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To cite this article: F. Clifford Rose (2009) Cerebral Localization in Antiquity, Journal of the History of the Neurosciences, 18:3, 239-247, DOI: [10.1080/09647040802025052](https://doi.org/10.1080/09647040802025052)

To link to this article: <https://doi.org/10.1080/09647040802025052>



Published online: 22 Jul 2009.



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Cerebral Localization in Antiquity

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Fragments of neurology can be found in the oldest medical writings in antiquity. Recognizable cerebral localization is seen in Egyptian medical papyri. Most notably, the Edwin Smith papyrus describes hemiplegia after a head injury. Similar echoes can be seen in Homer, the Bible, and the pre-Hippocratic writer Alcmaeon of Croton. While Biblical writers thought that the heart was the seat of the soul, Hippocratic writers located it in the head. Alexandrian anatomists described the nerves, and Galen developed the ventricular theory of cognition whereby mental functions are classified and localized in one of the cerebral ventricles. Medieval scholars, including the early Church Fathers, modified Galenic ventricular theory so as to make it a dynamic model of cognition. Physicians in antiquity subdivided the brain into separate areas and attributed to them different functions, a phenomenon that connects them with modern neurologists.

Keywords cerebral localization, Egyptian medicine, Greco-Roman medicine, Alexandrian neurology, medieval neurology, ventricular

Those about to study medicine, and the younger physicians, should light their torches at the fires of the Ancients.

—Karl Rokitansky

Introduction

Henry Head wrote, “The evolution of our knowledge of cerebral localisation is one of the most astonishing stories in the history of medicine” (Head, 1926). While cerebral localization now emphasizes cortical function, the concept began in the more general sense in the cerebral hemispheres, which ended only when the experimental methods of the early nineteenth century proved that phrenology was fallacious. For the purpose of this paper, I have divided our earliest knowledge of this subject into Egyptian, pre-Hippocratic, Classical Greek, Alexandrian, Greco-Roman, and medieval eras (Table 1).

Ancient Egypt

The oldest extant written description of the brain in any language is in the Edwin Smith surgical papyrus (Rose, 1993), copied in the seventh century BC but written probably in the time of the Pyramids (3000–2500 BC), perhaps by Imhotep, physician, architect, astronomer, and vizier to the Pharaoh Djoser (Sullivan, 1995). In practical terms the Egyptians did not consider the brain important. Indeed, the ancient Egyptians, in mummification, completely ignored it by first removing it via the nose or elsewhere.

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Table 1
Neurological eras in antiquity

Era	Approximate dates
Egyptian	3000–1000 BC
Pre-Hippocratic	1000–600 BC
Classical Greece	500–200 BC
Alexandrian	300 BC–100 AD
Greco-Roman	100–300 AD
Medieval	400–1400 AD

Table 2
Medical papyri

Papyrus	Century BC	Location
Edwin Smith	30th	New York
Ebers	Early 16th	Leipzig
Berlin	16th	Berlin
Beatty VI	14th	London
Carlsberg VIII	13th	Copenhagen
London	11th	London

Of the many extant papyri, the six of the most medical interest are shown in Table 2. Edwin Smith was an American student of the Egyptian language and, after studying in Paris, moved in 1858 to Luxor, where he remained for nearly 20 years. He obtained the papyrus in 1862 and his daughter presented it to the New York Historical Society in 1906, after her father died.

The Egyptologist James Henry Breasted was asked in 1920 to undertake a translation of the Edwin Smith papyrus that was published ten years later (Breasted, 1930). It dealt with 48 traumatic surgical cases, about 17 of which concerned mainly wounds of the head and neck. Case 6 of this papyrus (Clarke & O'Malley, 1972, pp. 164–174) described a gaping wound in the head with fractured skull and refers to pulsation of the brain, the anterior fontanelle, the meninges, and possibly the cerebrospinal fluid. Even as early as this, it was recognized that an injury to one side of the brain affected the leg on the other side of the body (Sachs, 1952, p. 21).

Pre-Hippocratic Period

Homer

Homer is considered to have lived about 900 BC even though the *Iliad* was not written down until hundreds of years later. In this account of the Trojan wars, there is mention of Nestor's horse that, wounded in the head by an arrow from Paris, made continuous gyratory movements, possibly due to a cerebellar lesion (Sachs, 1952, p. 23). Also in Homer, there was debate as to whether the brain or the heart was the seat of the soul, meaning the emotions and the intellect. Some felt it was the whole body, others the blood, but most opted for one particular organ, e.g., the spleen or liver; most thought it

was the heart. Many were in favor of this organ because of experience from the battle-field, where the fatal results of a heart wound were well recognized. Furthermore, the heart's pounding changed with emotion, and speech appeared to come from that region. The brain was, perhaps surprisingly, not considered important, possibly because it was inaccessible.

Biblical Neurology

Most ancient civilisations, including the Egyptians, the Mesopotamians, and the Hebrews, chose the heart as the central organ of the body. In Biblical times there was no doubt that thought and intelligence were linked to the heart as evidenced by reading that “the heart of Kings is unsearchable,” the most secret part, and “I sleep, but my heart waketh” (Song of Songs), i.e., a man's conscience does not disappear during the night, and “let not thine heart envy sinners” (Proverbs 23:17), indicating the heart as the seat of moral values. The heart was also the seat of faithfulness “the heart is deceitful above all things (Jeremiah 17:5) and “their heart weird after idols” (Ezekiel 20:16).

Classical Greece

The Greeks were divided (Table 3) as to whether the heart or the brain was the more important organ, a controversy that continued for nearly 2000 years. Whereas Empedocles placed the seat of the soul in the blood, Parmenides and Epicurus in the chest, Strato between the eyebrows, Democritus and Plato in the head as a whole, others placed it in the meninges and Herophilus in the ventricles of the brain (Prioreschi, 1996, p. 536). We shall consider mainly those ancient Greeks who gave pre-eminence to the brain (encephalocentric) rather than the heart (cardiocentric).

Alcmaeon of Croton (fl c 500 BC) lived in the Greek colony in southern Italy about the same period as Pythagoras (c 572–c 490 BC). Few of their writings remain and a link between the two has not been substantiated, although both considered the brain as the central organ of higher activities. Aristotle believed that Alcmaeon advocated anatomical dissection in order to understand the human body but that he dissected only animals, although it may have been one of his pupils that did the first dissection of the human brain (Patten, 1992). In his treatise *Concerning Nature*, Alcmaeon recognized the primacy of the brain as the central organ that was the site of the mind, thought, memory, intelligence, and received messages from the sense organs, writing “A man smelled with his nostrils as he drew breath up to the brain” (Oeser & Seitelberger, 1989, p. 5).

Table 3
Greek theories of cognition

Cardiocentric	Cephalocentric
Empedocles	Alcmaeon
Democritus	Pythagoras
Aristotle	Hippocrates
Diocles	Plato
Praxagorus	Herophilus
The Stoics	Rufus of Ephesus
The Epicurean	Galen

Theophrastus (c 371–c 287 BC) wrote that “Alcmaeon was the first to define the difference between man and animals, saying that man differs from the latter in the fact that he alone has the power of understanding” (Clarke & O’Malley, 1996, p. 3). Just homage was paid to him 60 years ago: “Alcmaeon was first and foremost a physician with a keen interest in anatomy . . . he was the first physician to exercise any influence upon the course of Greek thought, and . . . the first to set forth clearly what may perhaps be called a philosophy of medicine. His anatomical researches, particularly into the structure of the eye and his connecting the senses with the brain, mark him as a pioneer in pure medical science” (Jones, 1946, p. 6). Alcmaeon thought each sensation had its own localization in the brain, a concept not confirmed until two and a half millennia later. “He is the most important figure in Greek medicine before Hippocrates” (Prioreschi, 1996, p. 171), not least because he said “that the governing faculty was the brain” (Prioreschi, 1996, p. 181).

The Hippocratic corpus includes a clear view of the brain’s primacy. One work says that “for all perceptions the brain alone is responsible. The eyes, the ears, the tongue, the hands, and the feet, only perform that what the brain has known as correct.” “It is the brain which permits the perception of hearing, vision and smell; from those memory and intuition arise; from memory and intuition, however, if they are settled and reposed, knowledge is built up” (Oeser & Seitelberger, 1989, p. 5). The corpus raises further knowledge on the contra-lateral effects of head injuries, in which it was accepted that a lesion of one cerebral hemisphere produced changes on the opposite side of the body.

Furthermore, Hippocrates’ son-in-law Polybus, in a treatise entitled *Wounds of the Head* (c 390 BC), warned against surgical interference in a temporal lesion for fear of palsy on the opposite side of the body. The Hippocratic text *Epidemics* contains a case report of a woman three months pregnant who had paralysis of the right arm. She developed inarticulate speech, followed on the fourth day by “indistinct speech.” A case has been made that this is the first written case of aphasia, possibly jargon aphasia (Fields & Lemak, 1989).

Plato also thought that the brain was the most important organ in the body. In his dialogue *Timaeus*, in which he surveyed natural science and dealt with man’s perceptions, he refers repeatedly to the nervous system. In *Phaedo*, Plato referred to mental activity taking part in three stages: “accumulation of sensations, reasoning and memory, in this order” (Clarke & O’Malley, 1996, p. 7). In *Charmides* “The young Charmides is suffering from a headache, and Socrates says that he had heard . . . that a physician cannot treat the eyes properly without treating the whole head, nor the head without treating the whole body, nor yet the body without treating the soul” (Jones, 1946, p. 16).

Hellenistic Neurology

The Alexandrian school (c 300 BC–200 AD) featured Herophilus of Chalcedon and Erasistratus of Ceos, who were the first to perform systemic dissections of fresh human brain. Little written material from the Alexandrian school survives; we know about it mainly from fragments of two Ephesians, Rufus and Soranus. Another source was Celsus, who wrote *De Medicina* and lived under Tiberias (42 BC–37 AD).

Herophilus (c 330 BC–250 BC) lived in Alexandria under Ptolemy I Soter and his son, Ptolemy II Philadelphus. Herophilus was a pupil of Praxagorus, a fellow townsman of Hippocrates of Cos. He worked as a physician at Antioch in the court of Selencus I Nicatar. He introduced into medicine the terms *duodenum* and *prostate*, and into neurology *calamus scriptorium*, *choroid*, and *torcular*, the latter being named after him. He also distinguished the motor from the sensory nerves and was the first to describe the

rete mirabile. All his works were lost, although some were said to have survived until the sixth century (Prioreschi, 1996, p. 488). As with Hippocrates, many legends arose surrounding Herophilus, including his reply on being asked to define the complete doctor: “The man able to distinguish what is possible from what is not possible.” Of his 11 treatises, the one most relevant to neurology was Anatomy. He acquired this knowledge “by dissecting, while still alive, criminal prisoners received from the kings” (Prioreschi, 1996, p. 489), a view that has been challenged, not least because he described the *rete mirabile* that does not exist in humans.

Although Anaxagorus (500–428 BC) mentioned the ventricles, Hippocrates did not, but Aristotle described three central cavities (Gibson, 1969, p. 5). Herophilus considered the ventricles the site for thought, namely judgement in the anterior part (lateral ventricles), cognition in the middle part (third ventricle), and memory in the posterior part (fourth ventricle). He defined the lateral ventricles further by describing their “horns” and elaborated the importance of the fourth ventricle.

Erasistratus (fl c 280 BC) was born on the island of Ceos in the Aegean and also thought that all nerves came from the central nervous system. He distinguished the *cerebrum* (the greater brain) from the *cerebellum* (the lesser brain). He thought that fast running animals had more extensive cerebral folia and compared the winding, jerking surface (convolutions) of the human brain to the coils of the intestine, relating them to man’s superior intelligence, a view criticized several centuries later by Galen who pointed out that donkeys, who were stupid, had very complex brains.

Whilst Herophilus discovered the nerves, Erasistratus distinguished between motor and sensory nerves (Prioreschi, 1996, p. 537). Initially, Erasistratus thought that the nerves came from the meninges but later traced them from the brain’s interior. Although Herophilus favored the ventricles as the seat of the soul, Erasistratus claimed the cerebral substance as the more important. He also identified the foramen of Monro.

Greco-Roman Neurology

Rufus (c110–180 AD) practiced in Ephesus, which was an important medical center with a museum and an association of physicians. Rufus clearly understood that the brain, cranial nerves, spinal cord, and peripheral nerves were a connected system, but it was a later contemporary, Galen, who gave the most accurate reports regarding cerebral localization.

Galen (129–c 210 AD) was born in Pergamon in 129 AD and went to Rome in 162 AD, dying there about 210 AD; he lived away from Rome for three years from 166–169 AD. His father, Nicon, was a successful architect who added medicine to his son’s studies when Galen was 17, apparently persuaded by Asklepius in a dream. When Nicon died, Galen was about 20 years old. His training was “the longest on record” (Rocca, 2003, p. 2), as he studied in Smyrna, Corinth, and Alexandria. After training he returned to Pergamon as surgeon to the gladiatorial school. Five years later he went to practice in Rome. He returned home to Pergamon four years later and, during his second visit to Rome (c 169 – c 193), he was physician to four successive emperors.

Galen wrote over 500 treatises in Attic Greek but many were lost in the fire in Rome in 191 AD; five of these texts were neurological (Table 4). In Galen’s book, *De usu partium*, Galen wrote “One says the heart, another the meninges, and one that the brain contains the hegemonikon of the soul; therefore, one will claim one use for the part in question here, one will claim another.” Although the brain’s convolutions had been mentioned in the Edwin Smith papyrus, further description was given by the ancient Greeks, who were criticized by Galen because they “considered the brain as a kind of

Table 4
Galen's neurological texts

<i>De usu partium</i>
<i>De anatomicis administrationibus</i>
<i>De facultatibus naturalibus</i>
<i>De loci affectis</i>
<i>Placita</i>

excrescence put forth by the spinal cord" and was "formed of long convolutions" that were likened to the corrugations of metallic slag (Clarke & O'Malley, 1968, p. 385).

Although he dissected many animals and used the word "autopsy," there is no evidence that he dissected humans. Diogenes of Carystus is credited by Galen for writing the first anatomical manual and according to Pliny the Elder was "second in age and fame" to Hippocrates. In spite of his fame as an anatomist, Galen recognized only 7 of the 12 pairs of cranial nerves.

Although the first mention of the cerebellum was by Aristotle in his biological writings of the fourth century BC, the earliest description of its forms and functions were by Galen, who contrasted its convolutions with those of the cerebrum and considered it the source of the motor nerves. It was Galen who thought that motor nerves were linked to the cerebellum and sensory nerves to the cerebrum. He characterized nerves as hard (motor nerves from the posterior brain) and soft (sensory nerves from the anterior part) to retain sensory impressions. He localized smell to that part of the brain that has a covering membrane (meninx).

Galen used the term "apoplexy" to describe the condition in which all limbs were deprived of both motor and sensory functions at the same time. If only one half of the body, or one limb or part of it was affected, he called this "hemiplegia." His concept of the localization of mental activity was that imagination, reason, and memory were the three intellectual functions that could be affected separately and, although he did not attempt to accurately localize them, he favored the cerebral parenchyma rather than the ventricles. Galen considered that the main function of the ventricles were to produce and distribute *psychic pneuma*, the vital force, throughout the nervous system (Rocca, 2003). He explained all the functions of the nervous system, intellectual, motor, and sensory, were due to *psychic pneuma*, which is a requisite for life and enters when the inspired air from the lungs goes to the left ventricle of the heart where it is changed to vital pneuma (spirits), this is then distributed through the arterial system to enter all parts of the body including the brain through two vascular structures—the *rete mirabile* and the choroid plexuses. Galen felt that the "vital spirits" were converted in the *rete mirabile* into "animal spirits" that were stored in the cerebral ventricles and then went into the hollow nerves to produce movement and sensation. He thought that the vermis acted as a valve in the ventricular system to govern the flow of animal spirits and distinguished the white matter from such deep collections of grey matter as the corpus callosum, thalamus, corpora quadrigemina, and fornix.

This hypothesis was supported by Galen's dissections on animals, which have a *rete mirabile*, whilst humans do not. "Quarrelsome and acrimonious, Galen had little patience with those who held views different from his own" (Pioreschi, 1996, III, p. 326). "He was arrogant, contentious, full of himself . . . gullible, superstitious and pompous" (Pioreschi, 1996, III, p. 484). But ". . . he was probably the first to advocate peer review for publication" (Pioreschi, 1996, III, p. 327).

Areataeus of Cappadocia lived towards the end of the second century AD, and it is strange that he was never mentioned by Galen. Areataeus explained how limb paralysis was due to a contra-lateral lesion of the brain: "The cause of this is the interchange in the origin of the nerves, for they do not pass along on the same side, the right on the right side, until their terminations; but each of them passes over to the other side from that of its origin, decussating each other in the form of the letter X" (Areataeus, 1865, p. 306).

Poseidonius (fl 400 AD), a surgeon from Byzantium, first attempted to localize mental functions, he thought that injury to the front of the brain affected only imagination, but damage to the middle ventricle interfered with understanding and reason, and that memory was destroyed by damage to the back of the brain.

Medieval Neurology

The concept in antiquity that mental activity was localized to the cerebral ventricles gave rise to the cell doctrine of brain function, proposed by the Church Fathers Nemesius, Bishop of Emesa (fl c 390 AD), St. Augustine of Hippo (354–430 AD), and St. Gregory of Nazianzus (c. 330–389 AD). The Cell Doctrine was represented in several ways, the first being a diagram with the mental faculties written on a head that is divided into three parts—anterior, middle, and posterior—labelled with their different mental activities. The lateral ventricles were considered to be the *first* cell, the third ventricle the *second*, and the fourth ventricle as the *third*. The first cell received sensations from the special senses of the rest of the body and constituted the "*Sensus Communis*" (not the common sense of modern usage). Images were created from this to serve "*imaginativa*" (imagination) and "*fantasia*" (image formation) and were sited either in the posterior part of the first cell or the second cell (which was in the third ventricle), which was also the seat for reasoning, i.e., "*aestimativa*" (judgement), "*cogitativa*" (thought), and "*ratio*" (reasoning). The third cell, in the fourth ventricle, was the site for "*memorativa*" (memory; Clarke & Dewhurst, 1972).

The cell doctrine of brain function held sway for more than a thousand years. Nemesius of Emesa published "*On the Nature of Man*" (in Greek), which was the first known compendium of theological anthropology with a Christian orientation. Nemesius integrated Hellenic philosophy and medical literature using Galenic physiology, and its importance is that it examined the mental functions of the brain, the operation of the senses, imagination, memory, reasoning, and speech; the abrupt ending of this book indicated that it had not been finished and was intended for revision and it was, sometimes wrongly, attributed to Gregory of Nyssa. Augustine of Hippo supported the views of Nemesius, specifying that sensation resided in the front (lateral) ventricle, memory in the middle (third) ventricle, and movement in the posterior (fourth) ventricle.

There were several variations on the basic concept of the cellular doctrine. In the tenth century AD, Avicenna favored a five-cell doctrine, the addition being a dynamic element to the static cell doctrine. This introduced the vermis, which did not then mean the midline structure of the cerebellum but rather the choroid plexuses of the lateral ventricles that regulated the flow of mental activity. An eleventh-century manuscript, the earliest known illustration of the brain in the Western world, shows the brain is labelled cold and moist whereas the heart is the opposite. This arrangement recapitulates Aristotle and the ancient Greeks as well as the more recent localization of mental functions. Albert the Great's thirteenth-century writings on the soul used simple circles to show the three cells. Avicenna confused the theory even more by adding a fifth cell for thought (*cogitative*).

Rhazes (860–922 AD), the Persian physician, wrote the book *Al-Mansuri*, a fourteenth-century manuscript copy contains an early depiction of the cell doctrine. These ideas were transmitted by Arabic and Western scholars until the seventeenth century. Vesalius (1514–1564 AD) in his 1543 *De humani corporis fabrica* accepted ventricular localization. He had been taught Galenic physiology but cast doubts on it, leading the greatest Renaissance anatomist to become the founder of modern neuroanatomy.

The discovery that the ventricles contained cerebrospinal fluid resulted in a transition to the belief that the brain parenchyma and not the ventricles were responsible for localization of function. This was reflected in the work of Leonardo da Vinci (1472–1519 AD) who, between 1504 and 1507, injected wax into the ventricles of oxen and thus obtained their exact shape. Nearly 20 years later Berengari da Carpi (1460–1580 AD) improved nomenclature so that the medieval designations of the ventricles were replaced by anatomical terms.

Little attention was paid to the surface of the brain, with its gyri and sulci, because the mantle of the brain was thought to be functionless until the seventeenth century. We can identify the gyri in Leonardo's drawings but, as usual with neuroanatomy, the best cortical illustration came with Vesalius, who did not think they had a standard pattern and compared them to a schoolboy's drawing of clouds.

Although Vesalius had published the first drawing of the base of the brain, and Eustachius followed, the first anatomist to dissect this view was Constanzo Varolio (1543–1575 AD) after whom the pons is named. Because of failure to recognize their different functions, it was not until 1586 that a distinction was made between the white and grey matter by Archangelo Piccolomini (c. 1526–1586) of Rome. Until the nineteenth century, only one part of the surface of the brain was named, and that was the Sylvian fissure after Franciscus de la Boë (1614–1672) by the Danish anatomist Caspar Bartholin (1585–1629).

The evolution of our thoughts regarding cerebral localization was slow but the value of its inexorable progress was summarized thus: "The most important development in the history of brain physiology came about when attempts were made to show that the brain . . . was comprised of many parts, each of which had a specific function" (Clarke & O'Malley, 1972, p. 458).

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