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Cranial Nerve Zero (CN0), True or Fiction: A Comparative Review Study on Cranial Nerves with Emphasize on CN0 Anatomy and Function

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Abstract

Context: Cranial nerves are integral components of the central nervous system in vertebrates. Throughout history, from the pre-Hippocratic era to 18 ADS, anatomists have debated the existence and classification of human cranial nerves. This review explores the evolution of understanding regarding cranial nerve anatomy and nomenclature.

Evidence Acquisition: The literature was examined through three separate historical phases: The early macroscopic phase, the microscopic phase, and the ontogenetic and geno-architectural phase. Important contributions from prominent individuals, especially during the Galenic period, were evaluated to grasp the historical background of cranial nerve categorization.

Results: The analysis revealed persistent disagreements regarding the number of cranial nerves. While contemporary anatomy recognizes 12 pairs, recent discussions have introduced the concept of a zero-numbered cranial nerve (CN0/13), further complicating the classification.

Conclusions: The ongoing debate about the number of cranial nerves underscores the complexities of anatomical classification. This review highlights the need for continued research and dialogue within the anatomical community to resolve these longstanding discrepancies.

Keywords: Cranial Nerve Zero, Cranial Nerves, CN0 Anatomy, Comparative Review

1. Context

The peripheral nervous system (PNS) consists of the remaining nerve pathways outside the brain and spinal cord, which include 12 pairs of cranial nerves and 31 pairs of spinal nerves (1). Among these, the cranial nerves are numbered I to XII in Roman numerals, reflecting their sequential emergence from the rostral (front) to the caudal (back) regions of the brainstem (2). With the exception of cranial nerves I and II, which are considered extensions of brain tissue, the remaining ten cranial nerves (III-XII) originate from the brainstem and possess specific nuclei within it (Table 1). While this traditional classification provides a framework for understanding cranial nerves, the scientific reality is more intricate, leading to ongoing debates regarding the categorization and identification of the pathways of distinct cranial nerve fibers, as well as the existence of lesser-known structures like the terminal nerve, also referred to as cranial nerve zero (CN0) (3).

2. History of the Discovery of Cranial Nerves

The earliest references to cranial nerves can be traced back to medical writings by Alexandrian physicians, such as Herophilus (circa 290 BC) and Erasistratus (280 BC). Most terminologies emerged during the 17th and 18th centuries (4). The nomenclature for the twelve cranial nerves was established through various anatomical discoveries made by renowned anatomists, from Galen to Von Sommerring (5). A Roman and Greek physician, surgeon, and philosopher, Aelius Galenus or Claudius (129 - 200 AD), contributed significantly to the field of nerve anatomy, providing crucial insights that benefited physicians. Similarly, Abu Ali Sina (Ibn Sina)

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Table 1. The Summary of Cranial Nerves and Their Function

Cranial Nerve Names and Types	Function	Explorer	Origin
Olfactory (CN I)			
Sensory	Sense of smell	Caspar Bartholin-1611	Olfactory epithelium
Optic (CN II)			
Sensory	Vision	Constanzo Varolio- (1543 - 1575)	Retina
Oculomotor (CNIII)		Gustav Fritsch- 1878	Brain stem
Motor	Eyeball movement		
Parasympathic	Pupil construction		
Trochlear (CN VI)			
Motor	Eyeball movement	Vesalius – (1514 -1564)	Brain stem
Trigeminal (CN V)		Winslow- 1732	Brain stem
Sensory	General sensation of face, scalp, nasal and oral cavity		
Motor	Chewing		
Abducens (CN VI)			
Motor	Eyeball movement	Sommerring-1778	Brain stem
Facial (CN VII)		Sommerring-1778	Brain stem
Sensory	Taste		
Motor	Facial expression		
Parasympathic	Secretion of tears and saliva		
Vestibulocochlear (CN VIII)			
Sensory	Hearing and balance	Galen- (129 - 216 AD)	Brain stem
Glossopharyngeal (CN IX)		Haller-1753	Brain stem
Sensory	Taste and sensation back of tongue		
Motor	Swallowing and speech		
Parasympathic	Secretion of saliva		
Vagus (CN X)		Bartholin-1611	Brain stem
Sensory	Taste and sensation epiglottis		
Motor	Swallowing and speech		
Parasympathic	Muscle construction of abdominal organs and secrete digestive fluids		
Accessory (CN XI)			
Motor	Head and shoulder movement	Willis- (1621 - 1675)	Brain stem-Spinal cord
Hypoglossal (CN XII)			
Motor	Head and shoulder movement	Winslow-1732	Brain stem
CN XIII/ CN0			
Unknown	Unknown	Fritsch	Olfactory tract

Abbreviation: CN, cranial nerve.

proposed that there are nine pairs of cranial nerves, correlating with the number of foramina at the base of the skull from which they emerge. In his "Book of Law", he detailed the vagus nerve and its extensive connections to the heart, lungs, respiratory tract, digestive system, and even the ears. Seyyed Isma'il Jurjani (1042 - 1137 AD), a prominent figure in Islamic and Iranian traditional medicine, wrote extensively about cranial nerves in his work "Zakhireh Khwarazm Shahi", which stands alongside Abu Ali Sina's "Canon of Medicine" (6).

In 1664, Sir Thomas Willis (1621 - 1675), known as the "founder of clinical neuroscience", listed and illustrated nine cranial nerve pairs, identifying the olfactory nerves as the first pair. He also counted the trochlear, trigeminal, and abducens nerves individually, numbering them IV to VI in their current order. Caspar Bartholin the Elder (1585 - 1629), a Danish physician and anatomist, was one of the first to accurately number the olfactory and trochlear nerves before Willis (7). In 1632, von Sömmerring (1755 - 1830), a German physician and anatomist, described the organization of cranial nerves in his doctoral dissertation, which remains relevant today. The discourse on naming and numbering cranial nerves continued, with all anatomists acknowledging

the existence of twelve pairs, but debates arose about an additional nerve (8).

The concept of a "zero" or "thirteenth" nerve, known as the terminal nerve (NT), was first discussed by Fritsch. Gustav Theodor Fritsch (1838 - 1927) identified it in sharks. This discovery complicated the counting of cranial nerves. The CN0 was later described in detail by Pinkus in 1895, and subsequently by Locy, who depicted it in selachians and referred to it as NT (9, 10). In 1987, Demsky and Schwanzel-Fukuda designated this nerve as cranial nerve zero, noting its rostral connections to all other cranial nerves. Due to the absence of a zero in Greek numeral systems, it was also called "Nulla nerve" (11). In 1914, Brookover and Johnston formally labeled it as the "0" pair of cranial nerves, and in 2007, CN0 was identified as a common finding in adult humans (12, 13).

3. Gross Anatomy

The CN0 nerve is situated anteriorly to the other cranial nerves on both sides, appearing as a microscopic network of unmyelinated peripheral nerves within the subarachnoid space. It covers the rectus gyrus and is located near the cribriform plate, extending posteriorly towards the olfactory trigone and the internal olfactory gyrus, linking the most anterior forebrain derivatives to nasal and olfactory structures (14).

4. Development

The origins of CN0 remain largely enigmatic during embryonic development. Establishing the terminal nerve and its fibers is challenging due to their migratory growth patterns and the differentiation of tissues forming the embryonic olfactory placode (15). Some researchers propose that CN0 develops from the olfactory placode, while others suggest it arises from the neural crest, given its location at the interface of migrating cranial neural crest cells. This nerve may result from the fusion of various migrating cells, with the neural crest potentially contributing to a subset of gonadotropin-releasing hormone (GnRH)-secreting neurons (16).

5. Physiological Function

Research indicates that CN0 fibers differ from those of the olfactory and vomeronasal nerves, suggesting a possible role in pheromone perception or other olfactory functions. Its fibers travel near the cribriform plate to regions like the olfactory trigone and medial olfactory gyrus (17). Although its exact function remains debated, it is believed to influence autonomic functions and may play a role in mate selection and reproductive behavior (18). The CN0, also known as the terminal nerve, is significant in regulating reproductive hormones, particularly GnRH, which stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the adenohypophysis, regulating sex steroid production and secretion. This nerve is located on the ventral surface of the human brain and is closely associated with the olfactory nerve (CNI). It is hypothesized to have neuromodulatory effects on GnRH and the blood vessels and glands of the nasal mucosa, indicating a role in developing the hypothalamic-pituitary-gonadal (HPG) axis and influencing human sexual behavior (15, 19-22).

The GnRH component of CN0 may enhance the detectability of pheromones through its neuromodulatory effects on the olfactory epithelium. Its anatomical connections to various neuroanatomical structures, including the hypothalamus and nasal mucosa, provide pathways to the limbic system. Within the hypothalamus, particularly in the preoptic and infundibular nuclei, the "kisspeptin neuronal network" (KP) regulates puberty and reproductive functions. Kisspeptin neuronal network neurons primarily induce GnRH secretion from the hypothalamus, which in turn influences LH and FSH secretion and the synthesis and release of sex steroids from the gonads. The potential neuromodulatory function of CN0 in sexual behavior through GnRH is intriguing, as it projects to the nasal mucosa, amygdala, and hypothalamus (21). If these projections reach the preoptic and infundibular nuclei, they could represent an afferent component to the KP neurons regulating GnRH secretion and, consequently, human sexual behavior and function. This hypothesis warrants further scientific investigation (23-26).

6. Clinical Implications

The clinical significance of CN0 lies in its potential association with Kallmann syndrome (KS), an inherited disorder characterized by hypogonadotropic hypogonadism (HH) and hyposmia or anosmia in both sexes. Research suggests that disruptions in the normal migration of basal forebrain GnRH cells during embryonic development may lead to the hypogonadism observed in KS (27). Additionally, mutations in the kisspeptin 1 gene (KISS1), which can result in hypogonadotropic hypogonadism or precocious puberty, are noteworthy (28). This gene is expressed in the central nervous system (CNS), particularly in the hypothalamus, but also in regions such as the amygdala, caudate, cingulate, globus pallidus, hippocampus, medial and superior frontal gyri, nucleus accumbens, parahippocampal gyrus, substantia nigra, putamen,

and thalamus (29). Furthermore, kisspeptin plays a crucial role in fear, anxiety, reward pathways, negative emotions, and olfaction, potentially influencing syndromes related to CNS structures and mood (30).

7. Conclusions

The CN0 is a recognized anatomical and functional nerve structure, yet it is often overlooked in medical literature and educational resources, which typically reference only twelve cranial nerves, as seen in texts like Gray's Anatomy. Recent studies affirm that CN0 is a well-established neural structure with significant implications for the development of the GnRH system and human reproductive neurophysiology. Additionally, macroscopic dissections of human cadavers (including adult and fetal specimens) have confirmed the consistent presence of the terminal nerve. The nerve is located as a small, delicate bundle of unmyelinated fibers just anterior to the olfactory nerve (CN I) and is often not recognized in routine dissection due to its small size and delicate texture. Therefore, it may be necessary to reconsider the numbering of cranial nerves to include this nerve. Cadaver examinations should be conducted to validate the presence of CN0.

Footnotes

Authors' Contribution: Study concept and design and developed the original idea: S. B. J.; Interpretation of data: F. B.; Drafting of the manuscript: S. B. J.; Critical revision of the manuscript for important intellectual content: Sh. T. and S. B. J.

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