

The History of the Olfactory Nerve: From Galen to Primary Amoebic Meningoencephalitis (Naegleriasis)

Historia del Nervio Olfatorio: De Galeno a la Meningoencefalitis Amebiana Primaria (Naegleriasis)

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GALASSI, F. M.; PINDINELLO, I.; PAPA, V.; ARTICO, M.; GIORDANO, B.; PALMIERI, M.; FRATINI, A.; SCIAMANNA, G. & COFONE, L. The history of the olfactory nerve: From Galen to primary amoebic meningoencephalitis (Naegleriasis). *Int. J. Morphol.*, 44(1):38-44, 2026.

SUMMARY: The central and peripheral parts of the olfactory system serve a crucial sensory role. The olfactory epithelium and nerve fibers make up its peripheral components, while the limbic areas and olfactory bulb comprise its center structures. Galen's historical exclusion of the olfactory nerve from his taxonomy of cranial nerves led to centuries of controversy. Its significance in sensory integration was suggested by Islamic academics such as Rhazes and Avicenna, who improved our comprehension of it. Its anatomical classification was further developed by Andreas Vesalius and Caspar Bartholin, and in the 17th century, Thomas Willis finally identified the olfactory nerve as the first cranial nerve. Recent studies have clarified its clinical relevance. SARS-CoV-2 interferes with the function of olfactory epithelium support cells, resulting in anosmia. The free-living amoeba *Naegleria fowleri* causes primary amoebic meningoencephalitis (PAM) by getting into the brain and spinal cord through the olfactory nerve pathway. These results highlight the olfactory nerve's susceptibility to infections and its critical function in the development of illness. From prehistoric hypotheses to contemporary therapeutic uses, the history of the olfactory nerve reflects the advancement of science in general. Prevention and treatment plans for neurological disorders affecting the olfactory system are still influenced by knowledge of its anatomy and function.

KEY WORDS: Cranial nerves; Clinical anatomy; Naegleriasis; Neuroanatomy; Olfactory nerve.

INTRODUCTION

One of the earliest sensory systems, the olfactory system is composed of both central and peripheral parts. The olfactory bulb and associated brain structures are located in the core portion, whilst the olfactory epithelium and nerve fibers make up the peripheral portion. In contrast to many other mammals, humans have a smaller olfactory structure, including fewer nasal turbinates, and no functional auxiliary olfactory system. The fundamental microanatomical features, however, are comparable to those of other mammals.

Odor-detecting sensory neurons with cilia are found in the olfactory epithelium, which is situated in the upper

nasal cavity. In the olfactory bulb, where mitral and tufted cells transmit information to higher brain regions, these neurons renew and send messages. The limbic regions and olfactory cortex, which are engaged in emotion and memory, are directly connected to the central olfactory structures, avoiding the thalamus (Smith & Bhatnagar, 2019). Sexual dimorphism is another feature of the human olfactory system; women frequently outperform men in olfactory tasks, possibly as a result of variations in the number of neurons in the olfactory bulb (Oliveira-Pinto *et al.*, 2014). Humans nonetheless have a strong and useful sense of smell, despite having a less complex olfactory system than macrosmatic animals like dogs.

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Within the olfactory epithelium are unmyelinated axons of olfactory sensory neurons that make up the olfactory nerve (Cranial Nerve I). These axons travel through the cribriform plate of the ethmoid bone in structures called fila olfactoria. The nerve fibers get in the olfactory bulb, which is located in the anterior cranial fossa, after passing through the cribriform plate. The axons in the olfactory bulb form synapses with the dendrites of tufted and mitral cells in olfactory glomeruli. The olfactory tract, which runs along the olfactory sulcus on the frontal lobe's orbital surface, is then used by these cells to transmit the sensory information. In order to convey olfactory information to central structures such as the piriform cortex, amygdala, and other limbic regions, the olfactory tract further splits into lateral, medial, and intermediate striae.

METHODOLOGY

In this article the historical evolution of anatomical concepts of the olfactory nerve are examined from their beginnings in the Classical world. To achieve this goal a historico-anatomical review was performed by searching the main engines and repositories (Scopus, Pubmed, Google Scholar, Web of Science) by searching for the keywords: “olfactory nerve” OR “cranial nerve I” AND “historical” OR “history”. The obtained results were summarized to offer a comprehensive historical perspective on the first cranial nerve.

This paper seeks to explore the historical trajectory of the olfactory nerve's study, from ancient perspectives to contemporary insights into its clinical implications, particularly in the context of diseases like Naegleriasis. By examining the contributions of key figures such as Rhazes, Avicenna, and Thomas Willis, we aim to elucidate the interplay between historical understanding and modern scientific advancements.

Historical analysis: The Classical Period

The olfactory nerve pathway differs from other sensory systems in that it connects peripheral sensory information directly to cortical and limbic areas, circumventing the thalamus (Smith & Bhatnagar, 2019).

The olfactory nerve, essential for the sense of smell, has undergone significant reevaluation throughout history. Its identification and classification as a cranial nerve reflect the broader evolution of anatomical knowledge. Galen of Pergamum (AD 129–c. 216) (Fig. 1) was among the first to describe the olfactory tracts, yet he excluded them from the cranial nerves (Davis *et al.*, 2014; Storey, 2022). This exclusion initiated centuries of debate among scholars, spanning diverse cultures and medical paradigms.

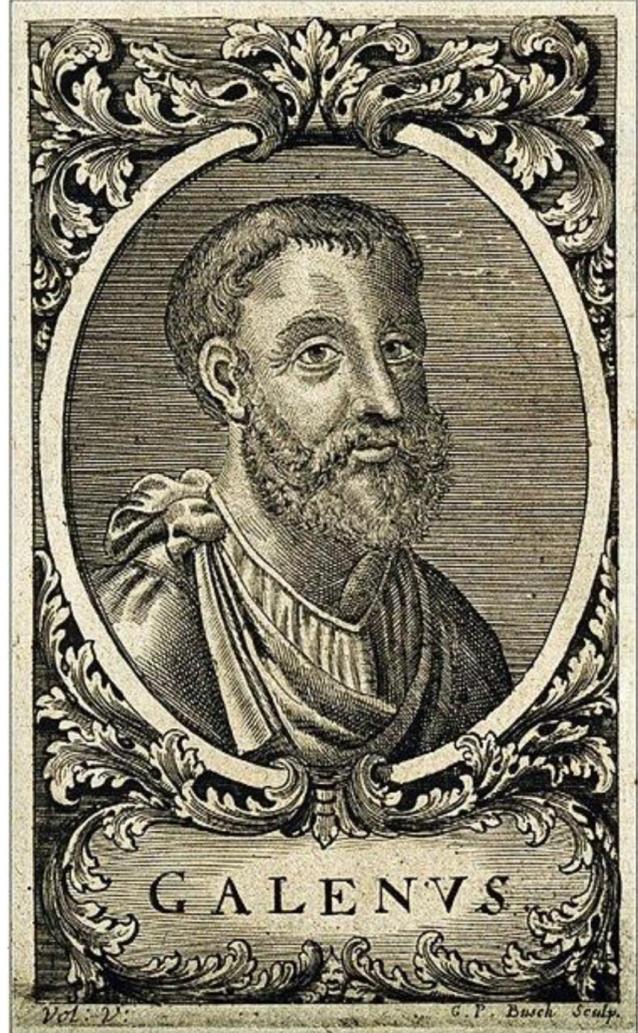


Fig. 1. Galen in an 18th-century engraving [<https://commons.wikimedia.org/wiki/File:Galenus.jpg>] From Wikipedia: This work is in the public domain in its country of origin and other countries and areas where the copyright term is the author's life plus 100 years or fewer.

Galen's classification of seven pairs of cranial nerves, which he discovered from dissecting animals including apes, pigs, and goats, is one of his major contributions to our understanding of the neurological system (Rajkumari, 2015).

Marinus of Alexandria, who lived in the late 1st and early 2nd centuries CE, was the most renowned anatomist of his time and his pioneering dissections and classification of the cranial nerves deeply influenced Galen, who was born shortly thereafter. Although Galen's works eventually overshadowed Marinus for centuries, Galen himself credited Marinus with reviving anatomical science and laying the foundations for the study of cranial nerves, including the olfactory nerve. Notably, in commenting on Marinus' work,

Galen appears to exclude the olfactory nerves from his final count of cranial nerves, as he believed that not all processes emerging from the brain should be classified as nerves. The olfactory nerve, which has soft bulbs that make it resemble brain tissue, was probably excluded because Galen claimed that objects without firm consistency were not actual nerves (Osen, 2022).

He highlighted the olfactory nerve's function in smell-related sensory input while describing it as one of these cranial nerves. According to his anatomical discoveries, the olfactory nerve connects to the nasal tissues after emerging from the brain, enabling the sense of odors (Eastwood, 1981).

Galen extrapolated his conclusions from animal models, which occasionally resulted in errors, despite the fact that societal barriers prevented him from accessing human cadavers. For instance, he believed that the olfactory systems of humans and animals were structurally similar, yet his research nevertheless improved our knowledge of sensory pathways (Rajkumari, 2015). The idea of a centralized control system for the senses was further supported by his theory that the brain processed sensory data, including olfactory input (Eastwood, 1981).

Galen's work served as a basis for later advances in anatomy and neurology because of his emphasis on experimentation and observation, which prepared the way for further research into the structure and function of cranial nerves (Rajkumari, 2015).

Similar to Galen and his forebears, modern anatomy's founder, Andreas Vesalius (1514–1564; transformed the study of the human body with his seminal work *De humani corporis fabrica* (1543).

Vesalius meticulously drew the base of the brain, but he omitted the olfactory tracts from the cranial nerve system in favor of Galen's enumeration of seven cerebral nerves. Despite their detail, his drawings reinforce rather than contradict the dominant Galenic worldview (Storey, 2022).

Historical Evolution of the Olfactory Nerve: From the Middle Ages to Bartholin

Ancient and Medieval Periods Galen was pivotal in early anatomical studies but notably excluded the olfactory tracts from his list of cranial nerves. This omission set a precedent for subsequent interpretations. Rhazes and Avicenna, prominent Islamic scholars, combined the olfactory nerves with the optic nerves as part of the “first pair” (Davis *et al.*, 2014).

The knowledge of cranial nerves and sensory integration was greatly advanced by Rhazes and Avicenna. Rhazes, a Persian polymath, made significant contributions to neuroanatomy. He considered the olfactory nerve part of the brain and did not classify it as a cranial nerve (Davis *et al.*, 2014).

Because of their close proximity in the brain, Rhazes postulated a connection between the olfactory nerve (Cranial Nerve I) and the optic nerve (Cranial Nerve II; implying a type of neural interaction. According to his theory, this anatomical proximity could enable indirect effects of scent and vision on one another. His observations represented a sophisticated anatomical theory at the time, even though they were not supported by experimental data (Davis *et al.*, 2014).

In his groundbreaking book *The Canon of Medicine*, Avicenna developed this thesis further. According to him, the brain is the genesis of a centralized sensory network that includes the olfactory and visual nerves as separate but related components. By presenting the olfactory and visual nerves as parts of a single system in charge of sensory experience and cognition, Avicenna's works highlighted the functional coordination of the cranial nerves. Additionally, he correctly explained how the optic chiasm, where optic nerves intersect, affects visual perception (Khamevar, 2021).

The olfactory bulbs, according to Avicenna, are “nipple-like protrusions” situated above the nasal openings and beneath the frontal portion of the brain. According to his description, these structures have a role in the early processing of smell. He understood that this area is the source of the olfactory nerves, which are essential for carrying sensory data from the nose to the brain. Avicenna also highlighted the importance of scent in perception by classifying it as one of the five exterior senses of the human body.

This explanation is in line with contemporary anatomy, which acknowledges the olfactory bulbs as essential components for processing olfactory signals. These bulbs are located above the cribriform plate of the ethmoid bone and are linked to the olfactory nerves (Mazengenya & Bhikha, 2017). These concepts contributed to a more comprehensive understanding of sensory pathways by bridging the gap between Islamic scientific philosophy and Greek anatomical traditions. They established the foundation for subsequent research and emphasized the significance of cranial nerve anatomy in sensory integration, despite the fact that their theories lacked the accuracy of contemporary neuroscience (Khamevar, 2021).

An important advancement in our knowledge of sensory functioning was made when Jorjani (1042–1137 AD)

highlighted their crucial role in olfaction. Seven pairs of cranial nerves were documented by Jorjani in his medical encyclopedia, *The Treasure of the Khwarazm Shah* he determined that the olfactory nerves in the first pair were two hollow projections that resembled nipples and came from the forebrain (Pish Damagh). He thought that the sense of smell was made easier by these neurons. Additionally, Jorjani called the nerves' junction the "Confluence of Light" (Majma al-Nour; currently referred to as the optic chiasma). In line with previous researchers, Jorjani and Rhazes recognized the olfactory nerves' sensory role but did not categorize them as distinct cranial nerves (Zarshenas *et al.*, 2012). The olfactory sense is essential to both sensory experience and medical diagnosis, according to renowned Persian physician Jorjani. He saw the direct connection between the olfactory nerve (Cranial Nerve I) and the brain as proof of its significance in human physiology. Jorjani underlined that by detecting changes in body fluids and exhalations, the olfactory system's capacity to detect scents played a crucial part in disease diagnosis. According to anatomy, Jorjani understood that the olfactory nerve carries sensory information from the nasal cavity to the olfactory bulb, which interprets it before sending it to the limbic system and other higher brain areas. This link demonstrated how the olfactory system affects memory, emotions, and bodily reactions. He also recognized the intimate connection between the respiratory and olfactory systems, pointing out that toxins inhaled can have an impact on both health and sensory experience. Jorjani's ideas, which combined an awareness of anatomy with real-world medical applications, were innovative for their day. He established the foundation for subsequent developments in our knowledge of the olfactory system's function in health and illness by fusing sensory function with diagnostic methods (Hosseini *et al.*, 2011).

The olfactory tract and bulb were not categorized as nerves in Vesalius's work (Fig. 2). They were instead referred to as the "organ of smell" that is situated at the base of the brain. Vesalius (1514-1564) made practical observations that were in line with his time. He hypothesized that pituitary-related processes caused mucus from the brain to travel to the nostrils via a funnel-shaped passageway called the infundibulum. In contrast to contemporary anatomy, he did not describe the olfactory nerve. Vesalius focused on the ventricles of the brain and the plexus that surrounds them. He considered how the "animal spirit" and "vital spirit" generated in the brain, which he thought played a part in mental processes, were not directly related to the olfactory nerve as we know it today (Gomes *et al.*, 2015).

The mammillary processes were frequently referred to as such by Vesalius, Columbo, Eustachius, Falloppio, and Bauhin. Nicolo Massa, in 1536, believed they were the first

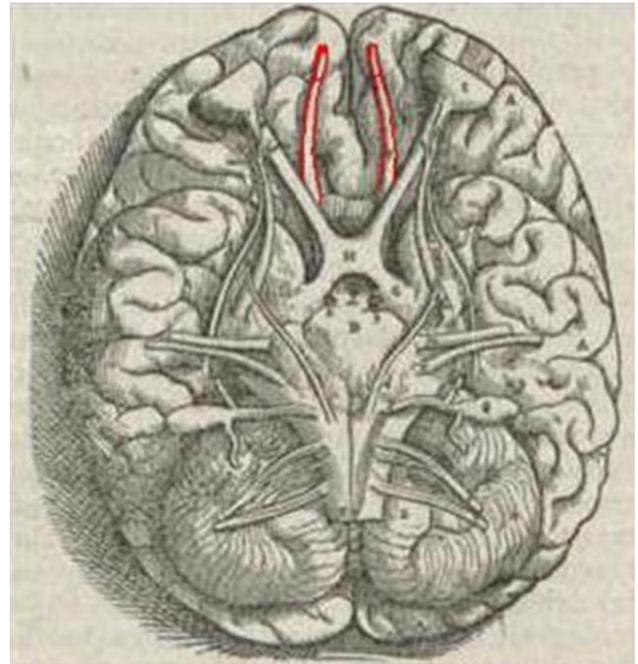


Fig. 2. 1543 Andreas Vesalius' Fabrica, olfactory bulbs and olfactory nerve [https://commons.wikimedia.org/wiki/File:1543,Vesalius%27OlfactoryBulbs.jpg]. From Wikipedia: "This work is in the public domain in its country of origin and other countries and areas where the copyright term is the author's life plus 70 years or fewer."

pair of cranial nerves, although he was the only one to do so until Thomas Willis' classification solidified their position as the first pair in the 17th century (Simon *et al.*, 2011; Davis *et al.*, 2014; Arráez-Aybar *et al.*, 2015; Porrás-Gallo *et al.*, 2019). Benedetti Alessandro (1445–1525 AD) had placed them as his third pair (Simon *et al.*, 2011; Davis *et al.*, 2014; Porrás-Gallo *et al.*, 2019). Caspar Bartholin the Elder coined the Latin word *olfactorius* in 1611 and called the olfactory nerves *primum par olfactorium* (first pair, olfactory) (Davis *et al.*, 2014; Simon *et al.*, 2011).

The Modern Era: From Casserio to Soemmerring

Significant progress was made in identifying the olfactory pathways as cranial nerves by Giulio Casserio (1552–1616). Using the conventional numbering scheme developed by Galen and Vesalius, Casserio included the olfactory processes as an eighth pair of cranial nerves in his *Tabulae Anatomicae* (1627). This recognition broke with previous ideas and opened the door for later anatomists to include the olfactory nerve in their lists of cranial nerves. Thomas Bartholin (1616–1680) and his father, Caspar Bartholin the Elder (1561–1629) were instrumental in the development of the nomenclature for cranial nerves. *Primum par olfactorium* was the word originally used by Caspar Bartholin to refer to the olfactory nerves as the first pair of

cranial nerves. Later writings by Thomas Bartholin, such as updated versions of *Institutiones Anatomicae*, strengthened this classification even further and were a crucial step in the olfactory nerves' acknowledgment as cranial nerves (Hill, 2007; Storey, 2022). Despite not leaving the skull or dura mater, Bartholin maintained that the olfactory pathways had to be regarded as nerves. He underlined how close they are to nerves in terms of course, color, and function, claiming that if they were not considered nerves, other cranial nerves inside the skull would become inconsistent (Simon *et al.*, 2011)

In his taxonomy of cranial nerves, renowned British anatomist Thomas Willis (1621–1675) formally included the olfactory nerves. Willis included nine cranial nerves in his 1664 *Cerebri Anatome* with the olfactory nerves being the first pair (Arráez-Aybar *et al.*, 2015; Porrás-Gallo *et al.*, 2019). The physical knowledge of the olfactory nerves and their connection to the brain was greatly enhanced by his use of intricate pictures, which are frequently credited to Christopher Wren. The final classification of the cranial nerves, which is still the foundation of contemporary terminology, was given by Samuel Thomas Soemmerring (1755–1830). Soemmerring listed 12 cranial nerves in his PhD thesis, *Anatomica de basi encephali et originibus nervorum cranium egredientium* (1778; with the olfactory nerves being the first pair. In later works, such as pictures of the human olfactory organs (1809; he included thorough pictures of the olfactory system and was the first to use the word *nervi olfactorii* regularly. Soemmerring's classification was accepted for a long time because of his artistic and scientific integrity (Storey, 2022).

A new pathological pathway for *Naegleria fowleri*

Understanding the anatomical trajectory of a cranial nerve, such as the olfactory nerve, is crucial for recognizing how certain infectious agents can exploit these pathways to breach the central nervous system and cause neurological disease. These developments opened the door for current studies on neurological conditions that impact the olfactory nerve, such as SARS-CoV-2-induced anosmia or Primary Amoebic Meningoencephalitis (PAM; which are brought on by *Naegleria fowleri* (Jarolim *et al.*, 2000; Butowt *et al.*, 2023).

The 18th and 19th centuries saw the advent of microscopic studies, further elucidating the cellular structure of the olfactory nerve. Advances in staining techniques and imaging technologies during these centuries deepened our understanding of its physiology and its role in pathologies. Electron microscopy studies by Van Gehuchten, Martin, Gasser, and De Lorenzo (Van Gehuchten & Martin, 1891;

Gasser & Palade, 1956; De Lorenzo, 1957) deepened the understanding of olfactory ultrastructure. The field was transformed in the 1990s when Richard Axel and Linda Buck discovered odorant receptors. Their ground breaking study demonstrated the existence of a large gene family encoding olfactory receptors and revealed the spatial organization of olfactory inputs in the olfactory bulb (Malnic *et al.*, 2010). This pivotal work earned them the Nobel Prize in Physiology or Medicine in 2004 (Nobelprize (2004).

SARS-CoV-2 infects support cells including sustentacular cells and Bowman gland cells within the olfactory epithelium rather than directly targeting olfactory receptor neurons. Because they produce mucus, transport glucose, and support the cilia of olfactory neurons, these cells are crucial for preserving the integrity of the olfactory system. A temporary loss of olfactory function results from damage to these support cells, which also causes disturbances in the energy supply, cilia maintenance, and mucus formation (Meinhardt *et al.*, 2021).

Smell recovery usually happens quickly in COVID-19 patients. This is explained by the restoration of cilia on surviving neurons and the regeneration of support cells. The quick recovery suggests that, unlike other processes that require cell turnover, many olfactory neurons survive the infection and return to normal function once their support structures are restored (Butowt *et al.*, 2023).

Numerous researchers have examined the possibility that SARS-CoV-2, travels from the nose to the brain along the olfactory nerve, due to the high viral load in the nasal epithelium and the nasal cavity's close proximity to the skull and brain (Burks *et al.*, 2021; Meinhardt *et al.*, 2021).

When breathed, *Naegleria fowleri*, an amoeba, can enter the central nervous system through the nasal mucosa and produce primary amoebic meningoencephalitis (PAM; a serious and frequently fatal illness.

The amoebas moved through the cribriform plate from the nasal submucosa into the olfactory nerve fibers and then into the olfactory bulb of the brain.

In the early phases of PAM, this verified that the olfactory nerve pathway was the main pathogen (Jarolim *et al.*, 2000).

The case of Naegleriasis PAM, a rare but severe condition, exemplifies the clinical relevance of the olfactory nerve. These recent studies highlight the continuity of the olfactory system and the course of the olfactory nerve as investigated by the great scientists previously described.

The susceptibility of the olfactory nerve and its crucial role in illness pathogenesis are highlighted by recent research that emphasize the significance of comprehending the anatomy and function of the nerve in order to create preventive and therapeutic measures against such infections.

CONCLUSIONS

The history of the olfactory nerve provides an engaging account of scientific advancement, demonstrating the centuries-long evolution of human anatomy knowledge. Due to its delicate form, the nerve was first left out of Galen's early classifications. However, it was eventually recognized by scholars like Rhazes, Avicenna, Vesalius, and Thomas Willis, who solidified its status as the first cranial nerve.

This development shows how our understanding of the sensory pathways was influenced by changes in scientific methodologies, from the dissection of animals to in-depth research on human anatomy. The olfactory nerve's special structure, which connects the nasal epithelium to the limbic system directly without going via the thalamus, emphasizes how important it is for perception and emotion.

Its clinical significance has been validated by recent studies, especially in relation to pathogens like SARS-CoV-2 and *Naegleria fowleri* that can use the olfactory pathway to enter the brain. These findings highlight the continued value of historical anatomical knowledge in tackling today's medical issues.

We can better understand the intricacy of the olfactory nerve and see how earlier findings continue to impact contemporary neuroscience and clinical practice by following its scientific development.

GALASSI, F. M.; PINDINELLO, I.; PAPA, V.; ARTICO, M.; GIORDANO, B.; PALMIERI, M.; FRATINI, A.; SCIAMANNA, G. & COFONE, L. Historia del nervio olfatorio: De Galeno a la meningoencefalitis amebiana primaria (*Naegleriasis*). *Int. J. Morphol.*, 44(1):38-44, 2026.

RESUMEN: Las partes central y periférica del sistema olfatorio desempeñan una función sensorial crucial. El epitelio olfatorio y las fibras nerviosas conforman sus componentes periféricos, mientras que las áreas límbicas y el bulbo olfatorio conforman sus estructuras centrales. La exclusión histórica del nervio olfatorio por parte de Galeno de su taxonomía de los nervios craneales dio lugar a siglos de controversia. Su importancia en la integración sensorial fue sugerida por académicos islámicos como Rhazes y Avicenna, quienes mejoraron nuestra comprensión de la misma. Su clasificación anatómica fue desarrollada aún más por Andreas Vesalius y Caspar Bartholin, y en el siglo XVII, Thomas Willis finalmente identificó el nervio olfatorio como el primer nervio craneal. Estudios recientes han clarificado su relevancia

clínica. El SARS-CoV-2 interfiere con la función de las células de soporte del epitelio olfatorio, lo que resulta en anosmia. La ameba de vida libre *Naegleria fowleri* causa meningoencefalitis amebiana primaria (MAP) al ingresar al cerebro y la médula espinal a través de la vía del nervio olfatorio. Estos resultados resaltan la susceptibilidad del nervio olfatorio a las infecciones y su función crítica en el desarrollo de la enfermedad. Desde las hipótesis prehistóricas hasta los usos terapéuticos contemporáneos, la historia del nervio olfatorio refleja el avance de la ciencia en general. Los planes de prevención y tratamiento de los trastornos neurológicos que afectan al sistema olfativo aún se ven influenciados por el conocimiento de su anatomía y función.

PALABRAS CLAVE: Nervios craneales; Anatomía clínica; Naegleriasis; Neuroanatomía; Nervio olfatorio.

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