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Review Article

Deciphering the Nucleus Ambiguus: Anatomy, Functions and Clinical Implications Explored

Gabriel Godson Akunna*, Abah ED

Department of Anatomy, Benue State University, Makurdi, Nigeria

ABSTRACT

The Nucleus Ambiguus, a lesser-known brainstem nucleus, plays a significant role in various physiological processes that are essential for human functioning. This review offers a comprehensive exploration of the Nucleus Ambiguus, encompassing its anatomy, functions, clinical implications, and research methodologies. The introductory section provides a succinct overview of the Nucleus Ambiguus, emphasizing the importance of understanding its functions in the broader context of neural regulation.

Moving forward, the anatomy section delves into the precise location of the Nucleus Ambiguus within the brainstem, elucidating its structural components and highlighting its connections to the vagus and glossopharyngeal nerves. Subsequently, the review investigates the motor functions of the Nucleus Ambiguus, including its role in controlling motor neurons, its innervation of muscles and organs, and its contribution to speech and swallowing. Intriguingly, the Nucleus Ambiguus does not function in isolation, and the subsequent section explores its interactions with other brainstem nuclei. This includes an examination of its connections with adjacent nuclei and its role in coordinating various physiological processes, revealing its integral role within the neural network. The autonomic functions section addresses the Nucleus Ambiguus' influence on heart rate, its contribution to respiratory control, and its interactions with the parasympathetic nervous system, demonstrating its involvement in regulating fundamental autonomic responses.

The clinical implications section underscores the importance of understanding Nucleus Ambiguus-related disorders and the diagnostic and therapeutic relevance of such knowledge. Furthermore, it offers insights into ongoing research and future prospects in Nucleus Ambiguus studies, highlighting the continually evolving nature of this field. The review culminates in a section dedicated to research methodologies, which outlines various techniques and tools employed in Nucleus Ambiguus research. Additionally, it highlights the dynamic and evolving nature of Nucleus Ambiguus studies by highlighting important studies in this field and providing information about current research areas.

In conclusion, this review provides a holistic perspective on the Nucleus Ambiguus, underlining its functions, clinical relevance, and the significance of understanding this brainstem nucleus within the broader context of neuroscience and medical research.

Keywords: Neuroscience; Anatomy; Nucleus ambiguus; Brainstem; Motor; Autonomic; Speech; Swallowing

Correspondence to: Gabriel Godson Akunna, Department of Anatomy, Benue State University, Makurdi, Nigeria, E-mail: ggakunna@gmail.com

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INTRODUCTION

Nestled within the intricate network of the brainstem lies the enigmatic Nucleus Ambiguus a region of the central nervous system that has long piqued the curiosity of researchers [1]. This unassuming nucleus serves as the central hub for efferent fibers responsible for the glossopharyngeal Cranial Nerve (CN IX) and vagus (CN X) nerves, linking it to essential physiological functions [2].

The name 'ambiguus' aptly reflects the challenge of pinpointing its precise location and acknowledging variations across different species. It adds to the medulla oblongata's air of invisibility by living elegantly inside its reticular formation. [3].

The Nucleus Ambiguus extends its influence to the somatic muscles of the pharynx, larynx, and soft palate, playing a pivotal role in the orchestration of these vital anatomical structures. Moreover, this unassuming nucleus assumes a parasympathetic role, contributing to cardiac inhibition through the vagus nerve (CN X) [4].

The intrigue deepens as unilateral lesions of the Nucleus Ambiguus reveal their impact, potentially leading to distressing symptoms such as dysphagia and project, often classic indicators of lateral medullary syndrome (Wallenberg syndrome) [5-7]. This unexplored territory within the brainstem continues to provide a rich landscape for researchers and holds the potential to show more of its information in the kingdom of neuroscience.

Usually abbreviated as NA, the nucleus ambiguus is a vital structure located within the medulla oblongata, which is a part of the brainstem [8]. This complex region plays a vital role in regulating various physiological and motor functions within the human body [9]. Named for its ambiguous or variable appearance under microscopic examination, the nucleus ambiguus contains motor neurons that primarily innervate the muscles of the throat and larynx, and it's responsible for controlling a variety of vital functions related to speech, swallowing, and cardiovascular regulation [10].

Understanding the functions of the nucleus ambiguus is of paramount importance due to its integral role in maintaining the fundamental aspects of human life. The proper functioning of this brainstem nucleus is vital for activities as basic as swallowing and speaking, as well as for regulating cardiac and respiratory activities [11]. Dysfunction in the nucleus ambiguus can lead to serious health issues, including dysphagia, speech disorders, and even life-threatening conditions such as arrhythmias and cardiac arrest [12]. A comprehensive understanding of this structure is therefore imperative for both clinicians and researchers in the fields of neurology, cardiology, and speech pathology.

The primary objective of this review article is to provide a comprehensive exploration of the anatomy, functions, and clinical implications of the nucleus ambiguus. By synthesizing existing knowledge and research on this intriguing brainstem nucleus, we aim to process on its intricate role in the regulation of vital bodily functions. This review will not only serve as a valuable resource for neuroscientists, clinicians, and researchers but will also contribute to the development of innovative diagnostic and therapeutic strategies for conditions associated with nucleus ambiguus dysfunction. We will delve into the intricate neuroanatomy, the neural pathways, and the various clinical conditions that implicate the nucleus ambiguus, offering a holistic perspective on this enigmatic structure and its significance in the field of medicine and neuroscience.

In this review, it started on an expedition to discover it works, beginning with its anatomical location and progressing to its manifold functions and clinical relevance.

LITERATURE REVIEW

Anatomy of the nucleus ambiguus

Location: The Nucleus Ambiguus, a cluster of motor neurons ensconced within the intricate landscape of the medulla oblongata, a crucial component of the brainstem, holds a place of significance [13]. Precisely, this nucleus finds its abode in the lateral expanse of the medulla oblongata, residing in proximity to the dorsal motor nucleus of the vagus nerve (DMX) and the solitary nucleus [14].

At its core, the Nucleus Ambiguus serves as the dwelling place of motor nerve cell bodies, orchestrating the symphony of the ipsilateral muscles of the soft palate, pharynx, larynx, and upper esophagus. Its domain is the land of actions fundamental to the swallowing and speaking [15].

Located within the reticular formation of the medulla oblongata, the most inferior segment of the brainstem, the Nucleus Ambiguus finds its home in the lateral reaches of the rostral medulla, a domain just posterior to the humble inferior olive [16]. Within this intricate anatomical landscape, the Nucleus Ambiguus fulfills its role with remarkable precision, contributing to the intricate web of neural connections that significant functions.

Structural components: The nucleus Ambiguus is primarily composed of motor neurons (Figure 1). These motor neurons are responsible for controlling various muscles in the head and neck region [17].

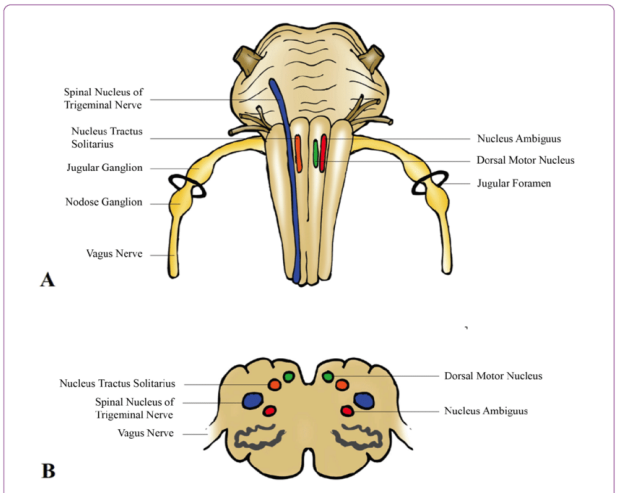

Figure 1: Schematic diagram showing the position of the nucleus Ambiguus. **Note:** A) Depicted here is an anterior perspective of the medulla oblongata and vagal nuclei; B) Depicted here is a superior perspective of a transverse section through the medulla oblongata.

The Nucleus Ambiguus is a noteworthy structure to explore, and it's essential to clarify that it doesn't manifest as a singular, isolated entity, rather, it comprises an intricate network of neurons dispersed throughout the medulla oblongata [18].

This involved nexus of neurons plays a pivotal role in motor functions associated with vital activities such as swallowing and speech. It acts as the wellspring for the efferent motor fibers of the vagus nerve (CN X), which in turn innervate an array of crucial muscles, including those of the soft palate, larynx, pharynx, as well as the stylopharyngeus and pharyngeal constrictor muscles connected to the glossopharyngeal nerve (CN IX) [19].

The orchestration of these muscles by the Nucleus Ambiguus initiates the intricate mechanism of swallowing and phonation, playing a vital role in these fundamental actions [20].

Moreover, the influence of the Nucleus Ambiguus extends into the domain of parasympathetic cardiac regulation. This is intrinsically connected to the vagus nerve, a multifaceted neural entity with motor, sensory, and autonomic functions that span multiple organ systems. Within the brainstem, three primary nuclei-namely, the dorsal motor nucleus, the nucleus ambiguus, and the nucleus solitaries-play a part in this intricate symphony [21].

The nucleus solitarius serves as the receiver of baroreceptor sensory input, while the nucleus ambiguus (and, to a lesser extent, the dorsal motor nucleus) participates in the orchestration of parasympathetic output [22].

Here's where the intricate dance of physiological responses comes into play: When the heart rate rises, baroreceptor afferents are set in motion and culminate in the Nucleus Tractus Solitarius (NTS) within the medulla [23]. These signals find their route through the afferent branches of CN IX and CN X.

The cells within the NTS then dispatch excitatory signals to the nucleus ambiguus, which, in turn, sends inhibitory signals to the sinoatrial node *via* CN X, effectively curtailing the heart rate. This tonic inhibition of heart rate serves a vital cardio protective function.

Conversely, when the heart rate requires acceleration, this parasympathetic response is bypassed, allowing the heart rate to ascend as needed [21].

Connection to the vagus and glossopharyngeal nerves: The nucleus Ambiguus is closely associated with the control of muscles involved in swallowing, phonation, and speech. It plays a pivotal role in the motor control of the vagus nerve (cranial nerve X) and the glossopharyngeal nerve (cranial nerve IX). These cranial nerves are essential for a variety of functions, including swallowing, speaking, and the regulation of cardiac and gastrointestinal activities [20].

Motor functions of the nucleus ambiguous

The motor neurons of the nucleus ambiguus provide efferent motor innervation to various muscles and organs within the pharynx and larynx [24]. These include the intrinsic muscles of the larynx, such as the vocal cords and the cricothyroid muscle, as well as extrinsic muscles like the stylopharyngeus and the muscles of the soft palate [25]. The nucleus ambiguus also plays a role in controlling the muscles involved in coughing and the coordination of respiratory and phonatory functions [26].

The nucleus ambiguus is essential for both speech and swallowing. It contributes to the fine motor control required for the articulation of speech sounds by innervating the muscles responsible for vocal fold tension and pitch modulation [24]. In swallowing, it coordinates the complex sequence of muscle contractions needed to move food or liquids from the mouth to the stomach while preventing aspiration into the airway [27].

Impairment of the nucleus Ambiguus can manifest as profound challenges, including dysphagia (swallowing difficulties) and dysphonia (voice disorders) [28]. This underscores the critical role played by the nucleus ambiguus in motor functions associated with swallowing and speech.

The nucleus ambiguus is the wellspring of efferent motor fibers of the vagus nerve (CN X), responsible for innervating the muscles of the soft palate, larynx, pharynx, the stylopharyngeus muscles, and pharyngeal constrictor muscles connected to the glossopharyngeal nerve (CN IX). The coordinated action of these muscles is pivotal in initiating the intricate mechanisms of swallowing and phonation.

Furthermore, the nucleus ambiguus plays a significant role in parasympathetic cardiac regulation. The vagus nerve, with its extensive array of motor, sensory, and autonomic functions spanning various organ systems, is intimately linked with three primary brainstem nuclei: The dorsal motor nucleus, nucleus ambiguus, and nucleus solitaries [29]. The nucleus solitarius is the recipient of baroreceptor sensory input, while the nucleus ambiguus (and, to a lesser extent, the dorsal motor nucleus) is intricately involved in the orchestration of parasympathetic output.

An elaborate interplay of signals is orchestrated in the following **manner:** When the heart rate surges, baroreceptor afferents are stirred into action and converge in the Nucleus Tractus Solitarius (NTS) within the medulla. These signals traverse *via* the afferent nerve branches of CN IX and CN X. NTS cells transmit excitatory signals to the nucleus ambiguus, which, in turn, dispatches inhibitory signals to the sinoatrial node *via* CN X to slow the heart rate. This tonic inhibition of the heart rate serves a vital cardio protective function. Conversely, when the heart rate dips too low, the parasympathetic response remains dormant, permitting the heart rate to ascend appropriately [30].

The fine-tuning of this parasympathetic reflex involves various peptides, with bradykinin taking the center stage. Bradykinin, an endogenous peptide endowed with cardio protective and vasodilatory properties, acts on receptors within the nucleus ambiguus, prompting bradycardia. Bradykinin stimulates the B1 and B2 receptors in the nucleus ambiguus, resulting in an increase in cytosolic calcium (Ca^{2+}) release and neuronal

depolarization. The intricate feedback loop of cardiac vagal tone through the nucleus ambiguus also implicates multiple other peptides and receptors, including the G-protein coupled estrogen receptor within the nucleus ambiguus. Activation of this receptor stimulates bradycardia, illustrating the cardio protective role of estrogen in heart function.

The nucleus ambiguus emerges as a vital orchestrator of cardiac activity and protective reflexes.

Interaction with other brainstem nuclei

The Nucleus Ambiguus (NA) is a conglomerate of neurons intricately located within the medulla oblongata, particularly ensconced in the lateral reticular formation (Figure 1) [23-25]. It maintains a profound association with motor control, autonomic functions, and sensory integration, making it a critical nexus in the brainstem. It establishes a web of vital connections with neighboring brainstem nuclei that serve as essential nodes in the control of motor functions and sensory processing. Here are some of the key connections:

Dorsal motor nucleus of vagus (DMX): The NA and DMX are closely related, and they collectively control the parasympathetic innervation of the heart, lungs, and gastrointestinal tract. The DMX provides motor innervation to the visceral organs, while the NA influences motor aspects of the pharyngeal and laryngeal muscles.

Nucleus solitarius: The Nucleus solitarius receives visceral sensory information from various organs, including the heart, lungs, and gastrointestinal tract. It relays this sensory input to the NA, which then coordinates the motor responses required for functions like swallowing, respiration, and speech.

Hypoglossal nucleus (XII): The Hypoglossal nucleus controls the muscles of the tongue. It collaborates with the NA in processes like swallowing and articulation of speech sounds, where precise coordination between tongue movements and the muscles controlled by the NA is essential.

Dorsal nucleus of the vagus (DNX): The Dorsal Nucleus of the Vagus is involved in various autonomic functions, including visceral sensory processing and regulation of parasympathetic output. The NA interacts with the DNX to coordinate autonomic responses, particularly during swallowing and cardiovascular regulation.

The Nucleus Ambiguus plays a pivotal role in coordinating various physiological processes, primarily related to motor control, autonomic regulation, and sensory integration. Some of its key functions include:

Swallowing: The NA is vital for the coordination of the intricate motor activities involved in swallowing. It ensures the synchronized contraction of pharyngeal and laryngeal muscles, allowing the safe passage of food and liquids into the esophagus while preventing aspiration into the airway.

Speech: The NA is a critical component of the brainstem's motor pathway for speech. It controls the muscles involved in vocalization, phonation, and articulation, enabling the production of clear and intelligible speech sounds [23].

Autonomic control: The NA contributes to parasympathetic control of the heart, lungs, and gastrointestinal organs. By influencing vagal efferent activity, it helps regulate heart rate, respiration, and digestive processes.

Sensory integration: The NA receives sensory input from the Nucleus Solitarius and integrates this information into motor responses. It plays a role in coordinating reflexive responses to visceral sensory input, such as reflex coughing or clearing the airway in response to irritation.

The Nucleus Ambiguus is a key brainstem nucleus with vital connections to adjacent nuclei, enabling it to coordinate a wide range of physiological processes [14]. Its functions encompass motor control, autonomic regulation, and sensory integration, making it an integral component of the brainstem's functional network. It's interactions with other brainstem nuclei are vital for understanding the functions and clinical implications of the Nucleus Ambiguus (NA).

Autonomic functions of the nucleus ambiguous

Influence on heart rate: The nucleus Ambiguus (NA) plays a key role in the regulation of heart rate. It is part of the parasympathetic nervous system, specifically the cranial component of the vagus nerve (cranial nerve X). Stimulation of the NA results in parasympathetic activity, which leads to a decrease in heart rate. This effect is primarily achieved through the release of acetylcholine at the cardiac sinoatrial (SA) node, which slows down the electrical impulses controlling heart rate [21].

Role in respiratory control: The nucleus Ambiguus is involved in the control of respiration, particularly in the generation of rhythmic breathing patterns. Neurons in the NA contribute to the efferent control of respiratory muscles, including the muscles of the larynx and pharynx. It is essential for coordinating the motor activity of these muscles during both voluntary and involuntary respiratory movements [31].

Interaction with the parasympathetic nervous system: The nucleus Ambiguus plays a vital role in the parasympathetic control of various visceral organs, including the heart, lungs, and digestive system. It receives input from higher brain centers, such as the central pattern generator for respiration, and integrates this information to modulate parasympathetic outflow to these organs. The parasympathetic activity originating from the NA is involved in promoting rest and digestion (the "rest and digest" response) by slowing heart rate, increasing digestive secretions, and promoting bronchoconstriction in the lungs.

Clinical implications

Nucleus ambiguus-related disorders: The nucleus ambiguus serves as a pivotal hub, governing both motor functions involving the muscles of the soft palate, throat, and tongue, and autonomic processes, including the gag reflex and cardiac parasympathetic activity. Any lesions or ischemic events affecting

the lateral medulla can profoundly compromise the functionality of the nucleus ambiguus.

The intricate interplay of functions and consequences becomes particularly evident when considering lateral medullary syndrome, also known as Wallenberg syndrome or PICA syndrome. This neurological constellation arises from ischemia in the lateral region of the medulla. The ischemic events often stem from blockages in the vertebral artery or its branch, the Posterior Inferior Cerebellar Artery (PICA), which primarily supplies the lateral medullary area. Clinical manifestations commonly encompass dizziness, loss of balance, difficulty swallowing, and slurred speech.

Unilateral lesions impacting the nucleus ambiguus result in an ipsilateral paralysis of the soft palate, larynx, and pharynx. This, in turn, leads to symptoms such as dysphagia, dysphonia, and dysarthria, primarily attributed to the loss of nucleus ambiguus function. Although hoarseness may occur, speech remains generally intelligible. Dysphagia, while typically not severe, may necessitate temporary feeding tube placement. During the testing of the gag reflex, the palatal muscles fail to contract, and the uvula deviates away from the affected side.

Beyond motor deficits, lesions affecting the nucleus ambiguus can also disrupt sympathetic and parasympathetic cardiac reflexes, potentially leading to orthostatic hypotension. While lateral medullary syndrome primarily arises from strokes, neoplastic conditions, such as medullary gliomas, can also induce similar symptoms, albeit rarely. However, the acute onset of symptoms typifies lateral medullary syndrome, distinguishing it from the more gradual onset and less favorable prognosis seen in neoplastic conditions.

The long-term prognosis for lateral medullary syndrome patients hinges on the size and location of the infarcted area. Notably, the extent of dysphagia post-lateral medullary stroke is correlated with the location and magnitude of damage within the lateral medulla. Damage to the nucleus ambiguus, in particular, appears to disrupt the swallowing process among these patients. The sequence of swallowing mechanics is observed to be altered in a cohort of patients with this syndrome. Additionally, the syndrome is associated with long-term dizziness and ipsilateral nystagmus as lasting sequelae.

Bilateral lesions of the nucleus ambiguus induce complete laryngeal paralysis, potentially posing a life-threatening risk due to the inability to move vocal cords during inspiration. Bilateral lesions, however, are rare and predominantly observed in severe cases of Amyotrophic Lateral Sclerosis (ALS).

Sandifer syndrome, a less widely recognized disorder, particularly affects infants and implicates the nucleus ambiguus within its reflex arc. This syndrome results in reflex torticollis in infants diagnosed with gastroesophageal regurgitation syndrome or a hiatal hernia. This reflex arc operates through afferent pathways traveling to the nucleus solitarius, subsequently reaching the nucleus ambiguus and the dorsal vagal nucleus. From these nuclei, visceral efferent nerves engage in anastomosis to reach the accessory nerve, ultimately contracting the trapezius and sternocleidomastoid muscles. This reflexive head positioning, leading to torticollis, is believed to alleviate acid regurgitation [25].

Cardiac vagal neurons, including the nucleus ambiguus and dorsal motor neuron, play a pivotal role in regulating cardiac parasympathetic tone. However, in conditions like myocardial infarction, cardiac vagal activity diminishes. This can subject the heart to undue stress, as reinstating parasympathetic function can reduce cardiac workload and mitigate the risks of ischemia and arrhythmias. Furthermore, diabetes can impair baroreceptor sensitivity, potentially leading to degeneration of the nucleus ambiguus in animal models [27]. This impairment of reflex bradycardia may be observed in diabetic patients.

Diagnostic and therapeutic relevance

Diagnostic imaging techniques, such as Magnetic Resonance Imaging (MRI) and functional MRI (fMRI), are some key diagnostic methodologies used to assess Nucleus Ambiguus function and integrity. Nucleus Ambiguus-related disorders are diagnosed through clinical examination and techniques such as Electromyography (EMG), and other relevant diagnostic methods. Therapeutic approaches for Nucleus Ambiguus-related disorders include but not limited to medical treatment, surgical interventions, and rehabilitation [31].

Research methodologies on the nucleus ambiguus

The Nucleus Ambiguus (NA) is a complex brainstem structure involved in various physiological functions, especially related to the autonomic nervous system and motor control. Researchers have employed a variety of techniques and tools to study the NA, including:

Histology: Traditional histological techniques involving brain tissue staining and microscopy are used to visualize the NA's anatomical structure.

Immunohistochemistry: Researchers use specific antibodies to target proteins or markers within the NA to identify its boundaries and cell types.

Tracing techniques: Various tracers, such as dyes and retrograde tracers are employed to map the connections of the NA with other brain regions.

Functional neuroimaging: Techniques like fMRI (functional Magnetic Resonance Imaging) and PET (Positron Emission Tomography) can provide insights into the NA's activation during specific tasks.

Electrophysiology: Single-unit recordings and extracellular field potentials can be used to study the electrical activity of neurons in the NA.

Lesion studies: Lesioning the NA in animal models or studying patients with damage to the NA can reveal its functional significance.

Key studies in nucleus ambiguus research

Over the years, several key studies have contributed to our understanding of the Nucleus Ambiguus. Some noteworthy ones are enlisted below:

Central regulation of autonomic functions, Oxford university press: This book provides an extensive overview of the NA's role in autonomic control.

Neurobiological insights into cardiovascular and respiratory regulation: Unraveling the functional organization of the parasympathetic nervous system *via* the nucleus Ambiguus. Published in the annals of the New York academy of sciences, this paper extensively explores the pivotal role played by the Nucleus Ambiguus (NA) in regulating cardiovascular and respiratory processes.

Mapping anatomical connections of the nucleus Ambiguus: Unraveling bulbar fiber pathways to motor nuclei in cats. In this comprehensive study conducted on feline brain structures, the authors employ autoradiographic tracing to shed light on the intricate anatomical connections involving the Nucleus Ambiguus (NA).

Current areas of ongoing research

Research on the Nucleus Ambiguus continues to evolve. Current areas of ongoing research include:

Functional connectivity: Investigating the NA's connectivity with other brain regions using advanced neuroimaging techniques.

Neurodevelopment and neuroplasticity: Exploring how the NA develops in early life and its capacity for plasticity in response to injury or disease.

Clinical implications: Examining the role of the NA in various clinical conditions, such as dysphagia, autonomic dysfunction, and neurological disorders.

Pharmacological interventions: Developing pharmacological interventions that target the NA for the treatment of specific medical conditions.

Neural control of swallowing and speech: Investigating the role of the NA in neural control of swallowing and speech, with potential implications for conditions like dysphagia and speech disorders.

CONCLUSION

The Nucleus Ambiguus plays a central role in regulating the efferent motor pathways of the autonomic nervous system, orchestrating parasympathetic outflow to the heart, lungs, and digestive tract. It is also intricately involved in the complex neural circuitry underlying vocalization and the modulation of speech and swallowing. This nucleus is a critical player in mediating these functions, and a thorough understanding of its organization and connectivity is imperative for elucidating the neural basis of many neurological disorders, particularly those affecting voice and swallowing.

The clinical implications of the nucleus ambiguus are broad and varied. Dysfunctions of this nucleus can result in a range of disorders, including dysphagia, vocal cord paralysis, and cardiac arrhythmias. Therefore, it is of paramount clinical importance to understand its structure and function thoroughly. Future research should focus on advancing our knowledge of the cellular and molecular mechanisms underpinning its functions and developing innovative therapeutic strategies for neurological disorders associated with the nucleus ambiguus. Furthermore, exploring its role in more diverse clinical contexts, such as neurodegenerative diseases or neuropsychiatric disorders, could uncover novel avenues for diagnosis and treatment.

In conclusion, the nucleus Ambiguus stands as a basis of neuroanatomy, additionally difference between autonomic control and speech-related functions. Its anatomy and functions are pivotal for comprehending normal physiological processes and addressing a wide spectrum of clinical challenges. By investigating the nucleus ambiguus, to the development of novel treatments, diagnostics, and interventions, not only for disorders directly linked to this nucleus but also for various conditions where autonomic dysfunction or speech deficits are prominent features.

Throughout this review, have the multifaceted functions of the nucleus ambiguus and underscore its paramount importance in both physiological and pathological contexts.

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