

TOPICAL REVIEW

The autonomic nervous system: Time for a conceptual reframing?

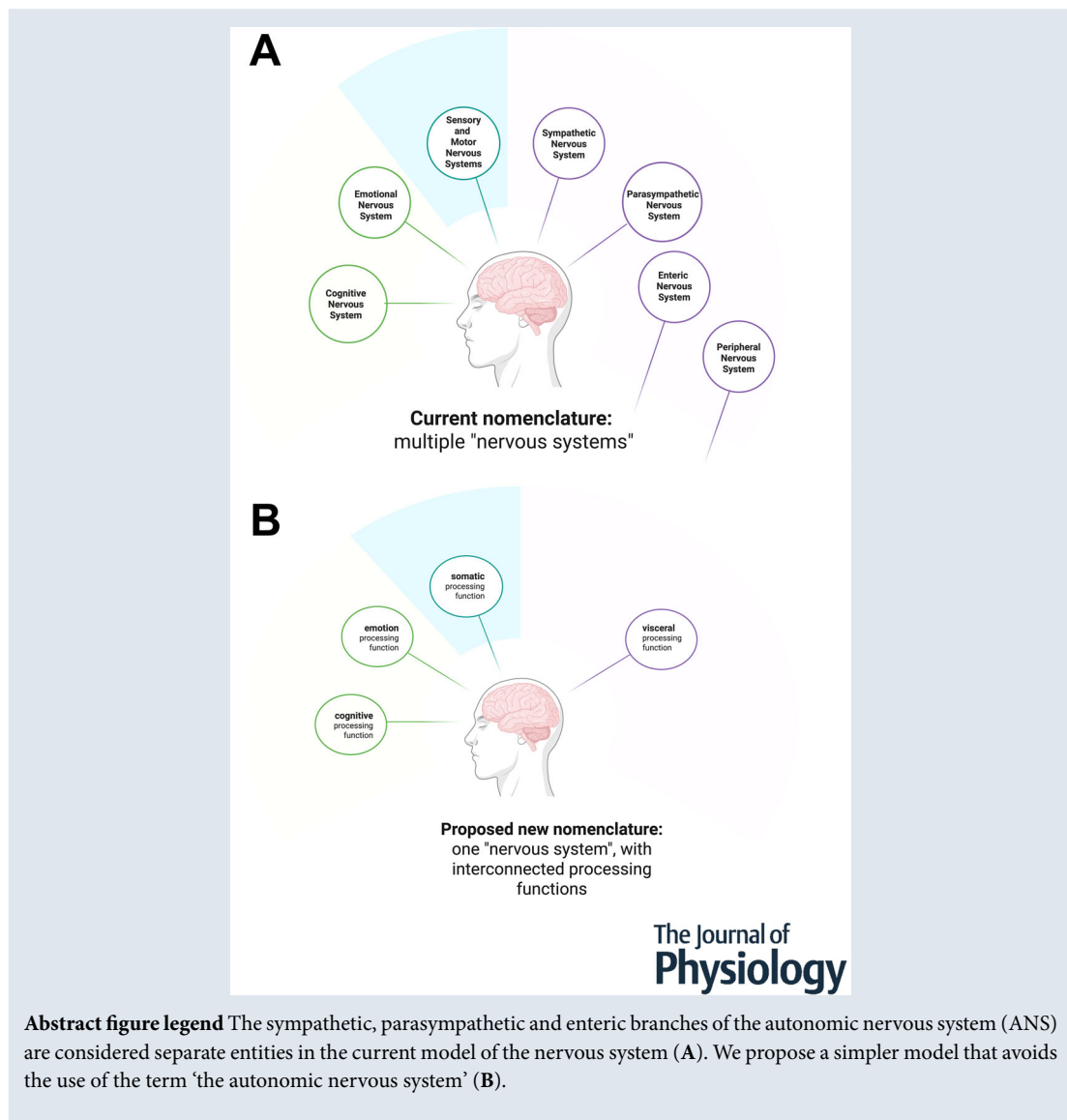
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Handling Editors: Laura Bennet & Beth Habecker

The peer review history is available in the Supporting Information section of this article (<https://doi.org/10.1113/JP288973#support-information-section>).



Abstract After having reviewed the history of the autonomic nervous system (ANS), and how Langley's concept of the ANS was born, we suggest that the terms 'cranial visceral' and 'spinal visceral' nerves are more appropriate. We discuss the limitations of the terms 'sympathetic' and 'parasympathetic' nerves and functions and suggest a way forward that avoids these terms altogether. We propose that the term 'autonomic' should not refer to a separate nervous system, because somatic components of the nervous system can also operate automatically, i.e. in a manner that is not under voluntary control.

(Received 30 March 2025; accepted after revision 29 August 2025; first published online 17 September 2025)

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Introduction

Is the concept of the autonomic nervous system (ANS), proposed 127 years ago, still valid? Scientific concepts are not experimentally obtained facts but forms of language representation that make assertions about structural and relational properties in nature. Like any concept, the concept of the ANS contains true, false and logical probability statements (Popper 1979). It has survived change, partly due to being repeated by scientists and clinicians alike and partly due to limited means of testability; for a concept to be scientifically validated, it has to be first formulated as a testable hypothesis, before being rejected or accepted and, ultimately, with enough evidence to support the hypothesis, accepted as a theory. With a few exceptions (Clarke & Jacyna 1987) previous attempts at understanding the emergence of the ANS concept were historiographies: they presented the emergence of the ANS concept as necessary, driven by a sequence of ideas and (not scientifically validated) theories slated to replace outmoded ones (Ackerknecht 1974; Langley 1916; Sheehan 1936, 1941).

Although history serves as a virtual experimental laboratory in which the ANS concept was forged, it requires the examination of contemporaneous epistemological practices for completeness. Thus, a more in-depth analysis should include not only the scientific but also the academic, cultural, social and philosophical contexts (Chimisso 2016). Although multiple research materials suggested the attribution of various discoveries to specific names, we recognize that this is often flawed,

due to the incompleteness of our contextual research. Here we took conceptual statements by past scientists, not at current-day value, and we did not allow these statements to substitute for their inspiring experimental work. For the initial discussion we will use the currently accepted nomenclature of the ANS.

The phylogenetically oldest part of the brain – the brainstem – contains nuclei essential for life, such as the homeostatic control of blood pressure and respiration, functions that occur in the background in an involuntary fashion. Massive cerebral brain damage can preserve these functions, and physiologists have long known that basic cardiovascular and respiratory control depends only on the brainstem. Unlike the cardiovascular system, the respiratory system uses skeletal muscles as its effector organs and can be engaged volitionally, such as for vocalization or defecation. Moreover no one would argue that respiration – whether it be the cyclical expansion of the gills in fish or of the thorax in terrestrial animals – is part of the ANS, despite its rhythmic activity being generated automatically in the brainstem. We will return to respiration later, but suffice to say that we believe that this is an example by which the concept of the ANS fails.

Sympathology: the pre-scientific concept of sympathy in natural philosophy and medicine. The belief in the laws of *sympathy* – like produces like – or the likeness principle in nature is an anthropological phenomenon across cultures (Schliesser 2015). Sympathy serves as a useful placeholder while searching for proper explanations of causal relationships.

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In natural philosophy, sympathy has five characteristics:

- (1) It takes place within a unified space, like the living organism.
- (2) It explains apparent bidirectional (mutual) action at a distance.
- (3) It occurs between parts that are alike.
- (4) Its cause is invisible to the naked eye.
- (5) Its effects are instantaneous.

The Hippocratic model of everything in the body suffering together transformed sympathy into a technical notion applied to causality in the clinical medical tradition. Informed by extensive anatomical dissections of animals, Claudius Galenus (AD 129–200) introduced the concept of the cerebrospinal axis and the idea that all nerves are prolongations of the cerebral organ that controls the body (Siegel 1968). These hollow nerves transported ‘animal spirits’ to various organs to assure consent or sympathy of function in both health and disease.

Until the first half of the 16th century, the Latin term ‘*sympathia*’ was used. The earliest-attested appearance of the word ‘sympathy’ in English is in 1567 (Schliesser 2015). Through extensive anatomical dissections and brainstem lesional work, Thomas Willis (1621–1675) postulated that the brainstem was the seat of the involuntary, materialistic but oddly named ‘animal spirits’ (respiration, heartbeat) (Clarke & Jacyna 1987). Willis confirmed the findings of Charles Etienne (1504–1564) and Bartolomeo Eustachi (1524–1574): the vagus nerve was a separate entity from the ganglionated nerve structure. He named the ganglionated paravertebral chain ‘intercostal nerves’ and thought the ganglia originated in the spinal cord and were simply ‘spirit storehouses’. Subsequent proposed roles for the intriguing ganglionated chain were ‘muscular pumps’, ‘divider of nerve fibres’ and ‘selective filters’ (Clarke & Jacyna 1987).

Jacques-Bénigne Winslow (1669–1760) proclaimed their independence and called them ‘little brains’. In 1732 based on anatomical and histological data (the so-called anatomical physiological method) in conjunction with the contemporary inference of the term, Winslow proposed changing the nomenclature of intercostal to sympathetic nerves. This paradigmatic shift separated visceral ‘involuntary’ function from the brain and was the first deviation from Galen’s axial cerebrospinal model (Clarke & Jacyna 1987). The ganglionic functional independence was reinforced by two other concepts that emerged in the mid-1800s: the existence of a connection between the nerve cell and its fibres (the neuronal doctrine) and the elevation of the sensorimotor reflex arc from a physiological phenomenon to an organismic principle of nervous system function. By 1840 sympathetic ganglia were regarded as independent reflex centres alongside the

brain and spinal cord. The reflex became a replacement concept for sympathy and, like its predecessor, was utilized to explain abnormal functions in many ailments. Due to insufficient corroborative experimental work, the two remained synonymous until at least the 19th century.

Other historical terminology pertinent for our analysis is ‘visceral nerves’ by James Johnstone (1730–1802) in 1795 and the ‘vegetative’ (concerned with nutrition) nervous system in 1807 by Johann Christian Reil (1759–1813). The term ‘vegetative’ was reaffirmed by Bichat’s (1711–1802) extensive anatomo-pathological study of 600 corpses between 1801 and 1802 (Shoja et al., 2008). Defining diseases by their tissue lesions paved the way for better cause-and-effect correlations and resulted in the localization-based anatomo-clinical method (Long 1992). From a single event in time, death became a succession of events affecting the organism (Bichat 1809; Foucault 1994): animal life (volitional and motor activity, sensory function) is extinguished first, followed by organic or vegetative life (lung, heart and brain function). The terms ‘animal’ (*vie de la relation*) and ‘organic’ (*vie de la nutrition*) life were subsequently developed along the lines of *voluntary versus involuntary*, *somatic versus visceral* and *separate and autonomous* nervous systems.

Greater preoccupation with biology, physiology and neurophysiology started in France in the last decade of the 18th century and followed later in Germany and Great Britain (Clarke & Jacyna 1987). By the mid-to-late 19th century, we witnessed the emergence of the independent (no clinical experience) physiologist at large and the neurophysiologist as the nervous system took the dominant role in organismic function. These scientists paved the way for experimental determinism: deriving physiological function underlying life’s phenomena only from quantifiable and reproducible experimental data (Radder 2009). Their research methods included external examinations, anatomical dissections, experiments in living (and not anaesthetized!) animals (responses to mechanical, electrical and chemical stimuli) and pathological observations (quality microscopy was in its infancy).

The ideology and research of the first half of the 19th century proposed the concept of an *autonomous sympathetic nervous system* (SNS). Experimental data obtained in the second half of the 19th century attempted to reassign the brain and spinal cord as the main centres of visceral nervous functional control and raised questions regarding the independence of a separate visceral nervous system.

The British school of neurophysiology. It is inspiring to learn about the dedication to experimental science and exquisite mentorship of John Langley’s predecessors, a

line that Langley continued with his own students. On the first pass the protagonists were firstly educated as rigorous critical thinkers despite their varied backgrounds and talents. They shared a lifelong passion for mentoring young disciples to carry on the scientific work. In the second analysis they were all members of a university learning system that was based not only on formal collegiate education but also on structured, directed and informal interactions among its learners (Frank 1973). This social affiliation led to patterns of mutual scientific subject interests and problem-solving, utilizing specific research techniques and tools, and required a mutually adopted language. This language was vernacular English, which started in the early 18th century and expressed the state of that scientific community.

William Sharpey (1802–1880) was a general anatomy and physiology professor at University College London (UCL) from 1836. He was a skilled lecturer who instilled a love of physiology and a preoccupation with experimental investigations even without access to proper laboratories (Hawgood 2008). Thomas Henry Huxley (1825–1895) and Claude Bernard (1813–1878) were his mentors. One of his students was Michael Foster (1836–1907), who received a distinguished undergraduate degree in classics and later, as a medical student, gold medals in anatomy, physiology and chemistry (Anonymous, 1963). Sharpey's influence moulded the young Dr Foster into continuing experimental work, and he started by studying cardiac rhythmicity. In 1867 Sharpey recalled Foster from his medical practice (McDowall 1936) and appointed him as a teacher of practical physiology and curator of the Museum of Pathology at UCL.

Taking after a German model of medical education, Foster organized non-compulsory, practical classes to illustrate Sharpey's lectures. As a physician-scientist he proved to be a tireless educator who also worked with Huxley to expand natural science education in schools. In 1870 at age 34 Foster was appointed praelector in physiology at Trinity College, Cambridge (1963). He and Sharpey visited beforehand and took note of the work performed in contemporary German physiology laboratories. Even though Sharpey's course was optional, and at first, he had no laboratory instruments, this strategic position allowed him to expand and transform education in physiology, biology, comparative anatomy, histology and embryology at Cambridge. The few students who took his course were inducted into learning experimental protocols and encouraged to learn from experimental data and complete an independent research project. His courses attracted and inspired two of the main protagonists of our inquiry: Walter Gaskell and John Langley. As Gaskell later put it Foster was 'a veritable discoverer of men rather than of facts and he worked for rather than at physiology' (Langdon-Brown 1939). Foster's friendship and collaboration with Albert Dew-Smith (1848–1915)

is a good example. Dew-Smith later became one of the financiers of the Department of Physiology. Led by Horace Darwin (1851–1928), the Cambridge Scientific Instrument Company, founded in 1870, provided most of the laboratory equipment used in the Cambridge Physiology laboratory (Cattermole & Wolfe 1987). In addition, the *Journal of Physiology* was first published in Cambridge in 1878, 10 years after *Pflügers Archiv: European Journal of Physiology* was established, with Michael Foster as editor. He then handed over the reins to John Langley in 1893–1894, who owned the journal and remained its editor until his death in 1925, when the rights of the journal were bought by The Physiological Society from Langley's wife.

The involuntary nervous system. Walter Gaskell was a Wrangler at the University of Cambridge: an accolade applied to a student who gains first-class honours in the gruelling Mathematical Tripos competition, held over several days (Garrison 1914). Gaskell was 5 years senior to Langley. Apparently he attended a lecture by Foster and ended up changing his career (Langdon-Brown 1939). Foster sent the young Gaskell to Germany in 1874 to study under Carl Ludwig (1816–1895), professor of comparative anatomy and physiology at the University of Leipzig (Lombard 1916). The German school of comparative anatomy and embryology's influence on physiological studies became obvious in Gaskell's future work. He returned to Cambridge in 1875 and became preoccupied with precise mechanical recording methods for laboratory experiments. Gaskell obtained his MD degree in 1878 (Ellis 2014). Quantified measurements of blood vessel wall reactivity led Gaskell to conclude that neural input was only one aspect of vasomotor tone. His 1880 paper elucidated the dual innervation of the heart (Gaskell 1880). Starting in 1882 Gaskell took up the study of the sympathetic nerves in general (Ellis 2014). Elegant experiments established that the vertebrate heart rhythm did not originate in regional vago-sympathetic ganglia but in an intrinsic cardiac cellular property (Gaskell 1883). Akin to Ludwig's work on secretory nerves, Gaskell extended his organ-centred studies in vascular and cardiac physiology to research their neural inputs. The narrative of his experiments is a veritable exercise in logical research and conclusion (Wilson et al., 1970). He grouped visceral-inhibitory and vasoconstrictor fibres as sympathetic and visceral-motor and vasodilator fibres as vagal, extended this functional antagonism to other visceral organs and hypothesized the existence of individual neurotransmitters (Langdon-Brown 1939).

His 1916, posthumously published, book *The Involuntary Nervous System* contains his preferred nomenclature and offers a retrospective reflection of his contributions to the subject before and after Langley's introduction of the autonomic terminology (Gaskell

1916). In this monograph we find a list of his starting research questions, which lead to the description of the organization of visceral nerve fibres:

- (1) Is it true that invertebrates and insects have only an SNS instead of a central nervous system (CNS)?
- (2) If SNS and CNS are separate in vertebrates, is there a reciprocal communication between them?
- (3) Do these isolated nervous systems have separate origins?
- (4) Can we trace the white rami into the spinal cord?
- (5) What is the relation between the 'medullated' white fibres and the fine 'non-medullated' fibres?

Gaskell combined physiology, comparative anatomy, embryology and histology to discover how form and function influence each other. He started at the effector involuntary tissue level, described the complete segmental nerve, traced it into the spinal cord and included the cranial segments (Fritzsch et al., 2017). He viewed the voluntary and involuntary muscles as having two separate inputs from a unified but segregated CNS: voluntary and involuntary. He classified the involuntary muscles based on their embryologic origin and suggested this determines their response to either adrenaline or pilocarpine. He applied the sensory-motor reflex concept to the involuntary nerves and sought a similar organization within the spinal cord as the main reflex centre for both. He traced the course of various nerves using physiological action combined with anatomical and histological observations. He concluded that the size of the nerves was related to the nature of the tissue they innervate. Voluntary nerves have a larger diameter than visceral, involuntary nerves (Gaskell 1886). He noted that involuntary nerves exit the CNS in three bundles separated by limb plexuses: cranial-cervical, thoracolumbar and sacral.

Even though the concept of white and grey rami is traced back to Galen and Albrecht von Haller (1708–1777), who called them *rami communicantes* (Clarke & Jacyna 1987), Gaskell's work clarified their anatomical and functional roles. He established that the white rami containing 'medullated' (myelinated) sympathetic fibres represent a communication (he called them connecting fibres) system between the CNS and the SNS and can be found only in the thoracolumbar region. He classified them as a CNS structure that migrated into the periphery as opposed to its voluntary counterpart, which is contained within the spinal cord.

Through careful anatomical studies in various animals, he re-discovered (unaware of but acknowledged the contribution of Thomas Beck 1814–1877) (Clarke & Jacyna 1987) that the grey rami do not return to the spinal cord but are distributed to spinal nerves (they are peripheral nerves), thus contradicting Bichat's theory of the anatomical and functional independence of the SNS. By

1885 it was clear that the involuntary nerves' sensory and motor components were ganglionated. Gaskell pointed out the wider distribution of the sympathetic ganglia as opposed to the segmental distribution of the dorsal sensory ganglia. The terms 'afferent' and 'efferent' terms started to be used. This coincided with the introduction of the neurone theory and the concept of relay stations in the nervous system. As we shall see, these findings were confirmed and functionally renamed by Langley. Gaskell traced the cranial nerve's three-root organization (ventral, lateral and dorsal) and the spinal nerve's two-root (ventral and dorsal) layout back to embryologic segmentation. Here again the language terms used then and now are imprecise. Ganglia along both sides of the vertebral column were called vertebral or lateral (paravertebral in our time), and ganglia along the lateral aspect of the aorta were called collateral or prevertebral then and now. Gaskell incorporated embryological origins into the involuntary/voluntary concepts. He defined the term 'somatic' (Greek *somatikos* = of the body) for striated (skeletal) body muscles, in contrast to the non-striated (smooth) visceral or splanchnic (Greek *splanchnikos* = of the viscera) muscles (masticatory and respiratory). He called the white rami connecting the cord to the pre-vertebral ganglia and the cranial non-somatic output splanchnic nerves. Through comparative anatomical studies Gaskell concluded that, in higher vertebrates, there are three groups of motor cells that travel out of the cerebrospinal axis to form the vagus, sympathetic and pelvic nerve groups.

Therefore Gaskell's work denied the existence of a separate, independent SNS but supported the concept of separate sensory-motor nerve fibres: somatic or voluntary and visceral or involuntary. This perfect arrangement, at a time when little was known about cerebral localization or the existence of a central autonomic network (CAN), maintained the inescapable idea of an independent, albeit involuntary 'nervous system'.

The ANS

The experimental science origin. John Langley entered St John's College the year after Foster's arrival and proceeded to graduate with First Class in the Natural Sciences Tripos competition (Langdon-Brown 1939). John Langley became a physiology researcher in 1876 at the age of 24 (Fletcher 1926). At first Langley was Foster's demonstrator, organizing and conducting all laboratory classes. In time he succeeded Foster as professor and chairman of the Biology Department in 1903. The history of Langley's research is a veritable window into his mind and sheds light on how he came up with the ANS concept in 1898 at age 46. John Langley started employing chemical probes (pilocarpine, atropine), like previous experimental pharmacologists

(Temkin 1946), and combined them with histological studies to understand the exocrine gland and cardiac chronotropic function (Langley 1873). He expanded his observations to visceral innervation: the role of vasomotor nerves in glandular secretion and the role of vagal fibres in cardiac function. Between 1881 and 1889 he employed histologic techniques in studying the effects of destruction of neural centres on lower regions of the nervous system hierarchy: brain structure changes after decortication in dogs, including effects on spinal cord tracts (Langley 1883, 1886; Langley & Sherrington 1884). By 1890 he applied the ganglionic blockade property of nicotine as a pharmacological dissection tool (Langley & Dickinson 1890). Nicotine paralyses the voluntary nerves to striated muscles and only the preganglionic part of the sympathetic nerves in a dose-dependent manner. Nicotine paralysis of the sympathetic white ramus connection with the ganglionic cells allowed for the differentiation of sympathetic fibres, which synapse in the ganglia from the ones that pass through to target organs. This led to the concept of preganglionic and postganglionic fibres. He then added sympathetic nerve stimulation experiments combined with nicotine application and mapped out the functional territory of each sympathetic ganglion.

Between 1891 and 1893 he characterized the function and relation of sympathetic skin fibres to their somatic counterparts (Langley & Sherrington 1891; Langley 1893). In the mid-1890s he began studying the functional role of sympathetic ganglia in visceral function (Langley 1896). To fully understand ganglionic function he combined splanchnic nerve stimulation with nicotinic ganglionic blockade with nerve degeneration/regeneration experiments. He concluded that presynaptic sympathetic lesions did not cause trans-synaptic ganglion degeneration and that regeneration was segmental and class specific (Langley 1895, 1897). Of note is that up to 1897, he utilized the available nomenclature to include vagal, sympathetic, visceral, splanchnic and pelvic nerves. His 1898 paper examined the outcome of postsection grafting of one visceral nerve to another (Langley 1898). Specifically what happens if the cranial and sacral visceral nerves, allied to the sympathetic fibres, are grafted onto each other?

‘When the central end of the vagus is joined to the peripheral end of the cervical sympathetic, some of the fibres of the vagus make functional connection with the cells of the superior cervical ganglion, so that stimulation of the vagus, or of its roots in the skull, will cause all the effects normally produced by stimulating the cervical sympathetic, and local application 1 p.c. nicotine to the ganglion temporarily abolishes the effect of stimulation.’

In the summary of his findings, he notes:

‘I propose the term “autonomic nervous system”, for the sympathetic system and the allied nervous system of the

cranial and sacral nerves, and for the local nervous system of the gut. In the foregoing experiments, it has been shown that preganglionic fibres of the cranial autonomic system can make connection with sympathetic nerve cells, and in so doing to change their function. I conclude that there is no fundamental difference between the preganglionic fibres of the body, whether they belong to the cranial, the sympathetic or the sacral autonomic systems. And that any preganglionic fibre in the body is capable of forming functional connection with any nerve cell of the sympathetic type wherever found. I conclude, further, that the function of any autonomic nerve fibre, depends not so much upon its inherent properties as upon the nerve cells with which it has an opportunity of becoming connected in the process of development. And I have earlier brought forward some facts to show that the function of the peripheral nerve cell depends upon the peripheral structure in which its axon has an opportunity of ending. So that, the physiological differences depend, in the main, upon the anatomical connections brought about by morphological laws.’

The outcome of this set of experiments prompted Langley to introduce a new nomenclature. In various texts prior quotations from this paper omitted an important preamble and left out another interesting aspect. This quote is from the beginning of Langley’s 1898 paper (Langley 1898):

‘By many of the earlier observers, the spinal ganglia and the various peripheral ganglia on the course of the spinal and cranial nerves, were grouped together under the head of the “ganglionic” system. And it was urged that the “ganglionic” system was specially related to the “organic” or “vegetative” functions of the body. The difficulty of generalizing became clearer with further knowledge, and the older terminology was gradually given up. Gaskell extended the meaning of the word “visceral” and used the term “visceral nervous system” to include the sympathetic system and the allied nervous elements of the cranial and sacral nerves. And this I have so far followed. But the word “visceral” is unsatisfactory, for the word loses its proper meaning if applied to nerve fibres such as those which run to the skin. In consequence, it seems to me advisable to adopt some new term. I propose to substitute the word “autonomic”. The word implies a certain degree of independent action but exercised under control of a higher power. The “autonomic” nervous system means the nervous system of the glands and of the involuntary muscle; it governs the “organic” functions of the body.’

Therefore the main reason the term ‘visceral’ is unacceptable is the innervation of the skin and the implication that the latter is not a visceral organ. This line of reasoning failed to take into consideration Gaskell’s embryologic classification. Langley’s analysis of the word itself contains the idea of independent action coupled with control by a ‘higher power’, although the term itself does not imply any control. He uses the term ‘autonomic

nervous system', implying sensory and motor fibres, and cerebrospinal axis integration. The paragraph also maintains Bichat's term 'organic' as a placement term for an independent, internal function control system.

The influence of the humanities. Regarding the word 'autonomic', in a footnote at the bottom of the second page, Langley wrote (Langley 1898):

'This word was suggested to me by Prof. Jebb, to whom I offer my cordial thanks.'

Autonomos comes from ancient Greek, *autos* (I, myself, the same self in opposition to another) and *nomos* (custom, law), living by one's own laws, be independent (Lidell & Scott 1889). Sophocles's *Antigone* (438 BC) is the first place in recorded history where we encounter the word 'αὐτονομος' (autonomous), though it does not appear in the contemporary English translation (Jebb 1891):

'Glorious, therefore, and with praise, thou departest to that deep place of the dead: wasting sickness hath not smitten thee; thou hast not found the wages of the sword; no, mistress of thine own fate, and still alive, thou shalt pass to Hades, as no other of mortal kind hath passed'. (Jebb 1891)

Richard Claverhouse Jebb (1841–1905) was a professor of Greek at Cambridge and a Sophocles scholar. Jebb's annotated translation, published in 1891, does not utilize the word 'autonomous' but offers his linguistic context for the word's meaning (Jebb 1891): 'αὐτονομος, i.e. of your own free will. No one constrained her to do the act for which she suffers, she knew death would be the consequence and she chose it. The word is fitting since she has her laws above Creon's. The implied contrast is with the helpless victims of disease or war. – The word could not mean, "by the ordinance peculiar to your case", i.e. "by the unique doom of a living death" '.

So how did this classic Greek tragedy word become a neologism in physiology and medicine? *Antigone* is the typical Sophoclean hero: an isolated character in a situation where her actions are constrained. Action must follow, only to expose the divide between customs and praxis. Sophocles places *Antigone* at the intersection of fate (duty to her dead family members) and moral autonomy (respect for life). By choosing to bury the body of her brother, *Antigone* places her duty to the dead above the duty to her own life. The acknowledgement of dependency necessarily limits her autonomy (Critchley 2020). It does not represent free will to choose your law but the choice of answering to the law of yourself (McNeill 2011). In philosophy there is a connection between sympathy and autonomy: accepting sympathy as a force operating in nature leads to failure to identify the causes of things. Ignorance of causal relations produces the idea of free will, where 'freedom' is understood as the absence of determination (Schliesser 2015). In neuro-

science and clinical neurology, the word 'autonomous' continues to imply that there are two nervous systems: one voluntary with freedom of decision-making and one involuntary, and also 'free'.

The defence of the ANS concept. The ANS concept fulfilled the correspondence principle: the new theory contained the old ones, was perceived as the better explanation of observed phenomena and was operational (Popper 1979). Langley's scientific rigor, personality and wordsmithing, coupled with his days running the *Journal of Physiology*, may represent other reasons why the term 'autonomic' has endured. At the *Journal of Physiology* he performed all functions: administrative, finances, press management, correspondence and editing. His editorial style relied on the principle that facts had to speak for themselves, using the fewest words possible. He frequently rejected supporting images, even histological ones, and excluded discussions unsupported by data. He rewrote whole papers before publication. Although his approach had sound reasoning and gave him and the *Journal of Physiology* a solid scientific standing, it was not always received well by his colleagues, who felt 'Langleyized' by the process (Bailey et al., 2023). After the death of Foster in 1907, Langley's perceived autocratic style led to the creation of a separate *Quarterly Journal of Physiology* (now known as *Experimental Physiology*) with an entirely different editorial style. In a 1905 lecture for medical students in Amsterdam titled 'Autonomic Nerves', Langley laid out the available terminology: voluntary nerves should be called somatic, and sympathetic nerves are only efferent. They should be called autonomic and not involuntary (Langley 1905). He classified the autonomic nerves depending on their segmental origin: midbrain autonomic, bulbar autonomic, thoracolumbar sympathetic and sacral autonomic. He also introduced a new term.

'The cranial and the sacral autonomic nerves have more in common with one another than either has with the sympathetic and in this account they may be grouped together as the para-sympathetic system'. 'Para' [Greek = beside] -. The common features cited were that the distribution of the parasympathetic fibres is regional, and the preganglionic fibres branch off at variable distances from the CNS and do not respond to adrenaline. This paper also contains the term 'enteric nervous system', separate from the sympathetic and parasympathetic systems. Langley stated that experimentally there was no classic reflex in the sympathetic fibres, only axon reflexes. In his 1921 monograph on the ANS, Langley reflected on the ANS concept while defending it against the history of prior discoveries:

'All the old terms had been used with different connotations at different times, and to use any of them

with another additional connotation was but to add to the inherent difficulty of understanding the point of view of earlier writers. I called the system the autonomic nervous system (1898). It was a “local” autonomy that I had in mind. The word “autonomic” does suggest a much greater degree of independence of the central nervous system than in fact exists, except perhaps in that part which is in the walls of the alimentary canal. But it is, I think more important that new words should be used for new ideas than that the words should be accurately descriptive. In any case the old terms have no advantage as descriptive terms’.

We respectfully disagree: new terms used for new ideas must be increasingly accurately descriptive, and magical naming should not substitute for understanding (Blessing 1997; Popper 1979). While discussing ‘local’ autonomy Langley continues to describe two separate nervous systems. Langley’s classification into somatic and autonomic divisions refers to only peripheral nerves and, for autonomic, only efferent ones. Keeping the older term ‘sympathetic’ the newer term ‘parasympathetic’ and the anatomical term ‘enteric’ in his scheme are confusing if all are, indeed, *autonomic*. In the same monograph we find the statement that the *afferent* autonomic fibres have no distinguishing features from other afferent fibres. Finally Langley recognized then that the central connections of the autonomic system are imperfectly known. More contemporary narratives defending the ANS concept fail to address the ideologic and linguistic underpinning of this concept, which explains, in part, the separate views (Espinosa-Medina et al., 2018; Horn 2018; Jänig & Neuhuber 2017; Neuhuber et al., 2017).

Consequences. The anatomically, pharmacologically and physiologically segregated and antagonistic sympathetic and parasympathetic nerves have been useful as a simplified model in neuroscience and clinical research (Ernsberger & Rohrer 2018). Unfortunately this reductionistic scheme does not go far enough to promote our understanding of organismic physiology and continues to leave out sensory visceral input and central regulatory activity (Macefield 2024). The autonomic ‘nervous system’ is still seen as the primary efferent homeostatic regulator, constituting a mereological fallacy, in which the sum does not explain the parts (Bennett & Hacker 2003). Due to its connection with fight or flight responses, the sympathetic output is commonly believed to be phasically active, whereas the parasympathetic one is continuous, that is, tonically active. Both outputs have tonic and phasic components, modulated continuously (Gibbins 2013). Moreover neither branch operates uniformly on the tissues it innervates. For example sympathetic neurones supplying the skeletal muscle and cutaneous vasculature are governed separately to subserve the roles of blood pressure control and thermoregulation,

respectively. There is also regional control. The term ‘autonomic’ has also contributed to the unified view of cranial and spinal visceral outflows, blamed on the apparent separation of thoracolumbar and cranio-sacral outputs. Despite the late-19th-century experimental work indicating cerebrospinal control, the term ‘autonomic’ brought back, yet again, an independent visceral nervous system. The idea of a separate nervous ‘system’ automatically regulating internal function involuntarily separated the fields of visceral and somatic science (cardiovascular and respiratory physiology is an example) in medicine and neurology (Blessing 1997; Macefield 2024). Clinicians continue to understand visceral integration as automatic, involuntary and separate from somatic and emotional integration. In neurology ‘autonomic’ created the reductionistic view of separate central and peripheral nervous systems: one for visceral and the other for somatic functions. Most neurology residency programmes graduate ‘somatic neurologists’. In medicine symptoms and signs are evaluated as originating only from primary organ pathology. Like in prior centuries clinical practice lags scientific research (Tsouyopoulos 1984): abnormal autonomic function has been elevated to the clinical diagnosis of ‘dysautonomia’ and is again attributed to a multitude of symptoms and disorders. The old belief that visceral ganglia have independent abilities has led to various injections into them with a wide range of expected outcomes.

An evolutionary view

The age of cellular phenotyping. Cellular phenotyping of visceral neurones has provided further insight but has also challenged these neurones’ age-old anatomical, pharmacologic and physiological definitions. Single-cell and spatial transcriptomic analysis of the neural crest lineage has evolutionarily reaffirmed the human nervous system evolutionary dichotomy envisioned by Aristotle, Bichat and Gaskell. Sensorimotor circuits in vertebrates have distinct transcription factor signatures and can be traced back to molluscs (D’Autr aux et al., 2011; Nomaksteinsky et al., 2013). Somatic or relational neurones sense the environment and respond by shaping bodily motions: somatic sensory neurones express Brn3, whereas somatic motor neurones express a combination of Mnx1 and Lhx3/4. Visceral neurones expressing Phox2b sense the internal environment and participate in regulating internal functions (Fritzsch et al., 2017). In vertebrates neural crest multipotent cells migrate widely, forming sympathetic, parasympathetic and dorsal root ganglia neurones (Espinosa-Medina et al., 2014). Gene expression determines neural crest cell progressive restriction of cell fates (Soldatov et al., 2019). For example neural crest-derived cranial Schwann cell precursors (SCPs) expressing Phox2b are the source of parasympathetic

neurones. SCPs migrate along cranial and peripheral nerve fibres, reach the future parasympathetic ganglion location site and adopt a neuronal cell fate (Kastriti et al., 2022). Cranial parasympathetic preganglionic neurones originate separately from the pMNV (post-mitotic Motor Neurone ventral) progenitor domain of the hindbrain, and their axons emerge through the dorsolateral exit points to innervate parasympathetic and enteric ganglia. Thoracolumbar and newly-minted sacral preganglionic neurones – which, it has been argued, should not be referred to as parasympathetic neurones but rather as *sympathetic* neurones (Espinosa-Medina et al., 2016), an idea which attracted much criticism (Horn 2018; Jänig & Neuhuber, 2017; Jänig et al., 2017; Neuhuber et al., 2017) – have a common origin with somatic motoneurones and express Olig2. Through ventral roots thoracolumbar preganglionic nerves project to the para and prevertebral ganglia and, in addition, the lower lumbar and sacral nerves project to the pelvic ganglia. Gene expression in postganglionic autonomic nerves also controls the number and types of neurotransmitters utilized (Ernsberger & Rohrer 2018).

Voluntary/involuntary. The first important development in this field in the 20th century has been the functional neuroanatomical definition of brain areas concerned with the control of visceral function. These are operationally subsumed under the central autonomic network to stress their specialization, again introducing the idea of a separate brain network for autonomic control (Benarroch 1993; Blessing 1997; Saper 2002). The second development is the functional characterization of target-specific postganglionic visceral neurones (Ernsberger et al., 2021). The third development concerns a better understanding of visceral afferents, visceral pathways and their central integration (Strigo & Craig 2016). Like exteroception and proprioception, interoception requires specific anatomical and functional connections from modality-specific sources. Interoception is now assigned to both sensing and integrating the whole-body physiological state (Craig 2009; Strigo & Craig 2016) and is coupled with predictive activity concerning perception, attention, cognition, memory, mood and behaviour. Cephalad, increasingly complex, brain structures receive multimodal afferents and converge upon organ-specific neurones to modulate function. Autonomic reflexes can minimize interoceptive prediction errors but cannot control allostatic variables without brain areas that integrate multimodal information (Berntson & Khalsa 2021).

Despite having brainstem and hypothalamic centres, a cortical insular representation of visceral function is necessary for generating a whole-body visceral experience and responses. The insula generates active interoceptive inferences, engaging autonomic motor activity and

sensorimotor tasks to resolve interoceptive prediction errors for the organism (Craig 2010; Fermin et al., 2022). In this model emotions are unconscious, situational configurations of brain networks triggered by sensory inputs that guide action and construct perception (Fermin et al., 2022). An evolutionary hypothesis is that this basic sensorimotor model is driven by anticipatory behaviour (active inference) aimed at efficient energy usage or allostasis (Craig 2013; Sterling 2012). In this context the ANS is nothing but a part of the organism's functions together with metabolic and immunological ones: the embodied predictive interoceptive coding (EPIC) model (Barrett & Simmons 2015).

Feelings, or the conscious experience of an emotion (Kandel et al., 2020), represent amodal patterns of neural activation generated for this purpose: a perceptual correlate of a behavioural motivation (Craig 2013). The idea that all behaviours are emotional behaviours occurring without subjective awareness has blurred the historic involuntary/voluntary dichotomy. Right- and left-anterior-insula-coordinated antagonism and functional specificity can be traced down to the efferent pathways and make up the parasympathetic (left) and sympathetic (right) divisions (Strigo & Craig 2016).

The role of the body in cognition has typically been reduced to a model of the nervous system working as a computer: the brain is the seat of cognition, autoanalyses itself, and commands the body. The embedded, embodied, enactive and extended (4E) model stresses the fact that the body's interaction with its environment plays a role in cognition (Newen et al., 2018). The autonomy of the whole organism and not the brain or its parts, including its visceral control, becomes the fundamental logic of the living (Barandian 2017).

Conclusions and a proposal for a new nomenclature

Nineteenth-century experimental science, clinical observations and the classics have all contributed to the autonomic terminology still in use today. This terminology attempted to replace prior terms and explain a significantly complex part of the nervous system. Without knowledge of interoception or a central pattern generator (CPG) for visceral function and relationship to feelings and emotions, studies in the periphery gave the impression of a separate, involuntary, autonomous nervous system. Rather, the so-called ANS is not so different from the somatic nervous system: both include sensory and motor neurones, and both are involved in local segmental reflex circuits as well as progressively more complex circuits at higher levels of the neuraxis. Moreover, both participate in CPGs. By definition a CPG is a collection of neurones that produce a set of sequential motor commands that, once initiated, can

run independently of conscious awareness, such as those responsible for respiration, swallowing and locomotion. They are usually located within the lower parts of the CNS: the basal ganglia, hypothalamus, midbrain, brainstem and spinal cord (Grillner et al., 2013). Whereas the motor output of a CPG is highly ordered and stereotyped, the motor pattern can be modified by sensory inputs, allowing adaptation to a particular sensory context. Of course a CPG does not mean that it is a single neurone (such as a pacemaker cell in the heart) or even a very small group of neurones: it can be a network of connected neurones that work together to produce, typically, a rhythmic motor output that can run continuously until terminated. Any network of neurones engaged in furnishing a stereotyped motor output can operate in the same fashion: it is the ability to run in an essentially unsupervised manner that is key here.

Unlike respiration, which does indeed run continuously without voluntary effort (except in the case of congenital central hypoventilation syndrome, which – usually due to a mutation of the *PHOX2B* gene – results in loss of automatic breathing during sleep; Moss, 2005), other CPGs – such as those that subserve swallowing and locomotion – can be initiated by voluntary effort, though their activity can also be triggered by events that are outside immediate conscious awareness. In addition, emotions can activate or modify the ongoing activity of a CPG; a surprise event may cause us to swallow, hold our breath or increase our breathing, also engaging CPGs that produce appropriate cardiovascular responses. Moreover we can think about something that is emotionally significant to us, and this will engage components of the ANS, bringing about changes in heart rate and respiration and the production of tears, for example, responses that are generated by higher-order areas of the brain.

We would argue, as proposed previously (Macefield, 2024), that any motor pattern that depends on a CPG can and *should* be considered as part of the ANS. Using the aforementioned examples both swallowing and respiration can run independently of conscious effort, just like the circuits of the enteric nervous system that produce peristaltic movements of the gastrointestinal tract. One might say that the ANS does not use skeletal muscles, which everyone knows are under voluntary control. But the reflex act of swallowing when a bolus is presented into the mouth involves skeletal muscles of the pharyngeal constrictors and upper oesophagus as well as the smooth muscle of the lower oesophagus, innervated by motoneurons travelling in the vagus nerve and branches of sympathetic nerves, respectively. And of course the respiratory pump muscles and laryngeal muscles are exclusively composed of striated (skeletal) muscle fibres, whereas the walls of the trachea, bronchi and bronchioles consist of smooth muscle. After all, muscle – regardless of type (skeletal, cardiac or smooth)

– is just an effector organ. Moreover it is interesting that intracellular recordings from spinal motoneurons supplying the inspiratory and expiratory intercostal muscles exhibit patterns of excitatory and inhibitory fluctuations in membrane potential that are not dissimilar to those that have been seen in spinal motoneurons responsible for locomotion (Grillner, 1974; Sears, 1964). Therefore if we are going to stick with the term ‘autonomic nervous system’, we should at least be consistent as to what it comprises and what it should include. The current use of the term is restrictive and inadequate.

Accordingly we argue the following:

- (1) Evolutionarily, the organism is equipped with CPGs and neural networks that reflexively integrate specific sensorimotor functions, including visceral functions. The CPGs are hierarchically organized, with more cephalad ones able to integrate multiple organ system functions.
- (2) Somatic functions, pertaining to somatosensory inputs and somatomotor outputs, have their own genetic fingerprints.
- (3) Visceral functions, pertaining to visceral inputs and visceromotor outputs, have their own genetic fingerprints.
- (4) No single sensory input mode activates ‘autonomic afferents’, and there are no specific autonomic afferent fibres, which travel within the spinal nerves, as well as in cranial nerves such as the vagus and glossopharyngeal nerves. However, it is common that somatic afferents elicit autonomic responses and vice versa.
- (5) Due to the embryologic origin of the skin and in keeping with the evolutionary view, the skin should be included in the visceral domain. Blood flow, sweat production and pilomotor activity all contribute to organismic adaptation.
- (6) There is no separate voluntary and involuntary ‘nervous system’. Voluntary and involuntary functions are built into both somatic and visceral functions.
- (7) If used, the terms ‘sympathetic’ and ‘parasympathetic’ require careful qualification: they pertain to historical terms and classically refer to only efferent nerve fibres that control visceral function, often without consideration of their afferent nerve fibres.
- (8) Not all organs receive dual innervation from the sympathetic and parasympathetic divisions, but even for those that do (e.g. the heart, pupil and cerebral and gastrointestinal vasculature), the concept that there is always an opposing action that serves to keep the ANS in balance is incorrect (Paton et al., 2005). The doctrine of functional autonomic reciprocity (increasing activity in one neural branch is coupled

with decreased activity in the other) has been replaced by a broader doctrine of a two-dimensional autonomic space (Berntson et al., 1991).

- (9) The spinal visceral ganglia are better referred to as medial (currently paravertebral), lateral (currently prevertebral) and distal (close to the organ).
- (10) There is only one nervous system equipped with different functions. There is no separate autonomic 'nervous system'. If we keep the term 'autonomic', this should refer only to the organism as a whole, meaning that the nervous system assures internal stability and regulation in order for the organism to live in this world (evolutionary view). Of necessity this must include breathing, swallowing and locomotion, all of which occur without conscious effort yet can be modified by top-down processes.
- (11) Although the term 'the enteric nervous system' remains useful, as it refers exclusively to the neurones within the walls of the gut, we propose the use of simpler terms to replace sympathetic and parasympathetic nerves: 'visceral cranial nerves' and 'visceral spinal nerves', with 'cranial' and 'spinal' referring to the sites of origin of the nerves. For example, the visceral spinal nerves include innervation of the skeletal muscle, bone, joints, skin, bladder and reproductive organs. Qualifying functional terminology can be added to these terms to denote their chemical neurotransmitter coding (Burnstock 2009) and dominant target tissue effect.

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Additional information

Competing interests

The authors declare no conflicts of interest related to this work.

Author contributions

A.C.B. wrote the initial draft of the manuscript and edited the final manuscript. V.G.M. prepared the initial draft and edited the final manuscript. All authors approved the final version of the manuscript. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

No funding was obtained for this work.

Acknowledgements

Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

Keywords

ANS, autonomic nervous system, history, Langley, parasympathetic, sympathetic

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