foix also studied the anatomy of the anterior and middle cerebral arteries and their clinical syndromes [50,51]. The distribution territories of both arteries were different to those described by Duret, but he did not discuss the variability of the cortical arterial territories in detail. Neither did he comment on the notion introduced at the same time by the Australian Joseph Lexden Shellshear (1885–1958) claiming that the cerebral territories vary insignificantly according to the slight variations of the functional areas of the brain cortex [52].

Among these anatomical masterpieces, Foix developed only one inaccurate hypothesis, which led to many controversies: the existence of the "artère de la fossette latérale du bulbe", a circumferential artery originating from the basilar artery. He wrongly believed that this artery was responsible for lateral medullary syndrome. Foix refuted the view of Adolf Wallenberg (1862–1949), who believed the vascularisation of the lateral fossette of the medulla oblongata to be multi-arterial [49,53].

Foix tempered some inaccurate concepts, such as the existence of the lenticulo-optic arteries. Presumably out of respect for his predecessors, Duret and Charcot, Foix mentioned the lenticulo-optic arteries in his early work, but over time, this arterial pedicle had a decreasingly prominent role in his presentation of the vascularization of the thalamus. Foix increasingly doubted the existence of the arteries and ultimately denied their involvement in thalamic infarctions [51].

The relationship between anatomy and clinical signs was a constant source of interest for Foix for each of the arteries he studied, resulting in the first reliable descriptions of vascular syndromes. He re-examined certain syndromes that had already become well established, such as pontine crossed syndromes: "Were it not for fear of being accused of paradox, we could say that encountering a clear case of Millard-Gübler syndrome or Raymond-Cestan syndrome almost allows us to eliminate the diagnosis of softening... Indeed, softening of the pons obeys constant rules according to the vascular disposition." [54].

Although some of Charles Foix's innovative ideas have only recently been rediscovered, he remains the first true vascular neurologist, the first who truly understood the importance of arterial anatomy in understanding semiology [55,56].

6. Building on a Legacy

Before the advent of neuroimaging, injection studies were the most effective method to examine the brain's vascular organization. Paired with anatomo-clinical correlations, they refined the seminal works of Heubner, Beevor, Duret, and Foix.

Charles Foix's descriptions provided a solid basis for subsequent anatomical works that were corroborated and supplemented by anatomists and vascular neurologists. Among them, the Australian anatomist Andrew Arthur Abbie (1905–1976) was particularly interested in the anterior choroidal artery, situating his experiments in a phylogenetic framework [57,58].

The brainstem's arterial vascularisation and corresponding vascular syndromes were thoroughly studied by Lois A. Gillilan (1911-1991), Guy Lazorthes (1910–2014) and Henri Duvernoy (1931–2021) (Figure 7). They supplemented the extra-parenchymatal classification of brainstem arteries suggested by Foix and Hillemand with the definition of the intraprenchymatous arterial territories we use nowadays. They also specified the complex arterial organization of the pons for a better clinical understanding of its syndromes [59–61].

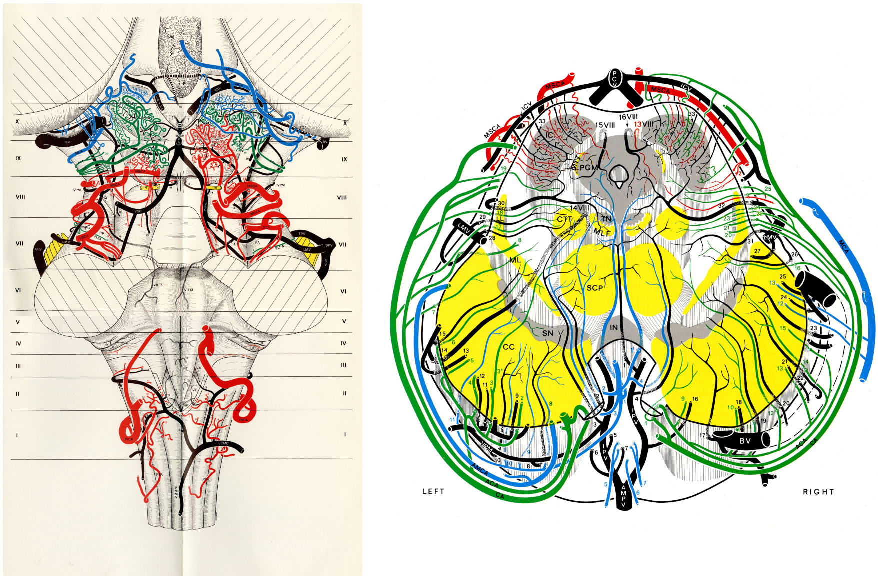

Figure 7. Diagrams of brainstem vascularization by Henri Duvernoy (1931–2021). Reprinted from [61], used with permission.

The princeps thalamus arterial supply described by Foix was also refined. Abbie formally confirmed that Duret's lenticulo-optic artery did not exist [56]. The arterial pedicles and participation of the anterior choroidal artery were confirmed by Christiaan Plets (1939–2015) [62]. The anatomical variations of the thalamic arterial pedicles were studied by Gérard Percheron (1930–2011) [63].

7. Conclusions

The question of the variability of the arterial cortical territories introduced by Beevor after the works of Heubner and Duret as well as the role of arterial anastomoses has been widely debated. The way in which anastomoses of the cortical arteries function in normal conditions compared to during a cerebral infarction was assessed by two anatomical and anatomo-pathological studies [64]. Improved techniques allowed anatomists to study microvascularization, and Duvernoy focused on the cerebral and cerebellar cortexes [65,66]. However, his magnificent studies did not completely resolve the still-debated question of the anastomoses and variability of the arterial cortical territories.

Author Contributions: Conceptualization, L.T. and J.B. Investigation L.T. and J.B. Writing—Original Draft Preparation L.T.; Writing—Review & Editing J.B.

Funding: This research received no external funding.

Acknowledgments: We would like to thank Jennifer Dobson for proofreading this manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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