Biological Psychology 182 (2023) 108626

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

Review

Signal processing in the vagus nerve: Hypotheses based on new genetic and anatomical evidence

Clare Shaffer [a,*], Lisa Feldman Barrett [a,b,1], Karen S. Quigley [a,*,1]

[a] Department of Psychology, College of Science, Northeastern University, Boston, MA, USA
[b] Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA

ARTICLE INFO

Keywords:
Molecular gradients
Viscerotopic mapping
Sensorimotor integration
Multisensory integration
Fascicles
Memory
Mood
Depression
Interoception
Allostasis

ABSTRACT

Each organism must regulate its internal state in a metabolically efficient way as it interacts in space and time with an ever-changing and only partly predictable world. Success in this endeavor is largely determined by the ongoing communication between brain and body, and the vagus nerve is a crucial structure in that dialogue. In this review, we introduce the novel hypothesis that the afferent vagus nerve is engaged in signal processing rather than just signal relay. New genetic and structural evidence of vagal afferent fiber anatomy motivates two hypotheses: (1) that sensory signals informing on the physiological state of the body compute both spatial and temporal viscerosensory features as they ascend the vagus nerve, following patterns found in other sensory architectures, such as the visual and olfactory systems; and (2) that ascending and descending signals modulate one another, calling into question the strict segregation of sensory and motor signals, respectively. Finally, we discuss several implications of our two hypotheses for understanding the role of viscerosensory signal processing in predictive energy regulation (i.e., allostasis) as well as the role of metabolic signals in memory and in disorders of prediction (e.g., mood disorders).

The vagus nerve is cranial nerve X (Fig. 1A). It consists of both ascending afferent sensory signals from the viscera that inform the brain on the sensory state of the body's internal milieu (Jänig, 2006; Wehrwein et al., 2016) and descending efferent parasympathetic motor signals from the brain to control the viscera and other tissues in the body (e.g., Hammer et al., 2018; Jänig, 2006; Loewy & Spyer, 1990).[2] There is a resurgence of interest in understanding vagus nerve anatomy, in part due to the increased popularity of vagus nerve stimulation as a trans-diagnostic intervention for various mental and physical disorders (e.g., Ben-Menachem, 2002; Nemeroff et al., 2006; Shen et al., 2011). The anatomy of the vagus nerve has also been debated in the context of the polyvagal theory (e.g., Porges, 1995, 2021), given that the anatomical description and evolutionary origins of the vagus nerve that underpin the polyvagal theory has been called into question (Berntson et al., 2007; Doody et al., 2023; Grossman, 2023; Grossman & Taylor, 2007; Neuhuber & Berthoud, 2022; Taylor et al., 2022). In this paper, we review new evidence about the molecular and anatomical architecture of vagal fibers and then outline two novel hypotheses about possible computational capacities suggested by that architecture. Our review of the evidence is not proof that these hypotheses are correct, of course, but rather describes how existing empirical data constrains what is functionally possible within the vagus and attests to these hypotheses as worthy of investigation.

Crucial to our approach is the hypothesis that a central nervous system builds a predictive internal model of its own body in an ever-changing and only partly predictable world, which reduces uncertainty and minimizes metabolic cost while guiding the organism's behavior (e.g., Sterling & Laughlin, 2015). A predictive strategy allows an animal to reduce uncertainty by generalizing from similar past experiences to prepare responses and anticipate the sensory consequences of those responses, with incoming sensory signals serving to confirm or correct the predictions (for review and additional references, see

* Corresponding authors.
E-mail addresses: shaffer.c@northeastern.edu (C. Shaffer), k.quigley@northeastern.edu (K.S. Quigley).
[1] Denotes co-senior authors.
[2] Some viscerosensory data from the carotid body is carried by both the vagus and the glossopharyngeal (the IXth cranial nerve), making the glossopharyngeal the only other cranial nerve to carry viscerosensory afferent signals (Jänig, 2006; Wehrwein et al., 2016). Other viscerosensory signals are carried in spinal visceral afferents from thoracolumbar and sacral organs. These fibers have their cell bodies in dorsal root ganglia (which lie along the spinal cord) and then typically pass into the spinal cord (Jänig, 2006)

https://doi.org/10.1016/j.biopsycho.2023.108626
Received 9 January 2023; Received in revised form 25 June 2023; Accepted 3 July 2023
Available online 6 July 2023

Hutchinson & Barrett, 2019). This strategy is more energy-efficient and less error-prone than stimulus-response strategies (Sterling & Laughlin, 2015). Energy efficiency is a major consideration both for immediate health but also for longer-term survival and reproductive fitness (Jékely et al., 2015; Niven & Laughlin, 2008; Sterling & Laughlin, 2015). Elsewhere, we have hypothesized that energy-efficient, predictive control of the body forms the anatomical and functional basis for the emergence and functioning of a mind (e.g., Atzil et al., 2018; Atzil & Gendron, 2017; Barrett, 2017; Hutchinson & Barrett, 2019; Katsumi et al., 2022, 2023). From this control perspective, a basic function of a brain is not to "perceive" the world per se, but to build and run an internal model of the body in that world that anticipates and efficiently adjusts for sensory inputs that are relevant to the physiological conditions of the body.[3] Here, we consider the role of the vagus nerve in this regulatory effort.

The first section of this paper briefly reviews the anatomical organization of the vagus nerve and the main brainstem nuclei to which it projects. These details ground discussions in the subsequent sections. The second section reviews two signal processing motifs in the nervous system, one mapping the spatiotemporal correlations between incoming sensory signals (i.e., coding by temporal coincidence over spatially restricted inputs) and the other mapping only temporal correlations (i.e., coding by temporal coincidence over a wide range of spatially distributed inputs; Fig. 2). This overview sets the stage for our hypothesis, discussed in the next section, that the sensory vagus nerve may do more than simply *relay* signals between the body and the brain — its anatomical features may allow for *signal processing*. We examine new genetic and structural evidence of vagal anatomy as a starting point from which we consider how the vagus may compute both spatial and temporal features of the sensory signals informing on the physiological state of the body, and how the architecture of the brainstem nuclei also may support these computational processing motifs. We also review anatomical evidence of the organization of vagal fibers within the nerve trunk and discuss the possibility that ascending and descending signals may modulate one another, calling into question the strict segregation of sensory and motor signals, respectively. The final section considers the broader implications of the two signal processing hypotheses that we introduced for understanding the role of viscerosensory signal processing in predictive energy regulation (i.e., allostasis) as well as the role of metabolic signals in memory and in disorders of prediction.

1. A brief overview of the vagus and its brainstem targets

The left and right nodose ganglia sit at the base of the head, while the peripheral processes for these ganglionic neurons are embedded in the visceral organs and other peripheral tissues and serve as the main afferent fibers of the vagus. The nodose ganglia are pseudo-unipolar, meaning that these peripheral processes are functionally 'dendritic' but are conventionally considered axons, bringing viscerosensory signals from the body to the nodose ganglion cell bodies (Câmara & Griessenauer, 2015; see Fig. 1B). From there, the axons continue and synapse in the nucleus tractus solitarii (NTS; Fig. 1B) and in the adjacent area postrema (AP) in the medullary brainstem (see Leslie & Gwyn,

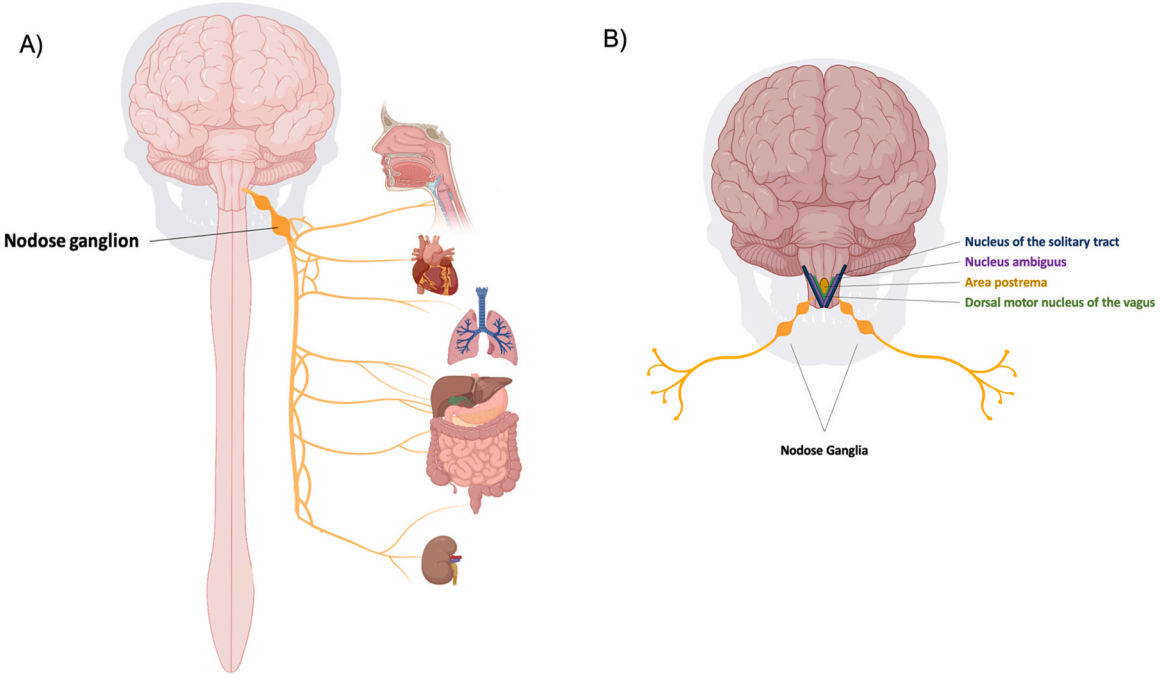

Fig. 1. Panel A shows a schematic representation of the gross anatomical distribution of the afferent vagus nerve. The enlargement just above the nodose ganglion represents the jugular ganglion (through which somatic and visceral afferents to the ear, pharynx and larynx pass; our focus here is on the neurons passing through the nodose ganglion). The nodose and jugular ganglia, as well as all cervical and thoracic branches shown are bilateral, with one side omitted here for clarity. Panel B shows a more detailed schematic view of the interface between the brainstem nuclei, vagus nerve, and target organs. The four brainstem nuclei have been spatially oriented to depict their proximity to one another, and their rough ordering relative to the midline of the brainstem; however, this is a simplified view and a precise rendering of the relative lengths of each nucleus and their proximity to other spinal cord structures is not depicted. Created with Biorender.com.

[3] Correspondingly, the evolutionary history of the brain is a history of the ways in which control of internal state is spatially extended, further and further, into the external world and temporally extended into past and future (Cisek, 2019).

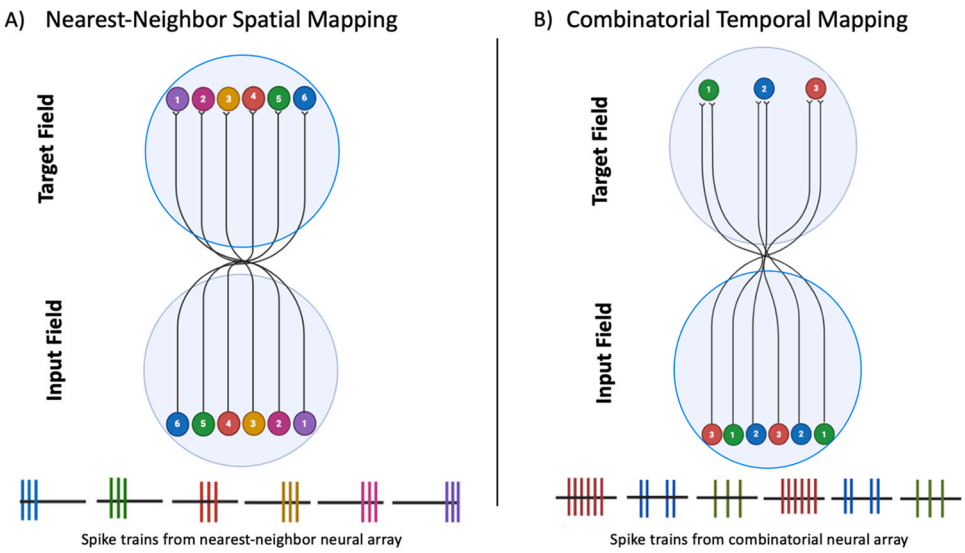

Fig. 2. A schematic of spatial and temporal mapping in sensory systems. This figure represents spatial and temporal coding themes across a variety of sensory systems and is thus highly abstracted away from anatomical details in service of a more general depiction. Panel A shows a schematic depiction of nearest-neighbor array-to-array spatial mapping exemplified by the visual system. Neurons in the input field (e.g., retinal ganglion cells) connect to neurons in the target field (e.g., lateral geniculate nucleus neurons) in a manner that preserves the spatial ordering (and spatial correlations) in signals from the input field. Each color represents a different spatial location in the visual field. Signals arising from neurons that are closer to one another in the input field are more highly correlated with one another than are signals arising from neurons that are spatially more distant. Panel B shows a schematic depiction of combinatorial temporal mapping exemplified by the olfactory system. Neurons expressing the same receptor type gene in the input field (e.g., olfactant receptors in the olfactory epithelium) converge onto the target field (e.g., glomeruli in the olfactory bulb) in a manner that preserves the signal co-occurrences in time. A given color represents an olfactory receptor neuron that expresses one specific odorant receptor gene, which converges on the same glomeruli. Local activity patterns for neurons that are co-activated by a common odorant in the input field are highly correlated in time, while activity patterns for other odorants are less correlated. Created with Biorender.com.

1984 for review).[4] In referring to afferent signals from the body before they reach the brain, we use "viscerosensory"; once these signals have reached the brain, we use the term "interoceptive".

Beyond receiving ascending neural signals directly from the nodose, the area postrema functions like a "circumventricular organ," by virtue of being highly vascularized by fenestrated[5] capillaries. As a result, pores between the vasculature and AP proper allow relatively free passage of large macromolecules (e.g., proteins and peptide hormones) into the brain, molecules that would otherwise remain segregated from the brain via the blood brain barrier. In this way, the AP acts as a unique chemoreceptive liaison between the peripheral bloodstream and the brain (Cottrell & Ferguson, 2004; Duvernoy & Risold, 2007; Price et al., 2008). Afferent axons from the nodose ganglia also project directly to the dorsal motor nucleus of the vagus (DMV), which lies adjacent to the NTS dorsally, and was originally assumed to be exclusively a vagal motor nucleus (see Fig. 1B; Champagnat et al., 1986; Kalia & Mesulam, 1980a,b; Kalia & Sullivan, 1982; Neuhuber & Sandoz, 1986).[6] Approximately 80% of vagal fibers ascend to carry viscerosensory signals to the brainstem (Hammer et al., 2018; Jänig, 2006; Loewy & Spyer, 1990; Wehrwein et al., 2016).[7]

The rest of the vagal fibers descend from the DMV and the nucleus ambiguus (nAmb) in the ventrolateral medulla, which are the primary origins of efferent parasympathetic motor control of organs in the periphery (below the neck). These efferent parasympathetic fibers bypass the nodose ganglia on their way to their visceral targets.[8,9] The majority (i.e., 80%) of the neurons in the DMV give rise to vagal efferents to the gastrointestinal tract and abdominal viscera, including the pancreas (e.g., Mussa & Verberne, 2013; Norgren & Smith, 1988), with fewer innervating the heart and lungs (e.g., Cheng & Powley, 2000). The nAmb is divided into a dorsal and ventrolateral portion, with the dorsal division giving rise to fibers innervating the striated muscle of the esophagus, the pharynx, and the larynx (e.g., Bieger & Hopkins, 1987; Hsieh et al., 1998; McLean & Hopkins, 1985b), and the ventrolateral division giving rise to the majority of vagal efferents targeting thoracic organs such as the heart and lungs (Bieger & Hopkins, 1987; Hopkins & Armour, 1998; Kitamura et al., 1993).

The NTS, AP, DMV, and nAmb are themselves densely interconnected. Fibers from the NTS modulate neurons in both the DMV (via DMV dendrites that extend into the NTS; e.g., Davis et al., 2004; McLean & Hopkins, 1985a; Shapiro & Miselis, 1985a) and the nAMB (via NTS projections to the rostral nAmb; Saper & Stornetta, 2015; Stuesse & Fish,

[4] The human NTS (composed of left and right nuclei) has several distinguishable subnuclei oriented along its rostro-caudal extent (McRitchie & Törk, 1993) distinguished by their locations relative to the area postrema. Although the number of subnuclei tends to vary, their organization is thought to be roughly consistent across species (e.g., in the rat, Altschuler et al., 1989; cat, Kalia & Mesulam, 1980a,b; and human, McRitchie & Törk, 1993).

[5] From the Latin "fenestrae", or "window".

[6] It was traditionally thought that afferent vagal signals first arrive at neurons in the NTS, which are then subsequently sent to the DMV, after which the signals become progressively more integrated as they travelled upward to the midbrain and forebrain (Goehler et al., 2000; Saper, 2002; Thayer et al., 2011) or descended again from the DMV to target organs (so-called "vago-vagal reflexes"; e.g., Powley & Philips, 2002).

[7] Some viscerosensory data from the carotid body is carried by both the vagus and the glossopharyngeal (the IXth cranial nerve), making the glossopharyngeal the only other cranial nerve to carry viscerosensory afferent signals (Jänig, 2006; Wehrwein et al., 2016). Other viscerosensory signals are carried in spinal visceral afferents from thoracolumbar and sacral organs. These fibers have their cell bodies in dorsal root ganglia (which lie along the spinal cord) and then typically pass into the spinal cord (Jänig, 2006).

[8] The nAmb is so named due to the ambiguity of the cytoarchitecture of its subdivisions, which are quite variable across different species, and the location of the neurons making up this nucleus, which are dispersed and extensively intermingle with neighboring brainstem structures (e.g., Ellenberger & Feldman, 1990).

[9] Other parasympathetic visceromotor fibers travel outside the vagus to the blood vessels of the cerebral circulation, the eye, and the salivary and lacrimal (tear) glands and to the bladder, colon, and genitalia (Wehrwein et al., 2016).

1984). Likewise, there are extensive reciprocal connections between the NTS and adjacent AP neurons (Leslie & Gwyn, 1984; Shapiro & Miselis, 1985b). While there are not significant direct projections between the AP and DMV, it has been suggested that the AP may influence the DMV indirectly, via AP dendrites that synapse in the NTS, which overlap with the dendrites of the DMV synapsing onto the same area in the NTS (e.g., Miselis & Shapiro, 1983; Shapiro & Miselis, 1985a, 1985b). The NTS also sends ascending signals to other brainstem nuclei such as the locus coeruleus (bed nucleus for norepinephrine), the dorsal raphe nucleus (serotonin) and ventral tegmental area (dopamine), as well as targets in the midbrain and forebrain including hypothalamic and amygdalar subnuclei, portions of the basal ganglia (e.g., nucleus accumbens) and the hippocampus via the septal nuclei (Rinaman, 2003, 2010; Rinaman & Schwartz, 2004; Suarez et al., 2018). The DMV receives projections from many of these same NTS targets in the midbrain and forebrain (Loewy & Spyer, 1990; ter Horst et al., 1984). The AP also projects to the parabrachial nucleus in the midbrain and to other nuclei of the medulla (Cunningham et al., 1994; Leslie & Gwyn, 1984; Shapiro & Miselis, 1985b). Taken together, these highly interconnected brainstem nuclei, their vagal inputs, and their shared projections to other brainstem nuclei as well as to midbrain and forebrain targets comprise a crucial infrastructure that is well suited to supporting efficient sensing in the service of metabolic control.

2. Signal processing motifs in the nervous system

The vagus nerve projects to the central nervous system (CNS), which is a sophisticated signal processor that continually receives ensembles of signals from the sensory surfaces of the body (in humans, some examples are the retina in each eye, the cochlea in each ear, pressure receptors in the skin, the taste buds, receptors in the olfactory epithelium of the nose, glucose sensors in the skeletal muscles, baroreceptors in the large arteries, and nutrient sensors in the gastrointestinal tract and other viscera). The signals from these surfaces continually stream to the brain to inform on the changing sensory state of the body. Neuron structure – such as neuron size, axonal diameter, degree of myelination, etc. – as well as the architecture of neuronal connectivity and the supporting glial cells afford signal transformations that enable an organism to survive, thrive, and reproduce in a highly variable and continually changing environment. A variety of signal processing computations exist in the CNS, including signal integration, modulating signal strength or duration, adding or reducing stochastic noise, transducing signals into a common format, and so on (e.g., Traynelis & Jaramillo, 1998; Wolff, 2016).

One particularly important type of computation for our purposes is signal compression, which involves removing redundancies for signals that are correlated in time and/or space to increase signal quality while decreasing processing cost. Signal compression effectively creates efficient summaries of the original signals. These summaries are sometimes referred to as "abstractions" of the original signals, not because they remove the sensory details entirely, but because they summarize those details in a more efficient format. The CNS has been viewed as a system for removing redundancies among incoming sensory signals at least since the time of Claude Shannon's information theory (Attneave, 1954; Barlow, 1961; Shannon & Weaver, 1964/1949). Its architecture affords compression along multiple gradients, across which signal ensembles of higher dimensionality (e.g., for many small, specific sensory details) are increasingly summarized into ever more efficiently packaged ensembles of lower dimensionality. Compression gradients have been identified within the cerebral cortex (e.g., Bethlehem et al., 2020; Bastos et al., 2020; Chanes & Barrett, 2016; Finlay & Uchiyama, 2015; Katsumi et al., 2022, 2023; Margulies et al., 2016; Paquola et al., 2019), the hippocampus (Kharabian Masouleh et al., 2020; Przeździk et al., 2019; Vos de Wael et al., 2018), and the cerebellum (Dong et al., 2020; Guell et al., 2018; see Katsumi et al., 2023 for discussion). There is also some evidence that somatosensory signals are compressed along a gradient as they arise in the dorsal column of the spinal cord (e.g., Cappe et al., 2009; Castejon et al., 2021; Saadon-Grosman et al., 2020), and signal compression may occur in the peripheral nervous system as well (Copelli et al., 2005).

There is spatial and temporal structure in the sensory signals that are transduced by a body's sensory surfaces (i.e., the "where" and "when" of signal co-occurrences). Distinctive architectural arrangements in the CNS give rise to signal processing, including signal compression, within spatial and temporal domains (see Fig. 2). To illustrate, we use the processing of light signals in the vertebrate visual system as an example of spatial mapping (coding the temporal co-occurrence of signals in a manner that preserves the spatial organization of receptors), and chemosensory signals in the olfactory system as an example of temporal mapping (coding the temporal co-occurrence of signals across receptors that are widely distributed). To be clear, our goal is not to provide comprehensive descriptions of the visual and olfactory systems here, but to focus on those details that are most relevant to our discussion of possible signal processing motifs in the vagus nerve. Nor we are claiming a strict double-dissociation; the world is filled with signals that vary in a spatiotemporal fashion and spatially coded signals can be transformed into temporal codes and vice versa (Buzsáki & Tingley, 2018). The visual system certainly processes the temporal relations between signals (e.g., Rucci et al., 2018; Price & Gavornik, 2022) and olfactory cues are used in spatial navigation (e.g., Jacobs et al., 2015; Reddy et al., 2022). Nonetheless, the architectural distinctions between these two different signal processing motifs may be a useful lens for considering the sorts of signal processing that might be possible in the afferent vagus nerve, given its anatomy.

2.1. *Nearest-neighbor spatial mapping*

Light signals from neighboring areas in the visual field activate receptors in neighboring areas of the retina, creating a retinal map of visual space. Corresponding retinotopic maps exist in the superior colliculus in the midbrain, in the lateral geniculate, pulvinar, and the lateral posterior nuclei of the thalamus, and in the early portions of visual cortex, including primary visual cortex (e.g., Chklovskii & Koulakov, 2004; Luo & Flanagan, 2007). The positioning of neuronal receptive fields in each of these regions mirrors the spatial array in the retina (Kandel et al., 2014). This is called "nearest-neighbor, array--to-array" mapping, whereby the spatial relationships in the signal array at their origin (the retina) correspond to the array at their termination (see Fig. 2A; for discussion, see Finlay & Uchiyama, 2015; MacIver & Finlay, 2022). The nearest-neighbor mapping for the spatial relationships among signals does not reference the spatial relations in the external world in any absolute, body-independent manner. Rather, the spatial mapping is relative to the sensory surface of the body (in this case, the retina), which necessarily depends on the body's position in the external world (e.g., when you turn your head from left to right, or move your eyes from left to right, your retinas change position in relation to the world, and so your visual field necessarily changes). It is this spatial array that is recapitulated in multiple parts of the brain. Nearest-neighbor mapping of the visual field occurs not because the brain is tracking the outside world, but because it is mapping what is happening on the retina. Other classic exteroceptive sensory systems also use nearest-neighbor mapping: in the somatosensory system, nearest-neighbor mapping is relative to positions on the skin, in the joints and muscles, etc. (e.g., Sanchez-Panchuelo et al., 2010; Servos et al., 1998), and in audition, nearest-neighbor mapping is relative to the tonotopic map of the cochlea (Allen et al., 2022; Mesik et al., 2022; Saenz & Langers, 2014; Thomas et al., 2015; von Békésy & Peake, 1990).

A complete discussion of the details establishing nearest-neighbor, array-to-array mapping that preserves the spatial topography of the retina across levels of the neuraxis is beyond the scope of this paper, but some details provide a useful starting point for formulating hypotheses about possible signal processing capabilities within the vagus by virtue

of its molecular and anatomical architecture (details summarized from Reese, 1987, 1993, 1996, 2011; Reese et al., 1991; Reese & Cowey, 1988). Retinal ganglion cells of all types and sizes with different neural features and response profiles are intermingled across the retina. As axons leave the retina within the optic nerve (cranial nerve II), they are bundled together into heterogeneous collections of fibers called fascicles, which are separated by connective tissue. Each fascicle contains axons of all types from a radial sector of the retina. As a result, the optic nerve has a mixed distribution of large and small diameter axons intermingled at every location along its extent. These axons are organized in a crude retinotopic manner.

Once retinal axons cross the optic chiasm, they are no longer bundled into fascicles and are referred to as the optic tract. Post-chiasm, axons become reordered according to their diameter, with finer axons positioned deeper within the tract and thicker axons positioned superficially. Axon diameter (and therefore axon position in the optic tract) is organized by the embryonic birthday of the retinal ganglion cell from which the axon derives. This organization is called chronotopy (Reese, 1993). This reorganization of axons by diameter crudely approximates the fact that axons of small diameter terminate in the deep layers of the LGN whereas axons of larger diameter terminate in the superficial layers.[10] In addition, the axons also undergo a retinotopic re-organization across the medio-lateral axis of the optic tract (corresponding to the dorso-ventral axis of the retina). Importantly, both reorganizations are insufficient to produce the retinotopic maps found elsewhere in the brain, including where retinal axons first synapse in target nuclei further up the neuraxis.

The retinotopic maps in the superior colliculus and thalamic nuclei take shape, at least in part, via a gradient of genetically-expressed guidance molecules, producing what is called gradient-matching. A gradient of gene expression in the retinal ganglion cells matches a corresponding gradient in the neurons of the superior colliculus and in the relevant thalamic nuclei. The matching gradients allow axons that originate in specific genetic classes of retinal ganglion cells to find their appropriate targets in the collicular or thalamic neurons, thereby producing retinotopic maps (Feldheim et al., 1998; Frisén et al., 1998; Triplett et al., 2012). The retinotopic maps in early visual cortex (i.e., in V1, V2, and so on) are established, in large part, by Hebbian learning. Here, signals from collicular and thalamic neurons that monitor neighboring regions of visual space fire in a coordinated fashion, sending coordinated signals to neurons in early visual cortex during development in the weeks and early months after birth. That is, retinotopic maps in early visual cortex emerge from spatially correlated, nearest-neighbor signals. Gradient-matching and Hebbian learning may not be the only processes at play in setting up nearest-neighbor, array-to-array (spatially correlated) maps, but they are important ones.

The processing of visual signals, including the compression of redundant spatial correlations (to increase transmission and computational efficiency), begins in the retina (e.g., the signals from about 120 million rods and 6 million cones in the human retina are transmitted out of the retina by about 1.2 million retinal ganglion cells; Kim et al., 2021). The degree of compression in retinal ganglion signals as they reach the LGN is still a matter of considerable research (e.g., Morgan et al., 2016). Importantly for our purposes, it is well known that a good deal of visual signal compression occurs along the main cytoarchitectural gradient of the cerebral cortex, anchored at one end by neurons of primary visual, auditory, or somatosensory cortex (computing specific sensory details that are relatively closer to the dimensionality of the sensory surfaces). At the other end, this gradient is anchored by neurons of the subgenual and pregenual anterior cingulate cortex (sgACC, pACC), entorhinal cortex (EC), the ventral anterior insula (vAI; which is adjacent to or part of the posterior orbital frontal cortex, pOFC; Öngür & Price, 2000) and other cortical limbic regions that assemble multimodal compressed summaries (for discussion, see Barbas, 2015; Chanes & Barrett, 2016; Katsumi et al., 2023, 2023 and references therein). Not surprisingly, these regions are some of the most well-connected hubs within the cerebral cortex (e.g., van den Heuvel & Sporns, 2013). These cortical regions are also heavily involved in allostasis and are the cortical origins of parasympathetic visceromotor regulation signals (e.g., Beissner et al., 2013; Vogt, 2016; Vogt et al., 2003), a point that we return to later in the paper.

This main gradient of signal compression in the cerebral cortex has been characterized in terms of evolutionary and developmental changes in cortical expansion, as changes in allometric scaling across species, and is manifest in several biological features that afford signal compression, including successive increases in intracortical myelination and in pyramidal neuron size and connectivity, successive decreases in neuronal density, and decreases in laminar development, as well as increases in cerebral metabolism in the upper layers of the cerebral cortex. A quick review of the cortico-cortical connections in this gradient is helpful to understand how signal compression is achieved.

In the visual system, the main gradient begins in V1, with many small, relatively less connected pyramidal neurons located in the upper cortical layers carrying signals for specific retinotopic details of high dimensionality. As signals flow to early visual cortical areas (e.g., Felleman & Van Essen, 1991; Rao & Ballard, 1999) and eventually to the multimodal integration regions of the cortex (e.g., Braga et al., 2013; Sepulcre et al., 2012; Szinte & Knapen, 2020), they converge on successively fewer and fewer upper layer pyramidal neurons with progressively larger cell bodies with increasing connectivity (e.g., Rao & Ballard, 1999). This convergence successively removes redundant correlations. The signal compression is lossy, meaning that redundant information is lost during compression. This 'many-to-fewer' cytoarchitectural pattern that achieves efficient signal compression is consistent with anatomical findings from Barbas (2015; Barbas & Rempel-Clower, 1997), Markov (e.g., Markov et al., 2013), and others (e.g., Hilgetag & Goulas, 2020) showing that patterns of cortico-cortical connections predict signal flow within the cerebral cortex. As signals traverse this cortical compression gradient, many signals of high dimensionality are reduced to multimodal summaries of lower dimensionality (described in Barrett, 2017; Chanes & Barrett, 2016; Finlay & Uchiyama, 2015; Katsumi et al., 2022, 2023; for related review, see Bastos et al., 2020). Such compression effectively computes "abstract" features, such as pleasure, threat, value, reward, and other features that map to multiple patterns of high-dimensional sensory and motor details discussed in (Barrett, 2017, 2022). With signal compression, array-to-array mapping becomes less and less fine-grained (Finlay & Uchiyama, 2015), until the most compressed, multimodal signal summaries are assembled in the cortical limbic areas (e.g., sgACC, pACC, EC, vAI/pOFC), at which point nearest-neighbor mapping no longer reflects

[10] Specifically, the small diameter axons arise from parvocellular neurons in the retina and carry high spatial frequency/low temporal frequency signals that give rise to color vision of high acuity. They are well designed for capturing small, slow, colorful objects, eventually synapsing in the parvocellular division of the LGN of the thalamus. Parvocellular neurons eventually constitute the ventral visual stream. Larger diameter axons arise from magnocellular neurons and carry signals that carry low spatial frequency/high temporal frequency signals that give rise to black and white vision of low spatial acuity. They are well designed for capturing visual motion, eventually synapsing in magnocellular division of the superior colliculus and of the LGN. Magnocellular neurons eventually constitute the dorsal visual stream. For a discussion of these pathways in relation to affect, see Barrett & Bar (2009).

the arrays across any particular sensory surface.[11]

2.2. Temporal co-occurrence mapping

The mapping of temporal relationships between incoming chemosensory signals in the primate olfactory system is also relevant to our discussion of possible signal processing motifs in the afferent vagus nerve. Our goal in this section is to highlight features that allow for mapping the temporal co-occurrence of molecules (called "olfactants" or "odorants") rather than to describe everything that has been discovered in the rapidly advancing research on signal processing in the olfactory system. Functionally, temporal coding (coding by temporal coincidence over a wide range of spatially distributed inputs) contributes to the ability to perceive billions of odors available in the chemosensory environment (the upper bound in humans having been estimated at close to two trillion (Gerkin & Castro, 2015; Meister, 2015). We draw on research from multiple vertebrate species (mostly mammals) because the anatomy and functioning of the olfactory system is strikingly similar across species (Manzini et al., 2022; with a few notable exceptions not relevant to this discussion, such as the existence or importance of the vomeronasal organ). Accessible reviews of olfactory anatomy can be found in Cleland and Borthakur (2020), Manzini et al. (2022), and van Hartevelt and Kringelbach (2012).

The sensory receptors for olfactant molecules are found in the olfactory epithelium that lines the nasal cavity. Receptors are part of the olfactory sensory neurons (also sometimes called olfactory receptor neurons). Each neuron is a bipolar cell equipped with a single dendrite embedded in the mucosal layer of the nasal cavity. Each dendrite expands into several microvilli called olfactory cilia containing a type of olfactory receptor. Olfactory receptors are highly diverse in molecular phenotype (~1000 types; Malnic et al., 1999; Niimura & Nei, 2005; van Hartevelt & Kringelbach, 2012). Studies using RNA sequencing indicate that the vast majority of olfactory sensory neurons express a single receptor gene at high levels, meaning that a given neuron is highly sensitive and selective for the molecules that bind to its dominant receptor (Hanchate et al., 2015; Saraiva et al., 2015; Xu et al., 2020; for additional references see Kurian et al., 2021).[12] Olfactory sensory neurons that express the same receptor gene are scattered across the olfactory epithelium.

The number of odor molecules that can be detected and discriminated by a mammalian nose (including a human nose) far exceeds the number of olfactory receptors available (Niimura et al., 2014) because each receptor responds to a variety of odor molecules and each molecule is coded by a combination of receptors, an arrangement called combinatorial receptor coding. Combinatorial receptor coding creates an olfactory epithelial map that discriminates odors in the chemical environment using widespread and overlapping receptor activity patterns (see Fig. 2B). The correlated signal input coming from the simultaneous activation of receptors distributed across the olfactory epithelium captures the temporal co-occurrence of olfactory signals, not their spatial co-occurrence (Carey et al., 2009; Cleland & Borthakur, 2020).

There is some evidence that full-blown chemosensory signal processing begins in the olfactory epithelium (in the sensory periphery), even before signals reach the olfactory bulb in the central nervous system (e.g., Gronowitz et al., 2021; Inagaki et al., 2020; Pfister et al., 2020; Xu et al., 2020; Zak et al., 2020). Within the complex mixtures of chemicals that exist in the natural world, receptors are also impacted by the concentration as well as quality of the molecules.[13] More than one molecule might compete for the same receptor, in effect impacting olfactory receptors as agonists (stimulating receptors) or modulators (e.g., suppressing receptors or participating in synergistic effects), in much the same way that neurons inhibit, enhance or modulate signals in one another within the brain (Gronowitz et al., 2021; Inagaki et al., 2020; Pfister et al., 2020; Xu et al., 2020; Zak et al., 2020; for examples, see Kurian et al., 2021 and references therein). These effects are largely non-linear, with antagonistic interactions (i.e., inhibition) often dominating. The ability to perceive a multitude of odors may be the result of complex non-linear dynamics within the olfactory epithelium that produce patterns that are more than the sum of individual olfactant molecules, meaning that olfactory sensory neurons and their receptors may function like a complex system in an ever-changing chemical timescape (e.g., Keller, 2016).

Olfactory sensory neurons that express the same receptor gene all send their unmyelinated axons (via the olfactory nerve) into the same small, spherical structures within the olfactory bulb called glomeruli, producing a chemotopic map of the olfactory epithelium. The architecture of projections effectively removes temporal redundancy in the correlated signals at or close to their source (i.e., the sensory neurons in the olfactory epithelium; Brann & Datta, 2020; Erskine et al., 2019; Giessel & Datta, 2014), compressing the olfactory signals into more efficient summaries. Each glomerulus within the olfactory bulb is selectively tuned to a narrow subset of the olfactants detected in the olfactory epithelium, i.e., it is tuned to the molecules that bind to the primary receptor expressed in the sensory neurons that project into that glomerulus (Burton et al., 2022). Unlike the nearest-neighbor mapping found in the visual system, the glomeruli in the olfactory bulb do not map the spatial relationships among the olfactory sensory neurons in the olfactory epithelium. Instead, olfactory sensory neurons that express the

[11] Signals also flow in the other direction along this cortical gradient, from neurons within cortical limbic areas to neurons of primary sensory areas — such that signals flow from neurons representing abstract multimodal summaries to neurons representing high-dimensional, specific sensory details in early sensory areas. The greater particularization of signals in this direction is called decompression. These decompressed signals play a key role in the predictive construction of perception, whereby the decompressed signals cascade in advance of, but are constrained by incoming signals from the sensory surfaces of the body (Ainley et al., 2016; Allen & Friston, 2018; Hutchinson & Barrett, 2019; Owens et al., 2018; Pezzulo et al., 2015; Schulkin & Sterling, 2019; Seth, 2013; Seth et al., 2012; Seth & Friston, 2016; Smith et al., 2017, 2021; Stephan et al., 2016). Decompression along a gradient occurs for skeletomotor control, as signals flow from primary motor cortex and premotor cortices to the spinal cord (Kalaska & Rizzolatti, 2013; Rizzolatti & Strick, 2013; Rizzolatti & Kalaska, 2013). Given that primary motor cortex contains visceromotor maps (e.g., Dum et al., 2016; Levinthal & Strick, 2012, 2020) and the MCC is both a primary visceromotor control region (Beissner et al., 2013; Vogt, 2016; Vogt et al., 2003), and a premotor area for the skeletomotor system (e.g., Devinsky et al., 1995; Rizzolatti & Strick, 2013; Vogt, 2016; Vogt et al., 2003; Wolpert et al., 1998), it is reasonable to hypothesize that visceromotor control also relies on successively particularized or decompressed signals at the organs.

[12] Immature olfactory sensory neurons express low levels of multiple gene receptors. Epigenetic regulation selects a single receptor by suppressing the others during development (Hanchate et al., 2015; Tan et al., 2015). While interesting, this observation is not directly relevant to the issue of distinguishing temporal mapping from spatial mapping.

[13] A single molecule stimulates a unique ensemble of receptors across multiple mature olfactory sensory neurons distributed across the entire olfactory epithelium, but with differing degrees of intensity. Some molecules bind to many olfactory sensory neurons and their receptors, while others bind to a small number, with the vast majority binding to two or more (Nara et al., 2011). The composition and number of receptors involved can change as odorant concentrations change, although some quick-responding receptors (<100 ms after inhalation) respond in a concentration-invariant manner (Wilson et al., 2017). Although each olfactory sensory neuron and the receptor it expresses respond to more than one molecule, most olfactory sensory neurons are narrowly tuned to respond to a small number, with some broadly tuned neurons responding to large numbers of molecules (Nara et al., 2011). Olfactory sensory nerves fire faster and perhaps for longer in response to olfactants for which their receptor has a strong affinity (for discussion, see Wilson et al., 2017).

same dominant receptor are scattered around the olfactory epithelium and converge into fewer glomeruli that themselves have a mosaic-like organization within the bulb, so that glomeruli with distinct odorant sensitivities are spatially interspersed (Burton et al., 2022). In effect, this anatomical arrangement generates a temporal map of olfactory receptor identity across the glomeruli of the olfactory bulb. Because many olfactory signals from sensory neurons project into far fewer glomeruli, a high-dimensional sensory array is summarized into one of lower dimensionality, reducing temporal redundancies, integrating signal intensities, (Zhang & Firestein, 2002; e.g., in humans, about 6 million receptors in the human nose converge onto an average of 5500 glomeruli, van Hartevelt & Kringelbach, 2012) and in effect, achieving signal compression. Given that olfactory sensory neurons with the same dominant receptor converge onto the same glomeruli, combinatorial coding of odorant identity is likewise found in the glomeruli, although the coding is considerably sparser due to the compression of signals via incoming axons from epithelial neurons (e.g., Chae et al., 2019; for review, see Cleland & Borthakur, 2020).[14] This signal compression further enables coding of temporal co-occurrence.[15]

Chemotopic temporal coding is maintained in the bulb's output neurons that project to the rest of the central nervous system. The apical dendrites of these output neurons (called projection neurons, or mitral and tufted cells) extend into the glomeruli, where they synapse with the axon terminals of the olfactory sensory neurons that terminate there. The excitatory signals for an individual projection neuron, therefore, derive from olfactory sensory neurons that express the same type of olfactory receptor. The inputs to the projection neurons are an example of divergent signal processing because there are more mitral and tufted cells than glomeruli (i.e., the 40,000 mitral cells receive synapses from 5500 glomeruli in the human olfactory bulb; van Hartevelt & Kringelbach, 2012). Adding divergent processing of signals after the initial convergence of signals into the glomeruli maintains the specificity of the combinatorial coding while providing functional flexibility (Brezina & Weiss, 1997). These output signals also modulate one another in complex ways, thanks to the dense interconnections among the glomeruli via different types of interneurons (bulbar or juxtaglomerular cells) as well as interneurons that connect the mitral and tufted cells (granular cells).

Projection neurons carry their compressed, temporal chemotopic mapping to the rest of the brain via multiple, parallel routes (Igarashi et al., 2012).[16] Each glomerulus, via its projection neurons, sends signals widely to primary olfactory cortex (or piriform cortex, between the insula and the temporal lobe, anterior and lateral to the amygdala), bypassing the thalamus, to create yet another temporal map of the olfactants detected by the olfactory epithelium.[17] Each cortical neuron receives inputs from many different glomeruli, without any apparent spatial topography (Illig & Haberly, 2003; Rennaker et al., 2007; Stettler & Axel, 2009). The signal ensembles code for odors in an emergent way rather than representing individual molecular features (Gottfried, 2010; Wilson & Sullivan, 2011; Yeshurun & Sobel, 2010). Other parts of the brain receiving olfactory inputs include the hypothalamus, amygdala, hippocampal complex, and parts of the striatum and orbitofrontal cortex (Milardi et al., 2017; van Hartevelt & Kringelbach, 2012). Unlike the visual system, which has a loose hierarchy in the flow of signals from peripheral receptors in the retina to the early parts of visual cortex (e.g., DiCarlo et al., 2012; Felleman & Van Essen, 1991), the olfactory bulb projection neurons send signals broadly in parallel to these many different parts of the brain.[18]

2.3. Summary

We have discussed two computational architectures within the central nervous system that map incoming signals from the sensory surfaces of the body: one capturing the relationships of signals in space and another capturing the relationships of signals in time. The visual system is optimized for input array-to-target array spatial mapping, such that the spatial array of light frequencies and positions in the world maps to the sensory surface in the retina, whose signals synapse in the superior colliculus or the thalamus, then make their way to early visual cortex, creating multiple maps that preserve the spatial organization of signals (i.e., nearest-neighbors) in the retina. In the olfactory system, the spatial input array of molecular concentrations in the world does not map to the spatial array of target receptors in the olfactory epithelium, which in turn does not correspond to the spatial output array of glomeruli. Instead, the architecture is optimized for coding the temporal relationships between signals. Correspondingly, visual and olfactory systems differ in their manner of signal compression. Visual signals are compressed to some degree in the retina and in the structures where neurons of the optic tract first synapse, but a large portion of their compression occurs along an anatomical gradient within the cerebral cortex, with structures closer to the sensory periphery computing simple signal features and signals increasingly compressed as they flow from early visual areas forward. Olfactory signals, on the other hand, are primarily compressed close to the sensory periphery and broadcast those compressed signals widely.

3. Afferent vagus nerve anatomy and its implications for signal processing

In this section, we consider new evidence about the internal molecular and anatomical structure of the nodose fibers within the afferent vagus in light of the signal processing motifs discussed in the prior section. We consider the question of *if* and *how* viscerosensory signals are integrated and/or compressed, and whether the processing is spatial, temporal, or both by virtue of the internal structure of vagal afferent neurons and the architecture of the brainstem nuclei that process those vagal inputs. We then turn to new evidence on the structural arrangement of vagal afferent fibers into fascicles, or fiber bundles enclosed in a sheath of connective tissue. We consider evidence for several types of interactions that can occur across neighboring nerve fibers running within a single vagal fascicle (including ephaptic coupling, cross-depolarization, etc.) to suggest how the fascicular organization of the vagus might afford signal integration at points along its length, from rostral to caudal. Ultimately, we propose new hypotheses about the computational capacity of the vagus nerve in terms of its potential for signal integration even before signals arrive at the brainstem.

3.1. Molecular and structural gradients in the afferent vagus nerve and brainstem targets

For many years it was assumed that the nodose ganglion neurons, which originate the ascending fibers of the vagus, and the NTS, the main

[14] The dimensionality remains high when the odorant concentrations are very low (Burton et al., 2022) although it is unclear how to interpret this finding.

[15] For example, imagine olfactory sensory neurons scattered across the olfactory epithelium that express a specific olfactory receptor (receptor X) that is highly sensitive to olfactant A; these neurons will respond and signal their glomeruli with a relatively short delay. Olfactory neurons that express a different receptor (receptor Y) are less sensitive to olfactant A and will signal to their glomeruli later (e.g., Cleland, 2014; Cleland & Borthakur, 2020; Spors et al., 2006)

[16] Projection neurons vary in their morphological, biophysical, and molecular characteristics (a discussion of which is beyond the scope of this article, but interested readers are referred to Imamura et al., 2020; Manzini et al., 2022). They are considered the starting points for parallel pathways of olfactory signaling in the brain.

[17] An indirect pathway via the medio-dorsal nucleus of the thalamus also exists (Öngür & Price, 2000).

[18] There are notable violations of the visual hierarchy, however (e.g., Hegdé & Felleman, 2007).

target of vagal afferent signals, both contained viscerotopic maps of the internal milieu consisting of fine-grained, high-dimensional signaling of sensory events in specific locations of specific organs, similar to the retinotopic maps in the earliest parts of the visual processing stream – that is, a nearest-neighbor array-to-array map of the body corresponding to the tissues where the sensory signals originate (for the nodose ganglia; Browning & Mendelowitz, 2003; Zhuo, 1997; for the NTS; Altschuler et al., 1989; Dennison et al., 1981; Loewy, 1990). Strict viscerotopic organization in the nodose ganglion neurons and in the NTS (i.e., signals segregated by the specific location of each end-organ) has been called into question, however, by evidence arising from new methodological approaches that instead suggest that the afferent vagus is capable of both spatial *and* temporal co-occurrence mapping, without precise viscerotopy (see Box 1 for additional details).

Using a variety of methods and analysis techniques, Zhao et al. (2022) examined the architectural arrangement of the more than 14,000 nodose ganglia neurons in mice. Seven visceral organs were injected with specially designed viruses, each with their own unique genetic projection barcodes, to retrogradely trace neuronal connections. Bioinformatic methods clustered subpopulations of vagal sensory nodose neurons tagged with *Phox2b*+, a genetic marker specific to (and necessary for) embryological development of viscerosensory-visceromotor reflex arcs (Dauger et al., 2003). Differentially expressed gene (DEG) transcription factors were used in both wild-type and Cre-line mice to label specific subpopulations of nodose neurons. These combined methods revealed that ascending nodose ganglion fibers from the viscera were organized according to two genetically-coded molecular gradients.

The first gradient coded the locations of nodose sensory endings along the body's rostro-caudal axis. This gradient did not produce a strong nearest-neighbor organ-specific viscerotopic map, however. Nodose neurons were distributed very sparsely in a so-called "salt-and-pepper distribution" with minimal to no organ-specific clustering (and see Bassi et al., 2022, which showed no discernable organization of any sort within the nodose ganglia). A *very rough* mapping of organ location might exist, with the sensory conditions of the more rostral organs like the heart and lungs somewhat spatially separated from the sensory conditions of more caudal organs like the colon, duodenum, and pancreas (see also Jayaprakash et al., 2023). Vagal afferent neurons innervating rostrally located organs (like heart and lungs) also maintain greater segregation from one another than do the neurons innervating the more distal organs, implying that the sensory signals informing on the metabolic and other sensory conditions of the heart, lungs and airways, pharynx, larynx and upper esophagus may be relatively more distinct (e.g., baroreceptor afferent signaling, see Andresen & Peters, 2008; or afferents in the cardiac nerve; see Jayaprakash et al., 2023), whereas the sensory signals informing on the metabolic conditions of the lower esophagus, stomach, intestines, and liver may be compressed into summaries (Jayaprakash, et al., 2023). Moreover, more caudally arising signals are more likely to influence rostral ones than vice versa simply due to the arrangement of fibers. The second "tissue layer" gradient, orthogonal to the first, coded the locations of nodose sensory endings across a gradient from the inner (lumenal or mucosal) organ layer to the outer (muscular) organ layer. Based on their findings, Zhao et al. (2022) concluded that afferent vagal fibers create a loose spatial map of sensory signals from the viscera but does not afford sufficient spatial segregation to be considered a viscerotopic map.

Zhao et al. (2022) interpreted their findings in terms of the organ and tissue locations they observed in the adult animals they studied, but we hypothesize that the gradients they observed might be best understood in terms of their developmental origin as they are laid down during embryonic development. Specifically, both of their observed molecular gradients bear a strong resemblance to the highly conserved molecular polarities that are organized from HOX genes during vertebrate embryonic development (for a discussion see Stiles, 2008 and references therein). These gradients are established when the embryo's organs are not yet in place. By implication, the ascending fibers of the vagus nerve may be organized by the embryonic birthday of the nodose ganglion cells from which those sensory fibers arise (i.e., chronotopy) in a manner similar to what has been observed in the optic tract, rather than by the organ-related signals they carry. These gradients within the ascending vagal fibers appear to be insufficient to produce a strict nearest-neighbor array-to-array end-organ (viscerotopic) map in their termination sites just as the chronotopic organization of the optic tract is insufficient for creating retinotopic maps in the superior colliculus and thalamic nuclei. Those structures develop retinotopic maps by other means (i.e., gradient mapping), but this did not appear to be the case in the NTS. The absence of a clear viscerotopic map in the NTS was empirically confirmed by Zhao et al. (2022; also see Andresen & Paton, 2011; Bassi et al., 2022; Cutsforth-Gregory & Benarroch, 2017). Another study (Ran et al., 2022, discussed in more detail below) using *in vivo* calcium imaging in mice, did observe something like a rostro-caudal gradient in the NTS, however, see Box 1. One opportunity for future research might involve assessing the hypothesis that embryological chronotopy is a major driving force for the spatial location of visceral organs, the spatial organization of the nodose ganglia and their afferent vagal fibers, and the termination of those fibers in their brainstem targets like the NTS.

In addition to the spatial gradients, a third genetic gradient using yet another method was observed in the organization of nodose axons as they synapsed on their brainstem targets (Zhao et al., 2022). Using specific types of Cre mice bred for specific conditional knockouts of specific types of tissue, highly specific anterograde tracers were injected into regions of visceral organs that contained nodose ganglion sensory nerve endings, thereby tracking vagal afferent pathways for 11 different nodose neuron subtypes to their termination sites in the NTS, AP and the DMV. In addition, nerve endings in visceral organs were stimulated via different modalities (e.g., by stretch (inflation) of the lungs or stomach, or by chemical stimulation such as delivering nutrients, salt, or water to the lumen of the intestines) during calcium imaging.[19] These investigations revealed that the genetically distinct nodose cell subtypes coded for modality (chemo-, mechano- or osmoreception) across different visceral organs in a many-to-many pattern reminiscent of the combinatorial receptor coding observed in the olfactory epithelium. Each stimulus modality (e.g., mechanostimulation) activated a pattern across multiple nodose cell subtypes, and each subtype was stimulated by more than one modality. For example, pulmonary stretch produced a fast but sustained signal in one cell subtype but a transient response in another cell subtype. On the other hand, the same cell subtype that showed a transient response during pulmonary stretch was also responsive to stretch stimuli in other organs as well as to chemical stimulation in the intestines. Interestingly, nearly every one of the 11 nodose neuron subtypes projected to multiple subnuclei of the NTS, and most subnuclei of the NTS, as well as other nuclei in the brainstem (i.e., DMV, AP) received convergent inputs from multiple different nodose neuron subtypes, recapitulating a combinatorial pattern that results in temporal co-occurrence maps for different types of sensory change across organs and tissues in the body. Temporally correlated signals of any specific modality (chemical, mechanical, etc.) across multiple organs are processed as a pattern of activation across nodose cell subtypes, with each pattern reaching partially overlapping targets in the

[19] Zhao et al. developed a novel method they called "vagal calcium imaging transformed fluorescence in situ hybridization' (vCatFISH)" (See their Fig. 3a). In brief, they first imaged in vivo the neuronal activity of hundreds of nodose afferent neurons while they stimulated an organ or organ regions, including (in different animals), lung inflation, esophagus and stomach stretch, intestinal stretch, and chemical stimulation of the intestinal lumen by water, salt, nutrient or acid. Then using Cre-line mice that expressed specific genetic markers, post-sacrifice of the animal they identified the nodose neurons using 21 marker genes to identify neuronal subpopulations (see their Extended Data Fig. 9a–d). Finally, labeled cells served as landmarks to co-register nodose neurons from the two separate analyses (See their Extended Data Figs. 9e, 10a).

Box 1
A possible rostro-caudal specificity gradient in brainstem nuclei.

The NTS has at least 10 subnuclei that are often divided into rostral, intermediate, and caudal divisions (e.g., McRitchie & Törk, 1993). Rostral NTS subnuclei receive afferent vagal fibers from more rostrally located tissues, which are relatively segregated by specific organ (tongue/-epiglottis and pharynx; e.g., Altschuler et al., 1989; Kalia & Mesulam, 1980b). Intermediate and caudal NTS subnuclei receive intermingled afferent vagal fibers from more caudally located tissues, with less specificity in their spatial array (e.g., heart, lungs, GI tract; for reviews and further discussion, see Andresen & Paton, 2011; Cutsforth-Gregory & Benarroch, 2017; Neuhuber & Berthoud, 2022; Paton, 1999). Many of these studies were conducted with horseradish peroxidase as a labeling method. In contrast, a more recent viral mapping study traced connections along vagal afferent fibers and found virtually no spatial specificity in the NTS (Bassi et al., 2022). Yet another study, which used two-photon calcium imaging replicated the rostro-caudal specificity gradient when examining NTS neuron responsivity to organ stimulation (Ran et al., 2022, also described in the main text). It is possible that the inconsistent results are due to differences in methodology.

A rostro-caudal specificity gradient has also been observed, albeit with some caveats, in the efferent fibers arising from nAmb (e.g., described in Neuhuber & Berthoud, 2022). The nAmb contains a dorsal subdivision and a ventrolateral subdivision (as discussed in the section entitled "*A Brief Overview of the Vagus and its Brainstem Targets*"). The dorsal subdivision gives rise to efferent fibers that innervate the most rostrally located organs (e.g., pharynx, larynx, upper esophagus) with relatively high spatial segregation (e.g., Bieger & Hopkins, 1987). The ventrolateral subdivision gives rise to visceromotor efferent fibers that innervate the relatively more caudally located heart and lungs (e.g., Hopkins & Armour, 1998). These efferent fibers are relatively more intermingled with one another than the efferent fibers arising dorsally but are nonetheless themselves arranged along a loose rostro-caudal gradient with pulmonary neurons clustered rostrally and cardiac neurons arranged more caudally (Hopkins & Armour, 1998; Hsieh et al., 1998; McAllen & Spyer, 1978). Other evidence suggests that the cardiac and pulmonary vagal efferents arising from the nAmb may be further organized by cardiorespiratory function (Gatti et al., 1996; Massari et al., 1995; Veerakumar et al., 2022).

The DMV sends efferent visceromotor projections to organs along the rostro-caudal axis of the body from esophagus to colon (e.g., Huang et al., 1993; Karim et al., 1984; McLean & Hopkins, 1985a; Mussa & Verberne, 2013), but no conclusions can be drawn about organizing gradients, given the extensive species-related differences in the architecture of the visceromotor efferents to the more caudal organs in the body – the abdominal viscera, including the GI tract and pancreas (Huang et al., 1993). For many years, researchers segmented the DMV in rodents into a series of columnar subnuclei, with each column corresponding to each of the five subdiaphragmatic vagal branches (anterior gastric, posterior gastric, hepatic, celiac, and accessory celiac; e.g., Fox & Powley, 1985; Norgren & Smith, 1988). However, these columnar subnuclei are not viscerotopically arranged, as there is not a one-to-one mapping between subdiaphragmatic vagal branches and visceral organ (e.g., Berthoud et al., 1991). Rather, most studies have found that abdominal vagal projections, particularly those to the stomach/gut, are arrayed across the entire length of the DMV rather than being clustered in close spatial proximity (Kalia & Mesulam, 1980a; Karim et al., 1981; Leslie et al., 1982; McLean & Hopkins, 1985a). Furthermore, they may be organized functionally (e.g., Tao et al., 2021) in a manner similar to the ethological maps described by Graziano (Graziano, 2016) for the motor cortex.

As we have previously noted, the DMV also receives some direct vagal afferents, in addition to sending vagal efferents to the viscera (e.g., Kim et al., 2020). There is some rostro-caudal patterning in vagal afferents to the DMV of the rat (Kalia & Sullivan, 1982) and cat (Kalia & Mesulam, 1980a,b), such that afferent vagal terminals from the nodose ganglion were segregated to one side of the DMV at the rostral end (ipsilaterally; only the right nodose ganglion was injected with the tracer; Kalia & Sullivan, 1982), while vagal afferents were more bilaterally distributed, and with greater density, throughout the DMV at the caudal end (Kalia & Sullivan, 1982; Neuhuber & Sandoz, 1986).

brainstem. Again, this mapping represents different sensory modalities rather than segregated, spatially organized viscerotopic maps in the brainstem (for additional viral mapping evidence consistent with temporal mapping, see Bassi et al., 2022; Neuhuber & Berthoud, 2022, p. 4).

The compression of multiple modalities of viscerosensory signals from certain organs appears to occur in the NTS (Ran et al., 2022, mentioned above). *In vivo* calcium imaging in mice enabled real-time analysis of thousands of NTS responses to ascending vagal inputs. NTS neurons were observed to be more broadly tuned to different signal modalities coming from the same organ (e.g., the larynx or the duodenum) than were the nodose neurons that sent the ascending signals, as indicated in Zhao et al. (2022), indicating a convergence (i.e., compression) of sensory signals from nodose neurons to NTS neurons (see Box 1 for additional details).

Taken together, these findings suggest the hypothesis that afferent vagal fibers organize sensory signals from the viscera in space (possibly according to embryonic gradients rather than specific viscerotopy) and time. The ascending viscerosensory signals have a multidimensional coding architecture that enables the "massively parallel presentation of interoceptive signals in an efficient manner" (Zhao et al., 2022, p. 6) but without evidence of specific maps of specific visceral organs. By combining across signals from tissues according to rostro-caudal location, inner layer-outer layer position, and modality of sensory stimulation, vagus neurons relay signals to brainstem targets in a way that indicates particular types of sensory signals at one time within larger regions of the internal milieu (e.g., the abdomen) rather than pinpointing changes in specific locations within specific organs. Correspondingly, maps within the NTS suggest the possibility of similar gradients for space and time, with minimal evidence for any specific nearest-neighbor array-to-array mapping but some for a possible rostro-caudal gradient. Rostro-caudal gradients are a possible organizational theme present in the nodose neurons and in the brainstem, across both afferent and efferent brainstem nuclei: NTS, AP, nAmb, and potentially even the DMV (see Box 1). We now turn to the fascicular organization of vagal fibers throughout the nerve trunk to elaborate on these hypotheses further, and to understand whether a similar rostro-caudal gradient exists within the vagus nerve itself.

3.2. *A "split and merge" fascicular organization within the afferent vagus nerve*

The afferent fibers of the vagus nerve that ascend through the nodose ganglia are arranged into fascicles, each of which is surrounded by its own connective tissue sheath called a perineurium. In a recent study in swine (which have similar vagal anatomy to humans; Pelot et al., 2020; Settell et al., 2020), afferent vagal fibers tended to segregate into organ-specific fascicles as they leave the tissues of the body, with progressively more merging of fibers from different organs into the same fascicles as signals ascended rostrally (Jayaprakash et al., 2023). A recent study in human vagus observed considerable merging and

splitting along the mid-cervical vagus, beginning rostrally at the nodose and terminating caudally at the level of the clavicle — vagal fibers running within one fascicle split off from that fascicle and merged with vagal fibers in another fascicle, approximately every ~560 μm, along the entire length of the cervical vagus (Upadhye et al., 2022). This "split and merge" architecture occurred regardless of fascicle diameter, or the diameter of fiber types carried within, suggesting a remarkable degree of fiber re-organization within fascicles as viscerosensory signals ascend to the nodose. Because Upadhye et al. (2022) examined only a 5 cm section from the middle of the cervical vagus, it will be important for future studies to examine whether the "split and merge" pattern holds across a longer swath of the vagus nerve (e.g., subdiaphragmatic vagus). The fact that vagal fibers carrying ascending viscerosensory signals assume new spatial configurations relative to one another within fascicles as they merge and split, at least in the cervical and thoracic vagus, suggests possible signal integration as the axons arise toward the nodose ganglion. This possibility is made even more likely by the observation that axons, including those in peripheral sensory nerve bundles, can dynamically modify the signals they carry in a variety of ways, a point to which we now turn.

3.2.1. *Possible ephaptic coupling within fascicles of the vagus*

The high frequency of fascicular splits and merges along the vagus may provide opportunities for axonal 'crosstalk' or ephaptic signaling, whereby spatially contiguous axon fibers modulate one another's activity (Katz & Schmitt, 1940; Ramon & Moore, 1978), an idea first suggested by Carvalho & Damasio (2021); Damasio & Carvalho (2013). In brief, neuronal action potentials generate extracellular local field potentials that can influence the excitability of nearby axons that are not in direct contact by synapses or gap junctions (e.g., Binczak et al., 2001; Clark & Plonsey, 1970), and these effects are thought to be especially likely between nearby unmyelinated fibers (e.g., Hartline, 2008). Importantly, a large proportion of vagal axons are unmyelinated (85% of fibers in the cervical vagus and nearly all (99%) in the abdominal vagus; Havton et al., 2021), providing considerable possibilities for ephaptic effects.

The hypothesis of ephaptic coupling in the vagus remains, to our knowledge, untested, but ephaptic interactions have been demonstrated in the mammalian olfactory nerve, which is composed of unmyelinated, densely packed axons, where all axons within a fascicle influenced one another, as did axons in neighboring fascicles (Bokil et al., 2001). Ephaptic interactions have also been observed between axons in the myelinated dorsal root and sciatic nerve fibers in intact rat nerve tissues (i.e., in the absence of any injury that disrupts myelin; Bolzoni & Jankowska, 2019). The majority of evidence for ephaptic signaling, however, comes from the study of neurons in cortical areas in rodents (e.g., Anastassiou et al., 2011; Blot & Barbour, 2014; Han et al., 2018, 2020; Qiu et al., 2015; Taylor & Dudek, 1982; reviewed in Anastassiou & Koch, 2015), studies of unmyelinated nerves of various invertebrates (Arvanitaki, 1942; Katz & Schmitt, 1940; Ramon & Moore, 1978), and mathematical models showing that adjacent myelinated axons within the same fiber bundle produce local phase-locking between action potentials (Arvanitaki, 1942; Binczak et al., 2001; Capllonch-Juan et al., 2017; Capllonch-Juan & Sepulveda, 2020; Marrazzi & de No, 1944; Schmidt & Knösche, 2022) or ephaptic coupling between unmyelinated fibers (e.g., Barr & Plonsey, 1992; Clark & Plonsey, 1970).

Some models have shown that greater fiber density within a fascicle increases the strength of ephaptic coupling, although greater heterogeneity of axon diameters within a fascicle can reduce ephaptic interactions (Capllonch-Juan & Sepulveda, 2020; Schmidt & Knösche, 2022). Such findings are potentially relevant for testing hypotheses about ephaptic coupling in the ascending vagus given the extensive variability in fascicular size and composition observed in both light- and electron-microscopic assessments of well-preserved human cervical and abdominal vagus samples (from 27 middle-aged donors undergoing organ harvesting at brain death; Havton et al., 2021). Specifically, many vagal fascicles contain a heterogeneous mix of axon diameters and myelination, with unmyelinated afferents distributed throughout, whereas other fascicles contain axons segregated by diameter and myelination (Jayaprakash et al., 2023), suggesting the possibility that ephaptic coupling effects might be uneven or patterned along the length of the ascending vagus. Greater ephaptic coupling might occur within fascicles that contain a more homogeneous distribution of fiber diameters, especially when many of those fibers are unmyelinated. In addition, ephaptic signaling is plausible even between nodose fibers that make up the more caudally-located ascending axons (from organ to ganglion), since ephaptic signaling also has been documented to occur between dendrites as well as axons (Han et al., 2018; Yip & Heiman, 2018). More generally, ephaptic coupling may contribute to synchronizing the independently generated cardiorespiratory rhythms of the heart and lungs, peristalsis in the gastrointenstinal (GI) tract, longer-scale circadian and ultradian rhythms, and so on (in addition to the usual sources of synchronization, such as descending visceromotor, peptidergic and hormonal influences).

Together, this evidence suggests that ephaptic coupling is a viable hypothesis for signal processing within the vagus nerve. If ephaphtic coupling is indeed a source of non-synaptic communication in vagal fascicles, then axons carrying signals from different tissues, organs, or stimulus modalities may effectively modulate one another as they ascend the vagal trunk. Furthermore, it is unclear whether ephaptic coupling could mitigate or enhance the rostro-caudal gradient of signals that we have previously described. Going forward, an imporant piece of any empirical work will be considering whether ephaptic coupling contributes to these gradients.

3.2.2. *Possible afferent and efferent signal interaction within the fascicles of the vagus*

As we noted in the first section of this paper, the vagus is often referred to as a "mixed" nerve because it carries both afferent (viscerosensory) fibers from the periphery to the brain (80%) and efferent (parasympathetic motor) fibers with signals moving the other direction (20%). In swine (e.g., Jayaprakash et al., 2023), ascending sensory fibers and descending motor fibers can be found within the same fascicles with varying degrees of myelination, suggesting opportunities for afferent signals to be influenced by efferent signals even before they reach the nodose ganglion or their brainstem targets, and correspondingly, for afferent signals to influence efferent signals before they reach their target tissues.[20] In other words, there may be sensorimotor signal integration, not just in the brain, but also along portions of the vagus nerve. Such a possibility is consistent with evidence of signal integration in other parts of the peripheral nervous system, such as the enteric nervous system (Fung & Vanden Berghe, 2020), where interactions between the vagal mechanosensory nerve endings in the GI tract and the myenteric ganglia (e.g., Neuhuber, 1987) suggest peripheral integration of vagal afferent signals even before those signals ascend in the vagus. If ascending signals have been modulated within the fascicles of the vagus by descending signals, then they may not, strictly speaking, be exclusively sensory by the time they reach the brainstem. Any signal integration in the vagus nerve, if it exists, would contribute to the extensive signal integration already known to occur in the brainstem nuclei (see Box 2; e.g., Ran et al., 2022), midbrain (e.g., Llewellyn-Smith & Verberne, 2011; Saper, 2002), and forebrain.

A familiar rostro-caudal gradient characterizes fiber mixing within fasciculi, such that ascending and descending fibers are relatively more segregated in rostral fascicles but converge more extensively within caudal fascicles (Jayaprakash et al., 2023). Correspondingly, the potential for efferent modulation of vagal afferent signaling may also vary along this gradient, since there is less mixing of afferent and efferent

[20] One human vagus nerve was also examined, and the authors reported seeing a similar pattern to what they reported in swine.

Box 2
Afferent/Efferent Integration in the Brainstem.

The DMV both receives direct vagal afferent fibers and sends visceromotor efferent fibers via the vagus (e.g., Kim et al., 2020; Neuhuber & Sandoz, 1986), making this brainstem nucleus a site for sensorimotor integration on its own. AP is also a site for sensorimotor integration. It receives a direct viscerosensory input from vagal neurons and expresses receptors for multiple peptides and hormones in the periphery (that arrive via fenestrated capillaries, which line the cerebral ventricles; see Cottrell & Ferguson, 2004; Price et al., 2008); these chemicals are considered motor signals. More broadly, the architectural connections among the DMV, AP, NTS, and nAmb facilitate integration between interoceptive and visceromotor signals from the vagus nerve as well as chemical motor signals circulating in the blood. The NTS, which receives direct vagal afferent signals, also contains DMV dendrites (Miselis & Shapiro, 1983; Shapiro & Miselis, 1985a) allowing for transmission of interoceptive signals to the DMV (in addition to the direct viscerosensory signals it receives from the vagus). The NTS also receives axons from AP, which as we just noted, carry interoceptive signals modulated by chemical motor signals. By virtue of these AP connections, the NTS can be considered a site of sensorimotor integration. In addition, AP signals influence the DMV, not directly (as it does not robustly connect to the DMV directly), but via its axons that terminate near or at the location of DMV dendrites in the NTS (e.g., Cunningham et al., 1994; Shapiro & Miselis, 1985a, 1985b).

fibers within fascicles of the more rostral vagus targeting the heart, lungs, and airways, but extensive mixing of afferent and efferent vagal fibers in more caudal vagus targeting the liver, stomach, and intestines. This pattern parallels the viscerosensory and sensorimotor convergence observed in brainstem nuclei, including the NTS, AP and even the DMV and nAmb (see Boxes 1 and 2). Moreover, the organizational arrangement of fascicles in the vagus also would suggest that intermixing of sensorimotor signals arising within the caudal vagus would necessarily influence more rostral signals.

3.3. *Possible asynaptic chemical modulation of signaling by glial cells within the nodose ganglia*

Yet another possible opportunity for signal processing within the vagus nerve comes from evidence of asynaptic chemical modulation of the nodose ganglion cells by specialized glia called satellite glial cells. Satellite glial cells support the metabolic function and transmission of sensory neurons in peripheral ganglia. A small number of satellite glial cells surround each cell body and as well as the neuron's axons, and neuron-specific communities of satellite glial cells communicate very rapidly with one another, quickly altering neuronal signal transmission (Hanani & Spray, 2020). Most of what is known about how satellite glial cells impact sensory neurons has come from studies of their role in chronic pain after different kinds of peripheral nerve injury (e.g., Dublin & Hanani, 2007; Feldman-Goriachnik & Hanani, 2021). In mouse models of systemic inflammatory pain, for example, satellite glial cells in the nodose ganglia upregulate the expression of a gene that creates membrane channels, thereby allowing for the release of ATP and a resulting increased sensitivity to ATP, which contributes to increased intercellular communication and hyperexcitability of neurons in the periphery (Feldman-Goriachnik et al., 2015).

Communities of neuron-specific satellite glial cells also surround each nodose ganglion cell (Hanani, 2010; Hanani & Spray, 2020). Cell bodies in the nodose ganglion appear to influence one another via non-synaptic means (using neurotransmitter diffusion to facilitate asynaptic cross-depolarization, which refers to the increased spike probability in the soma of some cells when the axons of neighboring cells fire repeatedly). This suggests the possibility of yet another source of signal processing, in this case within the nodose itself (Oh & Weinreich, 2002). If the satellite glial cells of the nodose ganglia function similarly to satellite glia around other peripheral sensory ganglia, then these cells also could broaden the possibilities for signal integration by supporting and potentially even augmenting non-synaptic chemical communication occurring between cell bodies in the nodose,[21] although the extent to which this sensory integration would target spatial, temporal, or both types of coding remains to be seen.

3.4. *Summary*

The signals that flow up the individual fibers of nodose ganglion neurons result in two spatial gradients, one rostral to caudal (with respect to the spatial positioning of organs along the long axis of the entire body) and one from inner to outer layer of an organ, plus one sensory modality gradient that maps the temporal co-occurrences in the same modality of signals across organs and tissues. Interestingly and perhaps importantly, some of the signal processing within the vagus is likely occurring within *individual nodose neurons*. Based on the totality of this evidence, we hypothesized that viscerosensory signals are processed and, in some cases, compressed both spatially and temporally by virtue of the internal structure of vagal afferent neurons and the architecture of the brainstem nuclei that receive vagal afferents. Multimodal compression across signals and tissues appears to occur in the NTS, and not in the nodose ganglion neurons themselves (see Box 1). One hypothesis for future research is the idea that this two-dimensional (rostro-caudal and inner-outer layer) spatial organization of viscerosensory signals may arise from chronotopic polarities that set up gradient-matching – genetically-expressed guidance molecules that allow peripheral processes of the nodose to find their tissue targets as the nervous system is assembling itself during embryological development well before visceral organs have even formed. The degree of rostro-caudal organization of

[21] Empirical work in animals (e.g., Nassenstein et al., 2010) suggests that the nodose and jugular ganglia are fused in rodents (rats and mice), not separate as they are in humans (and also separate in embryological chicks; Baker, 2005). This may be important because if our hypothesis about signal integration via non-synaptic communication in the nodose is correct, then there is more potential for signal integration in rodents between the fibers making up the nodose (which are visceral sensory only and derived from the placodes embryologically) and those making up the jugular ganglion (which are strictly somatic sensory and derived from the neural crest embryologically), than potentially would be possible in humans (since these two ganglia are anatomically more separate in humans).

vagal afferents in the NTS, perhaps by gradient matching, would also be interesting and important to explore.

Furthermore, we hypothesized that some degree of sensorimotor integration, another type of signal processing, may be possible within the vagus nerve itself, blurring the line between afferent and efferent signals that are propagated along the nerve fibers to and from the sensory organs and brainstem targets. Various studies of asynaptic interactions (i.e., ephaptic signaling, cross-depolarization, and satellite glial hyperexcitation in nodose cell bodies) across adjacent peripheral nerve fibers suggest that this hypothesis is at least physiologically plausible, although the extent to which these interactions occur in the vagus nerve itself is a matter for future empirical study. In the next and final section, we consider several biological and psychological implications that would arise if these hypotheses were supported by future work on the computational capacity of the vagus nerve. We also address current barriers needing resolution and measurement tools required to test these hypotheses, which are aimed at better understanding signal processing in the vagus (see Box 3).

4. Implications and future directions

4.1. Signal processing gradients in the ascending vagus: implications for allostasis

Before we dive into the implications of the material we've discussed so far, it is necessary to provide a bit of background about signal processing throughout the brain. The framework that we outline below belongs to a larger, mathematically formalized, neuroscience-inspired account referred to as predictive processing (e.g., Clark, 2013; Keller & Mrsic-Flogel, 2018; Rao & Ballard, 1999). We start with a brief overview of predictive control of skeletomotor movements to motivate our discussion of allostasis, which is the predictive control of the visceromotor movements of the body.

For many years, it was assumed that the brain created a somatotopic array of muscles and appendages as elemental building blocks for skeletomotor movements. Primary motor cortex, for example, was thought to contain such a map, with feet represented at the top of the precentral sulcus and the tongue at the bottom. More recent discoveries vigorously challenge this idea, however, and instead suggest that primary motor cortex, as well as premotor cortices, appear to be mapping movement ensembles that are fundamentally rooted in the spatial and temporal statistics of ethologically meaningful behavior (Coffman et al., 2011; Gordon et al., 2023; Graziano, 2016, 2023 and references therein; Levinthal & Strick, 2020). The sensory features of the environment are integrated as part of these maps (e.g., Rizzolatti & Strick, 2013) in a way that accounts for the current sensory state of the animal's body (Dum et al., 2016; Herzfeld & Shadmehr, 2014; Levinthal & Strick, 2012, 2020).

The mechanical requirements for executing a specific set of muscle movements are never perfectly predictable, making stored patterns of precise neuromuscular activity triggered from fixed, preprogrammed circuits ill-suited to the task of skeletomotor control. It is now increasingly accepted that the specifics of skeletomotor movements are constructed, as needed, from these maps of ethologically meaningful behavior in a complex combinatorial fashion (e.g., Flash & Bizzi, 2016; Mussa-Ivaldi & Bizzi, 2000; for a discussion and additional references, see Barrett & Finlay, 2018). Movements are assembled (probabilistically and inferentially) in a signal processing hierarchy that spans the cerebral cortex to the ventral horn of the spinal cord.

Pre-motor and primary motor cortices assemble an ensemble of signals for ethologically meaningful behavior as abstract features; these are typically referred to as a "plan" or a "goal", to indicate their abstraction away from motor particulars (Graziano, 2016; Rizzolatti & Strick, 2013). However, we have described them as an action concept – integrated, compressed multimodal signals that plan action in a particular context (Barrett, 2017; Barrett & Finlay, 2018). These plans are low-dimensional summaries of sensorimotor signals (see section *"Signal Processing Motifs in the Nervous System"*) corresponding to the statistical relationships in spatial and temporal patterns of activity that have been compressed across multiple modalities. These summaries correspond to motor control signals or motor reference signals in the systems control literature. To be implemented as actual movements, these summaries must be decompressed (probabilistically and inferentially) to recruit ever more specific neural assemblies as the signals cascade through the midbrain and brainstem. Ultimately, they are particularized at greater spatial and temporal specificity in modules of the ventral horn of the spinal cord that implement the signals for a specific pattern of muscle fiber activity and joint angles (Flash & Bizzi, 2016; Mussa-Ivaldi & Bizzi, 2000). This cascade of assemblies at ever-greater particularization proceeds in a generative way that is more flexible and functional than what could be accomplished with pre-set motor programs. Flexibility and robustness derive not only from which action is executed, but also *how any given action is achieved* via a specific pattern of muscle contractions and joint angles in the spinal cord (for further discussion and references, see Barrett & Finlay, 2018). Even the 'reflexes' that are present in spinal cord circuits and pattern generators in the brainstem are flexibly modulated in a context-dependent way via this architecture (e.g., Bhattacharyya et al., 2012; Pearson & Gordon, 2014).

Action concepts are thought to control motor movements by prediction rather than reaction, embodying the inferred causal relationships between potential future actions and their expected sensory consequences (e.g., Lochmann & Deneve, 2011; Shadmehr et al., 2010; Wolpert et al., 2013).[22] They are the brain's best guess, generalized from past experience, as to which actions will be most functional in a given context and how those actions can be most efficiently implemented in that context. The cascade of signals that are decompressed from cortex to spinal cord are effectively inferences that predict forward in time and space, to anticipate how the motor system's state will change as a function of the motor commands. These cascading signals also infer the expected sensory consequences of those motor movements. In this way of understanding skeletomotor control, incoming signals from the sensory surfaces of the body do not trigger motor responses anew, but rather are modulatory signals that serve upcoming motor control. They either confirm the sensory prediction signals (and the associated skeletomotor plans from which those sensory predictions arose) or correct the prediction signals. It is hypothesized that incoming signals from the sensory periphery are compared to prediction signals at every synapse (Deneve, 2008) along the various processing gradients within the brain.[23] Within each gradient, the ascending signals closer to the sensory periphery are higher in dimensionality with a specificity that is closer to the signals from the receptor cells in those sensory surfaces; these signals become increasingly compressed into summaries of lower dimensionality as they flow to the limbic portions of the cerebral cortex (either as they ascend from the brainstem or flow from primary sensory areas along the main architectural gradient of the cortex; see section *"Signal Processing Motifs*

[22] Prediction signals are generatively constructed using memory – alternatively described as an "internal model" (e.g., Berkes et al., 2011), "top-down" processing (e.g., Friston, 2010; Jordan & Keller, 2020; Rao & Ballard, 1999), a "forward model" (e.g., Wolpert et al., 1998), or "feedback" signals (e.g., Lamme & Roelfsema, 2000). Prediction signals are thought to be weighted by their estimated value to explain the incoming sense data (i.e., as prior probabilities; Barrett, 2017; Feldman & Friston, 2010; Kanai et al., 2015; Katsumi et al., 2022, 2023).

[23] *Prediction errors* (or "bottom-up" processing, or "feedforward" signals) that are computed as the differences between sensory prediction signals and incoming sensory signals from the body's sensory surfaces. Prediction errors are potential teaching signals, but their capacity to update predictions is thought to depend on how they are weighted by precision signals, which are interpreted as the predicted value of the allostatic information they will provide (i.e., salience; for discussion and references, see Barrett, 2017; Katsumi et al., 2022, 2023; Parr & Friston, 2019).

Box 3
Methodological Considerations for Measuring the Vagus Nerve.

Vagal activity following metabolically significant events has been recorded using denoised compound action potentials, which represent the cumulative firing activity of multiple vagal fibers (Chang et al., 2020; Zanos, 2019). These measures might provide a future avenue for empirically testing hypotheses about the existence of visceromotor motifs and their relation to temporal coding. For example, compound action potentials recorded from the vagus nerve reflect events that were observed to correspond to changes in blood glucose levels (Zanos, 2019) and cytokine levels (Steinberg et al., 2016; Zanos et al., 2018). Blood glucose level is a highly relevant metabolic signal and likely to be represented across multiple organs of the body, suggesting the possibility that compound action potentials communicate multi-organ, temporally-concordant changes in blood glucose levels. If so, this may reflect the vagus nerve compressing temporal redundancies in the afferent signals that are important for the sensing and control of blood glucose. However, compound action potentials are notoriously prone to sources of electrical noise and measuring them in an animal requires anesthesia, which can confound the recording and interpretation of waveforms (e.g., Silverman et al., 2018). Recent work also has demonstrated the feasibility of single-unit recordings in the vagus nerve of awake humans (guided by microneurography) from both afferent and efferent fibers (Ottaviani et al., 2020). Once the technical demands of these newer methods have been reduced and some limitations addressed (building off existing work by Silverman et al., 2018 and Zanos, 2019), many of the hypotheses proposed here potentially could be tested, including whether the afferent and efferent signals in the vagus are modulating one another within fascicles.

in the Nervous System").

There are many reasons to hypothesize that visceromotor control works in a similarly complex, combinatorial, and predictive manner (including evidence from evolution and embryological development, as well as overlapping architecture throughout the brain discussed below). In the visceromotor domain, this predictive control is called allostasis – anticipating the body's metabolic needs and preparing to meet those needs before they arise (e.g., Sterling, 2012). Allostasis is one of the brain's core functions (for discussion of converging evidence, references with additional details and complementary views; see the following and references therein: Barrett, 2017; Barrett & Simmons, 2015; Chanes & Barrett, 2016; Hutchinson & Barrett, 2019; Katsumi et al., 2022, 2023; Kleckner et al., 2017; Schulkin & Sterling, 2019; Sterling & Laughlin, 2015). By implication, the brain appears to be mapping allostatic ensembles that are fundamentally rooted in the spatial and temporal statistics of ethologically meaningful behavior, as occurs in the skeletomotor domain, rather than attempting to separately control individual visceral organs or tissues. Consistent with this hypothesis, primary motor cortex and premotor cortex, which implement functional skeletomotor ensembles also implement maps of the viscera (e.g., Dum et al., 2016; Levinthal & Strick, 2012, 2020) and some of the functional movement ensembles described in primary motor cortex involve visceromotor components (see Graziano, 2016). In addition, a key premotor cortical area, the aMCC, is a primary site for visceromotor control via its connection to sgACC and pACC via the cingulum bundle (e.g., Vogt, 2016; Vogt et al., 2003). Such findings suggest that the cingulate cortex is involved in coordinating visceromotor movements and the skeletomotor movements that they support.

In this processing context, the gradients in the nodose ganglion and its brainstem targets seem to underscore the idea that allostasis may be *coordinating* tissue changes across the body prior to further processing and integration beyond the brainstem. Such coordination is consistent with Peter Sterling's notion of allostasis as "stability through change," whereby a physiological system need not achieve stability by regulating back to specific set points or reducing metabolic costs per se, but rather by coordinating its various parts to maximize metabolic efficiency (e.g., Sterling, 2004; 2012). A corresponding hypothesis is that poor coordination in the face of changing energetic circumstances may be an indicator of dysfunction that could be associated with physical illness or mood symptoms.

Even at the level of the brainstem nuclei where prediction signals descending from the forebrain and midbrain meet sensory signals ascending from the nodose that inform on the metabolic conditions of the body's internal milieu, there seems be relatively little spatial specificity like that achieved with nearest-neighbor array-to-array mapping, as in vision and audition. One possibility is that high-dimensional viscerotopic specificity, if required for allostasis, can be computed on the fly. Alternatively, the rostro-caudal gradient in spatial specificity in the nodose ganglia (e.g., Jayaprakash et al., 2023; Williams et al., 2016; Zhao et al., 2022) suggests that such specificity may not be required to accomplish all aspects of allostasis – knowing when and approximately where a sensory change is occurring may be sufficient for some regions of the periphery (e.g., the GI tract), whereas other organs may evidence greater specificity (e.g., heart and lungs).

The hypothesis that visceromotor control is, like skeletomotor control, combinatorial and predictive is also consistent with empirical evidence that signals from visceral organs array into reliable and repeatable physiological "motifs" (Feng & Narayanan, 2019; Hoemann et al., 2020), just as there are signals from voluntary (skeletomotor) movements and behavioral "motifs" (Brown et al., 2013; Datta et al., 2019; Grover & Tavare, 2009; Luxem et al., 2022; Robie et al., 2017). A motif is a repeating ensemble of observed signals that can be statistically summarized by a pattern of lower dimensionality, such as the high-dimensional multitude of muscular movements and vascular control required for a person to raise their arms above their head. We hypothesize that different physiological or behavioral motifs begin in the brain as a compressed, multimodal action concept (where here, we mean 'action' in both the skeletomotor and visceromotor senses). Our lab has recently documented individual-specific, recurrent patterns of signal change across multiple physiological measures in humans; these patterns reflect the visceromotor (here, cardiovascular and hemodynamic) changes that support mental experiences and behavior in daily life (Hoemann et al., 2020; see also Feng & Narayanan, 2019).

One very well-studied multimodal physiological pattern relies specifically on signaling in the vagus: respiratory sinus arrhythmia (RSA). RSA is the variability in heart rate that is linked to respiration via cardiac vagal activity and is a result of both afferent and efferent signaling in the vagus nerve (as well as influence from the sympathetic nervous system; Grossman & Taylor, 2007; for a review, see Berntson et al., 1993). Heart rate increases during inhalation and decreases during exhalation, resulting in shortened and lengthened interbeat intervals, respectively. It is difficult to disentangle the afferent and efferent elements responsible for RSA (discussed in Berntson et al., 1993). This difficulty appears to be a more general feature given the architectures of the vagus nerve and the brainstem nuclei with which it communicates (see Box 2).

Specifically, RSA may represent an emergent[24] phenomenon arising from combinatorial coding that we have described, where converging interactions from multiple physiological sources (both the afferent and efferent vagus nerve, as well as indirect influence from sympathetic nerves) are reflected in a single physiological signal that yields a measurement capturing both cardiovascular and pulmonary sensorimotor dynamics. While speculative, such a hypothesis is consistent with the possibility of signal compression and combinatorial coding by temporal coincidence that the vagus architecture possibly affords, along with the afferent and efferent signal integration that occurs within brainstem nuclei (and possibly even within vagal fasciculi). Moreover, signals arising in the nodose ganglia, being lower in dimensionality and possibly entailing more signal compression than afferent spinal cord signals for skeletomotor control, might at some point be revealed to contribute to functional "visceromotor concepts" in the primary visceromotor control areas of the cerebral cortex (e.g., the anterior cingulate, the ventral anterior insula/posterior orbitofrontal cortex, etc.) in the same way that the abstract functional ensembles in primary motor cortex are action concepts. The existence of such concepts orchestrating particular physiological "motifs" might present a partial answer to the question of how gradients of viscerosensory signals can be processed in the service of visceromotor control in the absence of viscerotopic specificity.

4.1.1. A methodological note

The research on visceromotor and behavioral motifs discussed above was conducted with measurements from human and non-human animals while they freely moved in real-world contexts or laboratory situations constructed to be similar to real-world contexts. This methodological insight is important for future research on vagal signal processing functions. Standard laboratory procedures, by contrast, intentionally remove signal variation in the world that is inherently present in naturalistic ecological contexts; laboratory settings are both spatially constrained and temporally artificial. The result is impoverished signals and signal patterns inside the brain and body because the metabolic and movement possibilities are severely limited by design. The consequence of stripping away this multidimensional context is that there may be insufficient signal variance from which to discover and map the hypothesized signal motifs and their associated concepts. Evidence consistent with this concern comes from the studies that discovered action concepts in early motor cortices described earlier. These studies used extended trains of microstimulation in cortical areas to evoke movements, on the timescale of meaningful behavior, rather than the short bursts of stimulation that had been traditionally used and that resulted in a somatotopic map (e.g., Graziano, 2016, 2023). Other methodological considerations for testing signal processing hypotheses in the vagus can be found in Box 3.

4.2. Temporal mapping in the vagus and event segmentation: Implications for memory

The possibility of temporal coding in the vagus nerve can be extended further to hypothesize that physiological and behavioral motifs (i.e., temporally co-occurring events in the sensory periphery) may play a role in structuring learning, memory and prediction (maybe even establishing integrated skeletomotor and visceromotor concepts in early development) via their impact on the hippocampus. Ascending vagal signals reach the hippocampus and the rest of the forebrain via multiple pathways from its brainstem targets, but for present purposes we focus on inputs that project to the medial septal nuclei in the basal forebrain (Castle et al., 2005; Takeuchi et al., 2021).[25] The vagus projects to the medial septum via a variety of multi-synaptic pathways, including prominent projections from the NTS (as well as brainstem monoaminergic nuclei and the hypothalamus; Takeuchi et al., 2021). Cholinergic, GABAergic, and glutamatergic neurons from the medial septum then project to various aspects of the hippocampal complex, with projections specifically to the entorhinal cortex, the dentate, and cornu ammonis regions (CA3 and CA1).[26]

The hypothesis that vagal afferents are important to hippocampal function is consistent with considerable functional evidence. For example, direct vagal nerve stimulation in rodents modulates the firing of neurons within the hippocampus (Broncel et al., 2017, 2018, 2021) and, correspondingly, has been shown to modulate neurotransmitter levels in hippocampal neurons (such as norepinephrine, serotonin, dopamine and GABA; e.g., Bocian et al., 2023; Broncel et al., 2019a, 2021; Raedt et al., 2011; Roosevelt et al., 2006). Mechanical distention of the stomach, intestinal infusion of nutrients, and electrical stimulation of the stomach all result in GI vagal signals that increase hippocampal neuron firing (Min, Tuor, & Chelikani, 2011; Min, Tuor & Koopmans, & Chelikani, 2011; Wang et al., 2006). Respiratory signals, potentially carried by the afferent vagus, serve as an "oscillatory pacemaker" (along with coordinated signals from the olfactory bulb) in freely moving rodents, modulating hippocampal and medial prefrontal cortex activity and their dynamics in a way that supports signal segregation and integration (e.g., Karalis & Sirota, 2022). Electrical stimulation of the cervical vagus has been shown to enhance memory consolidation (e.g., Clark et al., 1998, 1999; Ghacibeh et al., 2006; Ura et al., 2013) and facilitate neurogenesis in the hippocampus (e.g., Biggio et al., 2009; Follesa et al., 2007; Noble et al., 2011), and endogenous stimulation of the subdiaphragmatic vagus (via the GI tract) appears to be necessary for several hippocampal-dependent memory phenomena, including spatial working memory and contextual episodic memory for objects (Suarez et al., 2018). These effects specifically involve vagal inputs to the medial NTS, which project to the medial septum, which in turn innervates glutamatergic neurons in the dorsal hippocampal complex in rodents (equivalent to the posterior hippocampal complex in primates).

Viscerosensory afferent signals appear to influence hippocampus function (mediated by the medial septum) via endogenous theta

[24] Here, we mean causally emergent. We are not suggesting any specific evolutionary timing, nor that this phenomenon is evolutionarily recent since considerable evidence suggests that RSA is a phenomenon found in multiple vertebrate species across the phylogenetic tree (for a review see Taylor et al., 2022).

[25] In the primate brain, the septal nuclei are located medially, just below the corpus callosum, and anterior to the third ventricle. The nuclei are generally parsed into four sectors (Takeuchi et al., 2021) with most of the empirical focus on medial and lateral septal nuclei (Tsanov, 2018). The medial septal nuclei are thought to act like hubs that orchestrate the temporal coordination of neuronal activity within a widely distributed system for allostasis involving many so-called limbic areas, both cortical and subcortical (for reviews, see Buzsáki et al., 2022; Tsanov, 2018). The medial septum is densely interconnected, both directly and indirectly, to the lateral septal nucleus (for review, see Tsanov, 2018). Unlike the medial septum, which is characterized by widely reciprocal connections with other limbic targets, the lateral septum connections appear to be largely efferent (projecting to hypothalamic and brainstem targets and receiving hippocampal and cortical projections; Tsanov, 2018). The lateral septum projects directly to the medial septum, as well as to the hypothalamus, which then also projects to the medial septum (Takeuchi et al., 2021).

[26] The medial parts of the medial septal nuclei project to both ends of the hippocampus (ventral and dorsal ends in rodents / anterior and posterior ends in primates) as well as the dorsolateral portions of entorhinal cortex, whereas the lateral parts of the medial septal nuclei project to the ventral (rodent)/ posterior (primate) end of the subiculum, hippocampus, and both the medial and lateral parts of entorhinal cortex. The lateral and intermediate sectors of the medial septum efferents to the olfactory regions, taenia tecta, medial and cortical amygdaloid nuclei, and the lateral entorhinal cortices (dorsolateral and ventrolateral ECs). The medial part of the medial septum sends fibers to the vertical diagonal band, anterior cingulate cortex, retrosplenial cortex, medial precentral and motor areas, indusium griseum, olfactory regions, and the orbital prefrontal cortex.

oscillations (3–12 Hz signals) arising in the vagus itself. Medial septal inputs are known to be an important source of theta oscillations in the hippocampus (for discussions, see Butler et al., 2016; Tsanov, 2018), but recent evidence from studies of vagal nerve stimulation suggests that those oscillations arise in the vagus nerve itself. Vagal nerve stimulation has been shown to induce slower wave theta oscillations (3–6 Hz) in the hippocampal formation (Broncel et al., 2017, 2018, 2019a, 2019b, 2021, 2022; for corroborating evidence from pharmacological manipulations paired with large-scale electrical recordings in freely moving rodents, see Karalis & Sirota, 2022).[27] Theta oscillations from respiration in combination with theta oscillations from the olfactory bulb (another system known for temporal co-occurrence mapping) are particularly impactful (see Karalis & Sirota, 2022; for a recent summary of how breathing regulates the strength and synchronization of neural oscillations, see Brændholt et al., 2023).

The function of theta oscillations in the hippocampus is widely debated, but one prominent view suggests that they synchronize signals to result in segmented "events" (i.e., creating temporal windows, e.g., Buzsáki, 2006; Sirota & Buzsáki, 2005) that chunk or *compress* continuous streams of signals into temporally meaningful segments (e.g., Gupta et al., 2012). These segments allow neurons to fire in a phase-locked manner, creating time-compressed "cognitive maps" (Buzsáki & Llinás, 2017; Buzsáki & Tingley, 2018). There is evidence that theta rhythm-dependent event segmentation plays a necessary role in memory formation and consolidation (e.g., Kota et al., 2020) and disruption of septally-mediated theta oscillations impairs learning and memory (Takeuchi et al., 2021 and references therein).

A guiding hypothesis here is that theta oscillations originating in the vagus (specifically, temporal coding in the vagus) could allow the hippocampus to segment and sequence the temporal co-occurrences in signals transduced from the body's sensory surfaces; the resulting events would correspond to statistical regularities in the brain's periphery (Barron et al., 2020; Buzsáki & Tingley, 2018; Lisman & Redish, 2009; Pezzulo et al., 2017). Both the hippocampus (Schapiro et al., 2012, 2017; Sherman & Turk-Browne, 2020) and the cerebral cortex are generating and exchanging prediction and prediction error signals in a non-hierarchical fashion (Katsumi et al., 2022, 2023). From the perspective of the cortex, hippocampal events, which are constructed using temporal signal statistics of the body in the world, may function as prediction error signals. These error signals re-weight the cortical prediction signals, which are constructed using spatial, nearest-neighbor statistics of the surrounding environment (Kumaran et al., 2016). This hippocampal re-weighting of cortical prediction signals would ensure that all prediction signals – visceromotor, skeletomotor and sensory–- are calibrated to the current metabolic state of the body in an event-consistent manner (i.e., weighted for the current and predicted conditions of the body's sensory conditions; Kumaran et al., 2016). If correct, this hypothesis would suggest a formative role for the vagus nerve in predictive processing accounts for a variety of psychological phenomena including emotion and categorization (e.g., Barrett, 2017), attention and perception (see Hutchinson & Barrett, 2019 and Kleckner et al., 2017, and references therein), and social development (e.g., Atzil et al., 2018), just to name a few. Future research is required, of course, to fully test the hypothesis that event boundaries are drawn by the temporal coding of sensory changes in the body's internal milieu by the vagus nerve.

4.3. Sensorimotor integration in the vagus and the potential for self-fulfilling prophecy: Implications for disorders of prediction

Within the predictive processing framework described earlier, the main function of ascending viscerosensory signals in the vagus is not to represent the sensory conditions of the body per se, but to constrain and correct the descending visceromotor commands that are implementing allostasis in the service of reducing uncertainty and enhancing metabolic efficiency. Unexpected viscerosensory changes from the internal milieu of the body, via ascending nodose axons, are errors of prediction. For example, in a recent study, exerting optogenetic control over the beating of the heart allowed researchers to control cardiac rhythms in freely moving mice (Hsueh et al., 2023).[28] From the brain's perspective, the ascending sensory signals from these optogenetic manipulations function as prediction errors. Using genetic labeling, it was observed that these unexpected signals produced an increase in gene expression that is a marker of neural activation in various brain regions, including the NTS, posterior insular cortex (which is primary interoceptive cortex), as well as agranular anterior insular cortex (also called posterior orbitofrontal cortex) and the anterior cingulate cortex, both of which are key visceromotor regulation regions in the cerebral cortex (Hsueh et al., 2023; Öngür & Price, 2000; Vogt et al., 2003; for additional discussion, see Kleckner et al., 2017).

Unexpected changes in viscerosensory signaling computed as interoceptive prediction errors, like all sensory prediction errors, are teaching signals in the nervous system. Prediction errors informing on the actual energetic state of the body have the potential to adjust incoming visceromotor predictions in the moment and, if encoded and consolidated as memory, will modify future predictions, including visceromotor predictions and the anticipated interoceptive consequences (i.e., interoceptive prediction signals; see footnote 22, also see Barrett, 2017; Barrett & Simmons, 2015). One implication of possible sensorimotor integration in the fascicles of the vagus nerve, and certainly of sensorimotor integration in its brainstem targets, is that ascending sensory signals have the potential to be tuned by the brain's descending visceromotor signals, allowing for the possibility that errors of prediction can be either magnified or minimized before they reach their midbrain and forebrain targets. This dynamic points to the potential for an elegantly orchestrated self-fulfilling prophecy embodied within the architecture of the nervous system.

In addition, ascending viscerosensory signals potentially have the capacity to modulate descending visceromotor signals outside the CNS, allowing for visceromotor changes that the brain did not issue. Even if

[27] There are two categories of theta waves. In the rodent hippocampus, Type II theta oscillations fall within the lower frequency band of the theta range (3–6 Hz), are cholinergically mediated and tend to occur in the absence of major skeletomotor movements when an animal is licking, chewing, or during changes in arousal (increases or decreases); they have also been observed during cognitive tasks (e.g., Bland, 1986; Hoffmann et al., 2015). Type I theta oscillations are faster (7–12 Hz) and tend to occur during spatial navigation accompanied by physical movement (Broncel et al., 2017; Takeuchi et al., 2021). There are relatively few anatomical and functional studies of the human septal nuclei in general, and of septal-hippocampal theta oscillations in particular, but the evidence that does exist suggests similar relationships to those observed in rodents, with the exception that hippocampal oscillations tend to be slower in humans (1–14 Hz; Jacobs, 2014; although faster theta oscillations have recently been observed; e.g., Goyal et al., 2020; Vivekananda et al., 2021). Slower theta oscillations are found in the ventral (rodent)/anterior (primate) hippocampus, which processes signals of lower dimensionality, such as compressed multi-modal summaries (i.e., that are abstracted away from the sensory particulars; Broncel et al., 2017 and references therein) and which is more strongly connected with regions of the default mode network (Katsumi et al., 2023). Faster theta oscillations are found in the dorsal (rodent)/posterior (primate) hippocampus, which tends to process signals that are higher in dimensionality, associated with low-level sensory features (closer to the sensory surfaces of the body; Broncel et al., 2017 and references therein) and is more strongly connected to exteroceptive sensory networks and the salience network (Katsumi et al., 2023). Based on this pattern of findings, we might speculate that slower (Type II) theta oscillations help establish compressed multimodal summaries that retain temporal relations of signals whereas the faster (Type I) oscillations establish lower-level features with spatial mapping of signals.

[28] Cardiac rhythmic control occurred up to 900 beats per minute, relative to a typical rate of 500–700 beats per minute.

the ascending signals improve the efficacy of descending control signals at their ultimate tissue targets, the result would be viscerosensory consequences that the brain did not predict and does not expect. This dynamic points to the potential for increasing the magnitude of eventual interoceptive prediction errors or increasing the noise in (i.e., decreasing the precision of) those errors, both of which would heighten the metabolic demand on the brain, by making allostasis more effortful and expensive to achieve. This result could materialize even when the ascending signals in the vagus or in their brainstem targets are enacting allostasis by correcting descending signals that arose from poorly calibrated prediction signals in the forebrain.

These hypotheses suggest the possibility that early sensorimotor integration might contribute to mental and physical illness in a way that has not yet been fully appreciated. For example, the brain's processing of ascending interoceptive signals has been implicated in mood disorders such as depression and anxiety disorders. Symptoms of depression, such as insensitivity to context (e.g., Rottenberg et al., 2005), have been hypothesized to arise from metabolic problems and associated allostatic disruptions that make it difficult for the brain to update its prediction signals in the presence of prediction errors (for discussion and references, see Barrett et al., 2016; Shaffer et al., 2022). Symptoms of anxiety, in contrast, might arise when overly precise visceromotor predictions are routinely generated, resulting in noisy (less informative) prediction error signals (Paulus et al., 2019; Paulus & Stein, 2010).

If supported by empirical evidence, these hypotheses suggest other even broader implications for the role of the vagus in both sensing and control of metabolism, and would speak to our recent proposal that many disorders, both those traditionally considered physical (e.g., metabolic syndrome) and mental (e.g., major depression), can be reinterpreted as, at their core, disorders of metabolic inefficiency (Kleckner et al., 2017; Shaffer et al., 2022). Accordingly, the mood disruptions observed in both mood disorders, metabolic disorders such as diabetes and cardiovascular disease, and even disorders of the immune system (which have considerable metabolic cost; e.g., Bucks et al., 2008; Chrysohoou et al., 2018; Gavard et al., 1993; Kiriella et al., 2021) can be thought of as arising from disruptions in allostatic control, and the interoceptive contributions to those disruptions, which ultimately lead to prolonged energetic inefficiencies and the symptoms they produce. Evidence for this comes from the innumerable metabolic symptoms seen in depression, as well as aberrant functional and structural patterns in key limbic cortices that are the neural backbone of allostasis (Kleckner et al., 2017; Shaffer et al., 2022). This same architecture makes up the central autonomic network (CAN) that interfaces with the NTS and other brainstem nuclei to integrate viscerosensory signals from the vagus and other peripheral nerves in the service of physiological regulation (e.g., Benarroch, 1993; Valenza et al., 2019). The same architecture also contributes to the "pain connectome" (Kucyi & Davis, 2015) that implements varieties of pain (nociceptive and neuropathic).

5. Conclusions

We have reviewed recent empirical evidence to support the viability of several hypotheses regarding signal processing within the vagus nerve. The evidence revealed three signal gradients within the vagus that may afford spatial and temporal processing of viscerosensory signals, perhaps with relatively greater spatial specificity of afferent signals at the rostral end of the body's rostro-caudal axis. The evidence also suggests that the sensory and motor fibers of the vagus are not structurally separate and may not be as functionally separate as first supposed. These hypotheses await further study, possibly using innovative methods for studying signaling in the vagus (see Box 3). If supported by empirical evidence, these hypotheses would suggest more fundamental implications for the vagus in both allostatic and psychological phenomena such as learning, memory, and mood, as well as novel implications for the vagus's role in disorders of prediction.

Declaration of Competing Interest

The authors declare no conflicting interests.

Data Availability

No data was used for the research described in the article.

Acknowledgements

The authors would like to thank Barb Finlay and Benjamin Reese for providing crucial expertise on the visual and olfactory systems; we also thank Barb for her comments on an earlier draft of this manuscript. We thank Zoe Kross for her assistance in summarizing the literature on the brainstem nuclei. This article was supported by grants from the National Cancer Institute (U01 CA193632 and R01 CA258269-01), the National Institute of Mental Health (R01 MH113234, R01 MH109464, R21 MH129902-01), the U.S. Army Research Institute for the Behavioral and Social Sciences (W911NF-16-1-019), the National Institutes of Health (NIA-R01AG071173), and the Unlikely Collaborators Foundation. The views, opinions, and/or findings contained in this review are those of the author and shall not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documents, nor do they necessarily reflect the views of the Unlikely Collaborator Foundation.

Declaration

The author(s) did not use generative AI technologies for preparation of this work.

References

Ainley, V., Apps, M. A. J., Fotopoulou, A., & Tsakiris, M. (2016). 'Bodily precision': A predictive coding account of individual differences in interoceptive accuracy. *Philosophical Transactions of the Royal Society B: Biological Sciences, 371*(1708), Article 20160003. https://doi.org/10.1098/rstb.2016.0003

Allen, E. J., Mesik, J., Kay, K. N., & Oxenham, A. J. (2022). Distinct representations of tonotopy and pitch in human auditory cortex. *The Journal of Neuroscience, 42*(3), 416–434. https://doi.org/10.1523/JNEUROSCI.0960-21.2021

Allen, M., & Friston, K. J. (2018). From cognitivism to autopoiesis: Towards a computational framework for the embodied mind. *Synthese, 195*(6), 2459–2482. https://doi.org/10.1007/s11229-016-1288-5

Altschuler, S. M., Bao, X., Bieger, D., Hopkins, D. A., & Miselis, R. R. (1989). Viscerotopic representation of the upper alimentary tract in the rat: Sensory ganglia and nuclei of the solitary and spinal trigeminal tracts. *Journal of Comparative Neurology, 283*(2), 248–268. https://doi.org/10.1002/cne.902830207

Anastassiou, C. A., & Koch, C. (2015). Ephaptic coupling to endogenous electric field activity: Why bother? *Current Opinion in Neurobiology, 31*, 95–103. https://doi.org/10.1016/j.conb.2014.09.002

Anastassiou, C. A., Perin, R., Markram, H., & Koch, C. (2011). Ephaptic coupling of cortical neurons. *Nature Neuroscience, 14*(2), Article 2. https://doi.org/10.1038/nn.2727

Andresen, M. C., & Paton, J. F. R. (2011). The nucleus of the solitary tract: Processing information from viscerosensory afferents. In I. J. Llewellyn-Smith, & A. J. M. Verberne (Eds.), *Central Regulation of Autonomic Functions* (pp. 23–46). Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195306637.003.0002.

Arvanitaki, A. (1942). Effects evoked in an axon by the activity of a contiguous one. *Journal of Neurophysiology, 5*(2), 89–108. https://doi.org/10.1152/jn.1942.5.2.89

Attneave, F. (1954). Some informational aspects of visual perception. *Psychological Review, 61*(3), 183–193. https://doi.org/10.1037/h0054663

Atzil, S., Gao, W., Fradkin, I., & Barrett, L. F. (2018). Growing a social brain. *Nature Human Behaviour, 2*(9), 624–636. https://doi.org/10.1038/s41562-018-0384-6

Atzil, S., & Gendron, M. (2017). Bio-behavioral synchrony promotes the development of conceptualized emotions. *Current Opinion in Psychology, 17*, 162–169. https://doi.org/10.1016/j.copsyc.2017.07.009

Baker, C. (2005). The embryology of vagal sensory neurons. In B. J. Undem, & D. Weinreich (Eds.), *Advances in Vagal Afferent Neurobiology*. CRC Press.

Barbas, H. (2015). General cortical and special prefrontal connections: Principles from structure to function. *Annual Review of Neuroscience, 38*, 269–289. https://doi.org/10.1146/annurev-neuro-071714-033936

Barbas, H., & Rempel-Clower, N. (1997). Cortical structure predicts the pattern of corticocortical connections. *Cerebral Cortex (New York, N Y: 1991), 7*(7), 635–646. https://doi.org/10.1093/cercor/7.7.635

Barlow, H. B. (1961). Possible principles underlying the transformations of sensory messages. In W. A. Rosenblith (Ed.), *Sensory Communication* (pp. 216–234). The MIT Press. https://doi.org/10.7551/mitpress/9780262518420.003.0013.

Barr, R. C., & Plonsey, R. (1992). Electrophysiological interaction through the interstitial space between adjacent unmyelinated parallel fibers. *Biophysical Journal, 61*(5), 1164–1175. https://doi.org/10.1016/S0006-3495(92)81925-2

Barrett, L. F. (2017). The theory of constructed emotion: An active inference account of interoception and categorization. *Social Cognitive and Affective Neuroscience*, nsw154. https://doi.org/10.1093/scan/nsw154

Barrett, L. F. (2022). Context reconsidered: Complex signal ensembles, relational meaning, and population thinking in psychological science. *American Psychologist, 77*(8), 894–920. https://doi.org/10.1037/amp0001054.

Barrett, L. F., & Bar, M. (2009). See it with feeling: Affective predictions during object perception. *Philosophical Transactions of the Royal Society B: Biological Sciences, 364*(1521), 1325–1334. https://doi.org/10.1098/rstb.2008.0312

Barrett, L. F., & Finlay, B. L. (2018). Concepts, goals and the control of survival-related behaviors. *Current Opinion in Behavioral Sciences, 24*, 172–179. https://doi.org/10.1016/j.cobeha.2018.10.001

Barrett, L. F., Quigley, K. S., & Hamilton, P. (2016). An active inference theory of allostasis and interoception in depression. *Philosophical Transactions of the Royal Society B: Biological Sciences, 371*(1708), Article 20160011. https://doi.org/10.1098/rstb.2016.0011

Barrett, L. F., & Simmons, W. K. (2015). Interoceptive predictions in the brain. *Nature Reviews Neuroscience, 16*(7), 419–429. https://doi.org/10.1038/nrn3950

Barron, H. C., Auksztulewicz, R., & Friston, K. (2020). Prediction and memory: A predictive coding account. *Progress in Neurobiology, 192*, Article 101821. https://doi.org/10.1016/j.pneurobio.2020.101821

Bassi, J. K., Connelly, A. A., Butler, A. G., Liu, Y., Ghanbari, A., Farmer, D. G. S., Jenkins, M. W., Melo, M. R., McDougall, S. J., & Allen, A. M. (2022). Analysis of the distribution of vagal afferent projections from different peripheral organs to the nucleus of the solitary tract in rats. *Journal of Comparative Neurology, 530*(17), 3072–3103. https://doi.org/10.1002/cne.25398

Bastos, A. M., Lundqvist, M., Waite, A. S., Kopell, N., & Miller, E. K. (2020). Layer and rhythm specificity for predictive routing. *Proceedings of the National Academy of Sciences, 117*(49), 31459–31469. https://doi.org/10.1073/pnas.2014868117

Beissner, F., Meissner, K., Bär, K.-J., & Napadow, V. (2013). The autonomic brain: An activation likelihood estimation meta-analysis for central processing of autonomic function. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 33*(25), 10503–10511. https://doi.org/10.1523/JNEUROSCI.1103-13.2013

von Békésy, G., & Peake, W. T. (1990). Experiments in hearing. *The Journal of the Acoustical Society of America, 88*(6). https://doi.org/10.1121/1.399656

Benarroch, E. E. (1993). The central autonomic network: Functional organization, dysfunction, and perspective. *Mayo Clinic Proceedings, 68*(10), 988–1001. https://doi.org/10.1016/S0025-6196(12)62272-1

Ben-Menachem, E. (2002). Vagus-nerve stimulation for the treatment of epilepsy. *The Lancet Neurology, 1*(8), 477–482. https://doi.org/10.1016/S1474-4422(02)00220-X

Berkes, P., Orbán, G., Lengyel, M., & Fiser, J. (2011). Spontaneous cortical activity reveals hallmarks of an optimal internal model of the environment. *Science (New York, N York), 331*(6013), 83–87. https://doi.org/10.1126/science.1195870

Berntson, G. G., Cacioppo, J. T., & Grossman, P. (2007). Whither vagal tone. *Biological Psychology, 74*(2), 295–300. https://doi.org/10.1016/j.biopsycho.2006.08.006

Berntson, G. G., Cacioppo, J. T., & Quigley, K. S. (1993). Respiratory sinus arrhythmia: Autonomic origins, physiological mechanisms, and psychophysiological implications. *Psychophysiology, 30*(2), 183–196. https://doi.org/10.1111/j.1469-8986.1993.tb01731.x

Berthoud, H. R., Carlson, N. R., & Powley, T. L. (1991). Topography of efferent vagal innervation of the rat gastrointestinal tract. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 260*(1), R200–R207. https://doi.org/10.1152/ajpregu.1991.260.1.R200

Bethlehem, R. A. I., Paquola, C., Seidlitz, J., Ronan, L., Bernhardt, B., Consortium, C.-C., & Tsvetanov, K. A. (2020). Dispersion of functional gradients across the adult lifespan. *NeuroImage, 222*, Article 117299. https://doi.org/10.1016/j.neuroimage.2020.117299

Bhattacharyya, S., Atakan, Z., Martin-Santos, R., A. Crippa, J., & K. McGuire, P. (2012). Neural mechanisms for the cannabinoid modulation of cognition and affect in man: A critical review of neuroimaging studies. *Current Pharmaceutical Design, 18*(32), 5045–5054. https://doi.org/10.2174/138161212802884636

Bieger, D., & Hopkins, D. A. (1987). Viscerotopic representation of the upper alimentary tract in the medulla oblongata in the rat: The nucleus ambiguus. *The Journal of Comparative Neurology, 262*(4), 546–562. https://doi.org/10.1002/cne.902620408

Biggio, F., Gorini, G., Utzeri, C., Olla, P., Marrosu, F., Mocchetti, I., & Follesa, P. (2009). Chronic vagus nerve stimulation induces neuronal plasticity in the rat hippocampus. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), 12*(9), 1209. https://doi.org/10.1017/S1461145709000200

Binczak, S., Eilbeck, J. C., & Scott, A. C. (2001). Ephaptic coupling of myelinated nerve fibers. *Physica D: Nonlinear Phenomena, 148*(1), 159–174. https://doi.org/10.1016/S0167-2789(00)00173-1

Bland, B. H. (1986). The physiology and pharmacology of hippocampal formation theta rhythms. *Progress in Neurobiology, 26*(1), 1–54. https://doi.org/10.1016/0301-0082(86)90019-5

Blot, A., & Barbour, B. (2014). Ultra-rapid axon-axon ephaptic inhibition of cerebellar Purkinje cells by the pinceau. *Nature Neuroscience, 17*(2), Article 2. https://doi.org/10.1038/nn.3624

Bocian, R., Broncel, A., & Konopacki, J. (2023). Noradrenergic α1, α2, and β1receptors mediate VNS-induced theta oscillations. *Brain Research, 1804*, Article 148266. https://doi.org/10.1016/j.brainres.2023.148266

Bokil, H., Laaris, N., Blinder, K., Ennis, M., & Keller, A. (2001). Ephaptic interactions in the mammalian olfactory system. *The Journal of Neuroscience, 21*(20), RC173. https://doi.org/10.1523/JNEUROSCI.21-20-j0004.2001

Bolzoni, F., & Jankowska, E. (2019). Ephaptic interactions between myelinated nerve fibres of rodent peripheral nerves. *The European Journal of Neuroscience, 50*(7), 3101–3107. https://doi.org/10.1111/ejn.14439

Brændholt, M., Kluger, D. S., Varga, S., Heck, D. H., Gross, J., & Allen, M. (2023). Breathing in waves: Understanding respiratory-brain coupling as a gradient of predictive oscillations. *Neuroscience and Biobehavioral Reviews.* , Article 105262. https://doi.org/10.1016/j.neubiorev.2023.105262

Braga, R. M., Sharp, D. J., Leeson, C., Wise, R. J. S., & Leech, R. (2013). Echoes of the brain within default mode, association, and heteromodal cortices. *Journal of Neuroscience, 33*(35), 14031–14039. https://doi.org/10.1523/JNEUROSCI.0570-13.2013

Brann, D. H., & Datta, S. R. (2020). Finding the brain in the nose. *Annual Review of Neuroscience, 43*(1), 277–295. https://doi.org/10.1146/annurev-neuro-102119-103452

Brezina, V., & Weiss, K. R. (1997). Functional consequences of divergence and convergence in physiological signaling pathways. *Molecular Psychiatry, 2*(1), Article 1. https://doi.org/10.1038/sj.mp.4000191

Broncel, A., Bocian, R., Kłos-Wojtczak, P., & Konopacki, J. (2017). Vagus nerve stimulation produces a hippocampal formation theta rhythm in anesthetized rats. *Brain Research, 1675*, 41–50. https://doi.org/10.1016/j.brainres.2017.08.030

Broncel, A., Bocian, R., Kłos-Wojtczak, P., & Konopacki, J. (2018). Medial septal cholinergic mediation of hippocampal theta rhythm induced by vagal nerve stimulation. *PLoS One, 13*(11), Article e0206532. https://doi.org/10.1371/journal.pone.0206532

Broncel, A., Bocian, R., Kłos-Wojtczak, P., & Konopacki, J. (2019a). GABAergic mediation of hippocampal theta rhythm induced by stimulation of the vagal nerve. *Brain Research Bulletin, 147*, 110–123. https://doi.org/10.1016/j.brainresbull.2019.02.010

Broncel, A., Bocian, R., Kłos-Wojtczak, P., & Konopacki, J. (2019b). Hippocampal theta rhythm induced by vagal nerve stimulation: The effect of modulation of electrical coupling. *Brain Research Bulletin, 152*, 236–245. https://doi.org/10.1016/j.brainresbull.2019.07.025

Broncel, A., Bocian, R., Kłos-Wojtczak, P., & Konopacki, J. (2021). Noradrenergic profile of hippocampal formation theta rhythm in anaesthetized rats. *Neuroscience, 473*, 13–28. https://doi.org/10.1016/j.neuroscience.2021.08.008

Broncel, A., Bocian, R., & Konopacki, J. (2022). Vagal nerve stimulation: The effect on the brain oscillatory field potential. *Neuroscience, 483*, 127–138. https://doi.org/10.1016/j.neuroscience.2021.12.023

Brown, A. E. X., Yemini, E. I., Grundy, L. J., Jucikas, T., & Schafer, W. R. (2013). A dictionary of behavioral motifs reveals clusters of genes affecting *Caenorhabditis elegans* locomotion. *Proceedings of the National Academy of Sciences, 110*(2), 791–796. https://doi.org/10.1073/pnas.1211447110

Browning, K. N., & Mendelowitz, D. (2003). II. Integration of afferent signaling from the viscera by the nodose ganglia. *American Journal of Physiology-Gastrointestinal and Liver Physiology, 284*(1), G8–G14. https://doi.org/10.1152/ajpgi.00322.2002

Bucks, R. S., Gidron, Y., Harris, P., Teeling, J., Wesnes, K. A., & Perry, V. H. (2008). Selective effects of upper respiratory tract infection on cognition, mood and emotion processing: A prospective study. *Brain, Behavior, and Immunity, 22*(3), 399–407. https://doi.org/10.1016/j.bbi.2007.09.005

Burton, S. D., Brown, A., Eiting, T. P., Youngstrom, I. A., Rust, T. C., Schmuker, M., & Wachowiak, M. (2022). Mapping odorant sensitivities reveals a sparse but structured representation of olfactory chemical space by sensory input to the mouse olfactory bulb. *ELife, 11*, Article e80470. https://doi.org/10.7554/eLife.80470

Butler, J. L., Mendonça, P. R. F., Robinson, H. P. C., & Paulsen, O. (2016). Intrinsic cornu ammonis area 1 theta-nested gamma oscillations induced by optogenetic theta frequency stimulation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 36*(15), 4155–4169. https://doi.org/10.1523/JNEUROSCI.3150-15.2016

Buzsáki, G. (2006). *Rhythms of the Brain*. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195301069.001.0001

Buzsáki, G., & Llinás, R. (2017). Space and time in the brain. *Science, 358*(6362), 482–485. https://doi.org/10.1126/science.aan8869

Buzsáki, G., McKenzie, S., & Davachi, L. (2022). Neurophysiology of remembering. *Annual Review of Psychology, 73*(1), 187–215. https://doi.org/10.1146/annurev-psych-021721-110002

Buzsáki, G., & Tingley, D. (2018). Space and time: The hippocampus as a sequence generator. *Trends in Cognitive Sciences, 22*(10), 853–869. https://doi.org/10.1016/j.tics.2018.07.006

Câmara, R., & Griessenauer, C. J. (2015). Chapter 27—Anatomy of the Vagus Nerve. In R. S. Tubbs, E. Rizk, M. M. Shoja, M. Loukas, N. Barbaro, & R. J. Spinner (Eds.), *Nerves and Nerve Injuries* (pp. 385–397). Academic Press. https://doi.org/10.1016/B978-0-12-410390-0.00028-7.

Capllonch-Juan, M., Kölbl, F., & Sepulveda, F. (2017). Unidirectional ephaptic stimulation between two myelinated axons. *2017 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 230–233. https://doi.org/10.1109/EMBC.2017.8036804

Capllonch-Juan, M., & Sepulveda, F. (2020). Modelling the effects of ephaptic coupling on selectivity and response patterns during artificial stimulation of peripheral nerves. *PLOS Computational Biology, 16*(6), Article e1007826. https://doi.org/10.1371/journal.pcbi.1007826

Cappe, C., Morel, A., Barone, P., & Rouiller, E. M. (2009). The thalamocortical projection systems in primate: An anatomical support for multisensory and sensorimotor interplay. *Cerebral Cortex, 19*(9), 2025–2037. https://doi.org/10.1093/cercor/bhn228

Carey, R. M., Verhagen, J. V., Wesson, D. W., Pírez, N., & Wachowiak, M. (2009). Temporal structure of receptor neuron input to the olfactory bulb imaged in behaving rats. *Journal of Neurophysiology, 101*(2), 1073–1088. https://doi.org/10.1152/jn.90902.2008

Carvalho, G. B., & Damasio, A. (2021). Interoception and the origin of feelings: A new synthesis. *BioEssays, 43*(6), Article 2000261. https://doi.org/10.1002/bies.202000261

Castejon, C., Martin-Cortecero, J., & Nuñez, A. (2021). Higher-order thalamic encoding of somatosensory patterns and bilateral events. *Frontiers in Neural Circuits, 15*, Article 752804. https://doi.org/10.3389/fncir.2021.752804

Castle, M., Comoli, E., & Loewy, A. D. (2005). Autonomic brainstem nuclei are linked to the hippocampus. *Neuroscience, 134*(2), 657–669. https://doi.org/10.1016/j.neuroscience.2005.04.031

Chae, H., Kepple, D. R., Bast, W. G., Murthy, V. N., Koulakov, A. A., & Albeanu, D. F. (2019). Mosaic representations of odors in the input and output layers of the mouse olfactory bulb. *Nature Neuroscience, 22*(8), 1306–1317. https://doi.org/10.1038/s41593-019-0442-z

Champagnat, J., Denavit-Saubié, M., Grant, K., & Shen, K. F. (1986). Organization of synaptic transmission in the mammalian solitary complex, studied in vitro. *The Journal of Physiology, 381*(1), 551–573. https://doi.org/10.1113/jphysiol.1986.sp016343

Chanes, L., & Barrett, L. F. (2016). Redefining the role of limbic areas in cortical processing. *Trends in Cognitive Sciences, 20*(2), 96–106. https://doi.org/10.1016/j.tics.2015.11.005

Chang, Y.-C., Cracchiolo, M., Ahmed, U., Mughrabi, I., Gabalski, A., Daytz, A., Rieth, L., Becker, L., Datta-Chaudhuri, T., Al-Abed, Y., Zanos, T. P., & Zanos, S. (2020). Quantitative estimation of nerve fiber engagement by vagus nerve stimulation using physiological markers. *Brain Stimulation, 13*(6), 1617–1630. https://doi.org/10.1016/j.brs.2020.09.002

Cheng, Z., & Powley, T. L. (2000). Nucleus ambiguus projections to cardiac ganglia of rat atria: An anterograde tracing study. *The Journal of Comparative Neurology, 424*(4), 588–606.

Chklovskii, D. B., & Koulakov, A. A. (2004). Maps in the brain: What can we learn from them? *Annual Review of Neuroscience, 27*(1), 369–392. https://doi.org/10.1146/annurev.neuro.27.070203.144226

Chrysohoou, C., Kollia, N., & Tousoulis, D. (2018). The link between depression and atherosclerosis through the pathways of inflammation and endothelium dysfunction. *Maturitas, 109*, 1–5. https://doi.org/10.1016/j.maturitas.2017.12.001

Cisek, P. (2019). Resynthesizing behavior through phylogenetic refinement. *Attention, Perception, & Psychophysics, 81*(7), 2265–2287. https://doi.org/10.3758/s13414-019-01760-1

Clark, A. (2013). Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behavioral and Brain Sciences, 36*(3), 181–204. https://doi.org/10.1017/S0140525X12000477

Clark, J. W., & Plonsey, R. (1970). A mathematical study of nerve fiber interaction. *Biophysical Journal, 10*(10), 937–957. https://doi.org/10.1016/S0006-3495(70)86344-5

Clark, K. B., Naritoku, D. K., Smith, D. C., Browning, R. A., & Jensen, R. A. (1999). Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nature Neuroscience, 2*(1), 94–98. https://doi.org/10.1038/4600

Clark, K. B., Smith, D. C., Hassert, D. L., Browning, R. A., Naritoku, D. K., & Jensen, R. A. (1998). Posttraining electrical stimulation of vagal afferents with concomitant vagal efferent inactivation enhances memory storage processes in the rat. *Neurobiology of Learning and Memory, 70*(3), 364–373. https://doi.org/10.1006/nlme.1998.3863

Cleland, T. A. (2014). Chapter 7—Construction of odor representations by olfactory bulb microcircuits. In E. Barkai, & D. A. Wilson (Eds.), *Progress in Brain Research* (Vol. 208, pp. 177–203). Elsevier. https://doi.org/10.1016/B978-0-444-63350-7.00007-3.

Cleland, T. A., & Borthakur, A. (2020). A systematic framework for olfactory bulb signal transformations. *Frontiers in Computational Neuroscience, 14*. https://doi.org/10.3389/fncom.2020.579143

Coffman, K. A., Dum, R. P., & Strick, P. L. (2011). Cerebellar vermis is a target of projections from the motor areas in the cerebral cortex. *Proceedings of the National Academy of Sciences, 108*(38), 16068–16073. https://doi.org/10.1073/pnas.1107904108

Copelli, M., Oliveira, R. F., Roque, A. C., & Kinouchi, O. (2005). Signal compression in the sensory periphery. *Neurocomputing: An International Journal, 65–66*, 691–696. https://doi.org/10.1016/j.neucom.2004.10.099

Cottrell, G. T., & Ferguson, A. V. (2004). Sensory circumventricular organs: Central roles in integrated autonomic regulation. *Regulatory Peptides, 117*(1), 11–23. https://doi.org/10.1016/j.regpep.2003.09.004

Cunningham, E. T., Miselis, R. R., & Sawchenko, P. E. (1994). The relationship of efferent projections from the area postrema to vagal motor and brain stem catecholamine-containing cell groups: An axonal transport and immunohistochemical study in the rat. *Neuroscience, 58*(3), 635–648. https://doi.org/10.1016/0306-4522(94)90087-6

Cutsforth-Gregory, J. K., & Benarroch, E. E. (2017). Nucleus of the solitary tract, medullary reflexes, and clinical implications. *Neurology, 88*(12), 1187–1196. https://doi.org/10.1212/WNL.0000000000003751

Damasio, A., & Carvalho, G. B. (2013). The nature of feelings: Evolutionary and neurobiological origins. *Nature Reviews Neuroscience, 14*(2), 143–152. https://doi.org/10.1038/nrn3403

Datta, S. R., Anderson, D. J., Branson, K., Perona, P., & Leifer, A. (2019). Computational neuroethology: A call to action. *Neuron, 104*(1), 11–24. https://doi.org/10.1016/j.neuron.2019.09.038

Dauger, S., Pattyn, A., Lofaso, F., Gaultier, C., Goridis, C., Gallego, J., & Brunet, J.-F. (2003). *Phox2b* controls the development of peripheral chemoreceptors and afferent visceral pathways. *Development, 130*(26), 6635–6642. https://doi.org/10.1242/dev.00866

Davis, S. F., Derbenev, A. V., Williams, K. W., Glatzer, N. R., & Smith, B. N. (2004). Excitatory and inhibitory local circuit input to the rat dorsal motor nucleus of the vagus originating from the nucleus tractus solitarius. *Brain Research, 1017*(1–2), 208–217. https://doi.org/10.1016/j.brainres.2004.05.049

Deneve, S. (2008). Bayesian spiking neurons I: Inference. *Neural Computation, 20*(1), 91–117. https://doi.org/10.1162/neco.2008.20.1.91

Dennison, S. J., O'Connor, B. L., Aprison, M. H., Merritt, V. E., & Felten, D. L. (1981). Viscerotopic localization of preganglionic parasympathetic cell bodies of origin of the anterior and posterior subdiaphragmatic vagus nerves. *The Journal of Comparative Neurology, 197*(2), 259–269. https://doi.org/10.1002/cne.901970207

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain, 118*(1), 279–306. https://doi.org/10.1093/brain/118.1.279

DiCarlo, J. J., Zoccolan, D., & Rust, N. C. (2012). How does the brain solve visual object recognition? *Neuron, 73*(3), 415–434. https://doi.org/10.1016/j.neuron.2012.01.010

Dong, D., Luo, C., Guell, X., Wang, Y., He, H., Duan, M., Eickhoff, S. B., & Yao, D. (2020). Compression of cerebellar functional gradients in schizophrenia. *Schizophrenia Bulletin, 46*(5), 1282–1295. https://doi.org/10.1093/schbul/sbaa016

Doody, J. S., Burghardt, G., & Dinets, V. (2023). The evolution of sociality and the polyvagal theory. *Biological Psychology, 180*, Article 108569. https://doi.org/10.1016/j.biopsycho.2023.108569

Dublin, P., & Hanani, M. (2007). Satellite glial cells in sensory ganglia: Their possible contribution to inflammatory pain. *Brain, Behavior, and Immunity, 21*(5), 592–598. https://doi.org/10.1016/j.bbi.2006.11.011

Dum, R. P., Levinthal, D. J., & Strick, P. L. (2016). Motor, cognitive, and affective areas of the cerebral cortex influence the adrenal medulla. *Proceedings of the National Academy of Sciences, 113*(35), 9922–9927. https://doi.org/10.1073/pnas.1605044113

Duvernoy, H. M., & Risold, P.-Y. (2007). The circumventricular organs: An atlas of comparative anatomy and vascularization. *Brain Research Reviews, 56*(1), 119–147. https://doi.org/10.1016/j.brainresrev.2007.06.002

Ellenberger, H. H., & Feldman, J. L. (1990). Subnuclear organization of the lateral tegmental field of the rat. I: Nucleus ambiguus and ventral respiratory group. *Journal of Comparative Neurology, 294*(2), 202–211. https://doi.org/10.1002/cne.902940205

Erskine, A., Ackels, T., Dasgupta, D., Fukunaga, I., & Schaefer, A. T. (2019). *Mammalian olfaction Islem- a high temporal bandwidth Sense.* , Article 570689. https://doi.org/10.1101/570689

Feldheim, D. A., Vanderhaeghen, P., Hansen, M. J., Frisén, J., Lu, Q., Barbacid, M., & Flanagan, J. G. (1998). Topographic guidance labels in a sensory projection to the forebrain. *Neuron, 21*(6), 1303–1313. https://doi.org/10.1016/S0896-6273(00)80650-9

Feldman, H., & Friston, K. (2010). Attention, uncertainty, and free-energy. *Frontiers in Human Neuroscience, 4*. https://doi.org/10.3389/fnhum.2010.00215

Feldman-Goriachnik, R., Belzer, V., & Hanani, M. (2015). Systemic inflammation activates satellite glial cells in the mouse nodose ganglion and alters their functions. *Glia, 63*(11), 2121–2132. https://doi.org/10.1002/glia.22881

Feldman-Goriachnik, R., & Hanani, M. (2021). How do neurons in sensory ganglia communicate with satellite glial cells? *Brain Research, 1760*, Article 147384. https://doi.org/10.1016/j.brainres.2021.147384

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate. *Cerebral Cortex Cerebral Cortex (New York, N Y: 1991), 1*(1), 1–47. https://doi.org/10.1093/cercor/1.1.1-a

Feng, T., & Narayanan, S. S. (2019). Discovering optimal variable-length time series motifs in large-scale wearable recordings of human bio-behavioral signals. *ICASSP 2019 - 2019 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, 7615–7619. https://doi.org/10.1109/ICASSP.2019.8682427

Finlay, B. L., & Uchiyama, R. (2015). Developmental mechanisms channeling cortical evolution. *Trends in Neurosciences, 38*(2), 69–76. https://doi.org/10.1016/j.tins.2014.11.004

Flash, T., & Bizzi, E. (2016). Cortical circuits and modules in movement generation: Experiments and theories. *Current Opinion in Neurobiology, 41*, 174–178. https://doi.org/10.1016/j.conb.2016.09.013

Follesa, P., Biggio, F., Gorini, G., Caria, S., Talani, G., Dazzi, L., Puligheddu, M., Marrosu, F., & Biggio, G. (2007). Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. *Brain Research, 1179*, 28–34. https://doi.org/10.1016/j.brainres.2007.08.045

Fox, E. A., & Powley, T. L. (1985). Longitudinal columnar organization within the dorsal motor nucleus represents separate branches of the abdominal vagus. *Brain Research, 341*(2), 269–282. https://doi.org/10.1016/0006-8993(85)91066-2

Frisén, J., Yates, P. A., McLaughlin, T., Friedman, G. C., O'Leary, D. D. M., & Barbacid, M. (1998). Ephrin-A5 (AL-1/RAGS) is essential for proper retinal axon guidance and topographic mapping in the mammalian visual system. *Neuron, 20*(2), 235–243. https://doi.org/10.1016/S0896-6273(00)80452-3

Friston, K. (2010). The free-energy principle: A unified brain theory? *Nature Reviews Neuroscience, 11*(2), 127–138. https://doi.org/10.1038/nrn2787

Fung, C., & Vanden Berghe, P. (2020). Functional circuits and signal processing in the enteric nervous system. *Cellular and Molecular Life Sciences, 77*(22), 4505–4522. https://doi.org/10.1007/s00018-020-03543-6

Gatti, P. J., Johnson, T. A., & John Massari, V. (1996). Can neurons in the nucleus ambiguus selectively regulate cardiac rate and atrio-ventricular conduction? *Journal of the Autonomic Nervous System, 57*(1), 123–127. https://doi.org/10.1016/0165-1838(95)00104-2

Gavard, J. A., Lustman, P. J., & Clouse, R. E. (1993). Prevalence of depression in adults with diabetes. An epidemiological evaluation. *Diabetes Care, 16*(8), 1167–1178. https://doi.org/10.2337/diacare.16.8.1167

Gerkin, R. C., & Castro, J. B. (2015). The number of olfactory stimuli that humans can discriminate is still unknown. *ELife, 4*, Article e08127. https://doi.org/10.7554/eLife.08127

Ghacibeh, G. A., Shenker, J. I., Shenal, B., Uthman, B. M., & Heilman, K. M. (2006). The influence of vagus nerve stimulation on memory. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology, 19*(3), 119–122. https://doi.org/10.1097/01.wnn.0000213908.34278.7d

Giessel, A. J., & Datta, S. R. (2014). Olfactory maps, circuits and computations. *Current Opinion in Neurobiology, 0*, 120–132. https://doi.org/10.1016/j.conb.2013.09.010

Goehler, L. E., Gaykema, R. P. A., Hansen, M. K., Anderson, K., Maier, S. F., & Watkins, L. R. (2000). Vagal immune-to-brain communication: A visceral chemosensory pathway. *Autonomic Neuroscience, 85*(1), 49–59. https://doi.org/10.1016/S1566-0702(00)00219-8

Gordon, E. M., Chauvin, R. J., Van, A. N., Rajesh, A., Nielsen, A., Newbold, D. J., Lynch, C. J., Seider, N. A., Krimmel, S. R., Scheidter, K. M., Monk, J., Miller, R. L., Metoki, A., Montez, D. F., Zheng, A., Elbau, I., Madison, T., Nishino, T., Myers, M. J., & Dosenbach, N. U. F. (2023). A somato-cognitive action network alternates with effector regions in motor cortex. *Nature*, 1–9. https://doi.org/10.1038/s41586-023-05964-2

Gottfried, J. A. (2010). Central mechanisms of odour object perception. *Nature Reviews Neuroscience, 11*(9), Article 9. https://doi.org/10.1038/nrn2883

Goyal, A., Miller, J., Qasim, S. E., Watrous, A. J., Zhang, H., Stein, J. M., Inman, C. S., Gross, R. E., Willie, J. T., Lega, B., Lin, J.-J., Sharan, A., Wu, C., Sperling, M. R., Sheth, S. A., McKhann, G. M., Smith, E. H., Schevon, C., & Jacobs, J. (2020). Functionally distinct high and low theta oscillations in the human hippocampus. *Nature Communications, 11*(1), Article 1. https://doi.org/10.1038/s41467-020-15670-6

Graziano, M. S. A. (2016). Ethological action maps: A paradigm shift for the motor cortex. *Trends in Cognitive Sciences, 20*(2), 121–132. https://doi.org/10.1016/j.tics.2015.10.008

Graziano, M. S. A. (2023). Fundamental principles of cortical organization reflected in a new study. *Neuron*. https://doi.org/10.1016/j.neuron.2023.04.024

Gronowitz, M. E., Liu, A., Qiu, Q., Yu, C. R., & Cleland, T. A. (2021). A physicochemical model of odor sampling. *PLoS Computational Biology, 17*(6), Article e1009054. https://doi.org/10.1371/journal.pcbi.1009054

Grossman, P. (2023). Fundamental challenges and likely refutations of the five basic premises of the polyvagal theory. *Biological Psychology, 180*, Article 108589. https://doi.org/10.1016/j.biopsycho.2023.108589

Grossman, P., & Taylor, E. W. (2007). Toward understanding respiratory sinus arrhythmia: Relations to cardiac vagal tone, evolution and biobehavioral functions. *Biological Psychology, 74*(2), 263–285. https://doi.org/10.1016/j.biopsycho.2005.11.014

Grover, D., & Tavare, S. (2009). Finding behavioral motifs in fly trajectories. *Communications in Information and Systems, 9*(3), 283–294. https://doi.org/10.4310/CIS.2009.v9.n3.a5

Guell, X., Schmahmann, J. D., Gabrieli, J. D., & Ghosh, S. S. (2018). Functional gradients of the cerebellum. *ELife, 7*, Article e36652. https://doi.org/10.7554/eLife.36652

Gupta, A. S., van der Meer, M. A. A., Touretzky, D. S., & Redish, A. D. (2012). Segmentation of spatial experience by hippocampal theta sequences. *Nature Neuroscience, 15*(7), 1032–1039. https://doi.org/10.1038/nn.3138

Hammer, N., Löffler, S., Cakmak, Y. O., Ondruschka, B., Planitzer, U., Schultz, M., Winkler, D., & Weise, D. (2018). Cervical vagus nerve morphometry and vascularity in the context of nerve stimulation—A cadaveric study. *Scientific Reports, 8*(1), Article 1. https://doi.org/10.1038/s41598-018-26135-8

Han, K.-S., Chen, C. H., Khan, M. M., Guo, C., & Regehr, W. G. (2020). Climbing fiber synapses rapidly and transiently inhibit neighboring Purkinje cells via ephaptic coupling. *Nature Neuroscience, 23*(11), 1399–1409. https://doi.org/10.1038/s41593-020-0701-z

Han, K.-S., Guo, C., Chen, C. H., Witter, L., Osorno, T., & Regehr, W. G. (2018). Ephaptic coupling promotes synchronous firing of Cerebellar purkinje cells. *Neuron, 100*(3), 564–578.e3. https://doi.org/10.1016/j.neuron.2018.09.018

Hanani, M. (2010). Satellite glial cells in sympathetic and parasympathetic ganglia: In search of function. *Brain Research Reviews, 64*(2), 304–327. https://doi.org/10.1016/j.brainresrev.2010.04.009

Hanani, M., & Spray, D. C. (2020). Emerging importance of satellite glia in nervous system function and dysfunction. *Nature Reviews Neuroscience, 21*(9), 485–498. https://doi.org/10.1038/s41583-020-0333-z

Hanchate, N. K., Kondoh, K., Lu, Z., Kuang, D., Ye, X., Qiu, X., Pachter, L., Trapnell, C., & Buck, L. B. (2015). Single-cell transcriptomics reveals receptor transformations during olfactory neurogenesis. *Science, 350*(6265), 1251–1255. https://doi.org/10.1126/science.aad2456

Hartline, D. K. (2008). What is myelin? *Neuron Glia Biology, 4*(2), 153–163. https://doi.org/10.1017/S1740925X09990263

Havton, L. A., Biscola, N. P., Stern, E., Mihaylov, P. V., Kubal, C. A., Wo, J. M., Gupta, A., Baronowsky, E., Ward, M. P., Jaffey, D. M., & Powley, T. L. (2021). Human organ donor-derived vagus nerve biopsies allow for well-preserved ultrastructure and high-resolution mapping of myelinated and unmyelinated fibers. *Scientific Reports, 11*(1), Article 1. https://doi.org/10.1038/s41598-021-03248-1

Hegdé, J., & Felleman, D. J. (2007). Reappraising the functional implications of the primate visual anatomical hierarchy. *The Neuroscientist, 13*(5), 416–421. https://doi.org/10.1177/1073858407305201

Herzfeld, D. J., & Shadmehr, R. (2014). Cerebellum estimates the sensory state of the body. *Trends in Cognitive Sciences, 18*(2), 66–67. https://doi.org/10.1016/j.tics.2013.10.015

van den Heuvel, M. P., & Sporns, O. (2013). Network hubs in the human brain. *Trends in Cognitive Sciences, 17*(12), 683–696. https://doi.org/10.1016/j.tics.2013.09.012

Hilgetag, C. C., & Goulas, A. (2020). 'Hierarchy' in the organization of brain networks. *Philosophical Transactions of the Royal Society B: Biological Sciences, 375*(1796), Article 20190319. https://doi.org/10.1098/rstb.2019.0319

Hoemann, K., Khan, Z., Feldman, M. J., Nielson, C., Devlin, M., Dy, J., Barrett, L. F., Wormwood, J. B., & Quigley, K. S. (2020). Context-aware experience sampling reveals the scale of variation in affective experience. *Scientific Reports, 10*(1), 12459. https://doi.org/10.1038/s41598-020-69180-y

Hoffmann, L. C., Cicchese, J. J., & Berry, S. D. (2015). Harnessing the power of theta: Natural manipulations of cognitive performance during hippocampal theta-contingent eyeblink conditioning. *Frontiers in Systems Neuroscience, 9*, 50. https://doi.org/10.3389/fnsys.2015.00050

Hopkins, D. A., & Armour, J. A. (1998). Brainstem cells of origin of physiologically identified cardiopulmonary nerves in the rhesus monkey (Macaca mulatta. *Journal of the Autonomic Nervous System, 68*(1), 21–32. https://doi.org/10.1016/S0165-1838(97)00112-4

ter Horst, G. J., Luiten, P. G. M., & Kuipers, F. (1984). Descending pathways from hypothalamus to dorsal motor vagus and ambiguus nuclei in the rat. *Journal of the Autonomic Nervous System, 11*(1), 59–75. https://doi.org/10.1016/0165-1838(84)90008-0

Hsieh, J. H., Chen, R. F., Wu, J. J., Yen, C. T., & Chai, C. Y. (1998). Vagal innervation of the gastrointestinal tract arises from dorsal motor nucleus while that of the heart largely from nucleus ambiguus in the cat. *Journal of the Autonomic Nervous System, 70*(1), 38–50. https://doi.org/10.1016/S0165-1838(98)00027-7

Hsueh, B., Chen, R., Jo, Y., Tang, D., Raffiee, M., Kim, Y. S., Inoue, M., Randles, S., Ramakrishnan, C., Patel, S., Kim, D. K., Liu, T. X., Kim, S. H., Tan, L., Mortazavi, L., Cordero, A., Shi, J., Zhao, M., Ho, T. T., & Deisseroth, K. (2023). Cardiogenic control of affective behavioural state. *Nature, 615*(7951), Article 7951. https://doi.org/10.1038/s41586-023-05748-8

Huang, X.-F., Törk, I., & Paxinos, G. (1993). Dorsal motor nucleus of the vagus nerve: A cyto- and chemoarchitectonic study in the human. *Journal of Comparative Neurology, 330*(2), 158–182. https://doi.org/10.1002/cne.903300203

Hutchinson, J. B., & Barrett, L. F. (2019). The power of predictions: An emerging paradigm for psychological research. *Current Directions in Psychological Science, 28*(3), 280–291. https://doi.org/10.1177/0963721419831992

Igarashi, K. M., Ieki, N., An, M., Yamaguchi, Y., Nagayama, S., Kobayakawa, K., Kobayakawa, R., Tanifuji, M., Sakano, H., Chen, W. R., & Mori, K. (2012). Parallel mitral and tufted cell pathways route distinct odor information to different targets in the olfactory cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 32*(23), 7970–7985. https://doi.org/10.1523/JNEUROSCI.0154-12.2012

Illig, K. R., & Haberly, L. B. (2003). Odor-evoked activity is spatially distributed in piriform cortex. *The Journal of Comparative Neurology, 457*(4), 361–373. https://doi.org/10.1002/cne.10557

Imamura, F., Ito, A., & LaFever, B. J. (2020). Subpopulations of projection neurons in the olfactory bulb. *Frontiers in Neural Circuits, 14*. https://doi.org/10.3389/fncir.2020.561822

Inagaki, S., Iwata, R., Iwamoto, M., & Imai, T. (2020). Widespread inhibition, antagonism, and synergy in mouse olfactory sensory neurons in vivo. *Cell Reports, 31*(13), Article 107814. https://doi.org/10.1016/j.celrep.2020.107814

Jacobs, J. (2014). Hippocampal theta oscillations are slower in humans than in rodents: Implications for models of spatial navigation and memory. *Philosophical Transactions of the Royal Society B: Biological Sciences, 369*(1635), Article 20130304. https://doi.org/10.1098/rstb.2013.0304

Jacobs, L. F., Arter, J., Cook, A., & Sulloway, F. J. (2015). Olfactory orientation and navigation in humans. *PLOS ONE, 10*(6), Article e0129387. https://doi.org/10.1371/journal.pone.0129387

Jänig, W. H. (2006). Visceral afferent neurons and autonomic regulations. Chapter 2. *Integrative Action of the Autonomic Nervous System: Neurobiology of Homeostasis* (pp. 37–65). Cambridge, New York: Cambridge University Press.

Jayaprakash, N., Song, W., Toth, V., Vardhan, A., Levy, T., Tomaio, J., Qanud, K., Mughrabi, I., Chang, Y.-C., Rob, M., Daytz, A., Abbas, A., Nassrallah, Z., Volpe, B. T., Tracey, K. J., Al-Abed, Y., Datta-Chaudhuri, T., Miller, L., Barbe, M. F., & Zanos, S. (2023). Organ- and function-specific anatomical organization of vagal fibers supports fascicular vagus nerve stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 16*(2), 484–506. https://doi.org/10.1016/j.brs.2023.02.003

Jékely, G., Keijzer, F., & Godfrey-Smith, P. (2015). An option space for early neural evolution. *Philosophical Transactions of the Royal Society B: Biological Sciences, 370*(1684), Article 20150181. https://doi.org/10.1098/rstb.2015.0181

Jordan, R., & Keller, G. B. (2020). Opposing influence of top-down and bottom-up input on excitatory layer 2/3 neurons in mouse primary visual cortex. *Neuron, 108*(6), 1194–1206.e5. https://doi.org/10.1016/j.neuron.2020.09.024

Kalaska, J., Rizzolatti, P., et al. (2013). Voluntary movement: The primary motor cortex. *Principles of Neural Science*.

Kalia, M., & Mesulam, M.-M. (1980a). Brain stem projections of sensory and motor components of the vagus complex in the cat: I. The cervical vagus and nodose

ganglion. *Journal of Comparative Neurology, 193*(2), 435–465. https://doi.org/10.1002/cne.901930210
Kalia, M., & Mesulam, M.-M. (1980b). Brain stem projections of sensory and motor components of the vagus complex in the cat: II. Laryngeal, tracheobronchial, pulmonary, cardiac, and gastrointestinal branches. *Journal of Comparative Neurology, 193*(2), 467–508. https://doi.org/10.1002/cne.901930211
Kalia, M., & Sullivan, J. M. (1982). Brainstem projections of sensory and motor components of the vagus nerve in the rat. *The Journal of Comparative Neurology, 211*(3), 248–265. https://doi.org/10.1002/cne.902110304
Kanai, R., Komura, Y., Shipp, S., & Friston, K. (2015). Cerebral hierarchies: Predictive processing, precision and the pulvinar. *Philosophical Transactions of the Royal Society B: Biological Sciences, 370*(1668), Article 20140169. https://doi.org/10.1098/rstb.2014.0169
Kandel, E. R., Schwartz, J. H., Jessel, T. M., Siegelbaum, S. A., & Hudspeth, A. J. (2014). The constructive nature of visual processing. *Principles of Neural Science (Fifth Edition)*. McGraw-Hill Education,.
Karalis, N., & Sirota, A. (2022). Breathing coordinates cortico-hippocampal dynamics in mice during offline states. *Nature Communications, 13*(1), 467. https://doi.org/10.1038/s41467-022-28090-5
Karim, M. A., Leong, S. K., & Perwaiz, S. A. (1981). On the anatomical organization of the vagal nuclei. *American Journal of Primatology, 1*(3), 277–292. https://doi.org/10.1002/ajp.1350010305
Karim, M. A., Shaikh, E., Tan, J., & Ismail, Z. (1984). The organization of the gastric efferent projections in the brainstem of monkey: An HRP study. *Brain Research, 293*(2), 231–240. https://doi.org/10.1016/0006-8993(84)91230-7
Katsumi, Y., Theriault, J. E., Quigley, K. S., & Barrett, L. F. (2022). Allostasis as a core feature of hierarchical gradients in the human brain. *Network Neuroscience*, 1–22. https://doi.org/10.1162/netn_a_00240
Katsumi, Y., Zhang, J., Chen, D., Kamona, N., Bunce, J. G., Hutchinson, J. B., Yarossi, M., Tunik, E., Dickerson, B. C., Quigley, K. S., & Barrett, L. F. (2023). Correspondence of functional connectivity gradients across human isocortex, cerebellum, and hippocampus. *Communications Biology, 6*, 401. https://doi.org/10.1038/s42003-023-04796-0
Katz, B., & Schmitt, O. H. (1940). Electric interaction between two adjacent nerve fibres. *The Journal of Physiology, 97*(4), 471–488.
Keller, A. (2016). *Philosophy of Olfactory Perception*. Springer International Publishing. https://doi.org/10.1007/978-3-319-33645-9
Keller, G. B., & Mrsic-Flogel, T. D. (2018). Predictive processing: A canonical cortical computation. *Neuron, 100*(2), 424–435. https://doi.org/10.1016/j.neuron.2018.10.003
Kharabian Masouleh, S., Plachti, A., Hoffstaedter, F., Eickhoff, S., & Genon, S. (2020). Characterizing the gradients of structural covariance in the human hippocampus. *NeuroImage, 218*, Article 116972. https://doi.org/10.1016/j.neuroimage.2020.116972
Kim, S.-H., Hadley, S. H., Maddison, M., Patil, M., Cha, B., Kollarik, M., & Taylor-Clark, T. E. (2020). Mapping of sensory nerve subsets within the vagal ganglia and brainstem using reporter mice for Pirt, TRPV1, 5-HT3, and Tac1 expression. *ENeuro, 7*(2). https://doi.org/10.1523/ENEURO.0494-19.2020
Kim, U. S., Mahroo, O. A., Mollon, J. D., & Yu-Wai-Man, P. (2021). Retinal ganglion cells—Diversity of cell types and clinical relevance. *Frontiers in Neurology, 12*. https://doi.org/10.3389/fneur.2021.661938
Kiriella, D. A., Islam, S., Oridota, O., Sohler, N., Dessenne, C., Beaufort, C., de, Fagherazzi, G., & Aguayo, G. A. (2021). Unraveling the concepts of distress, burnout, and depression in type 1 diabetes: A scoping review. *EClinicalMedicine, 40*. https://doi.org/10.1016/j.eclinm.2021.101118
Kitamura, S., Nagase, Y., Chen, K., & Shigenaga, Y. (1993). Nucleus ambiguus of the rabbit: Cytoarchitectural subdivision and myotopical and neurotopic representations. *The Anatomical Record, 237*(1), 109–123. https://doi.org/10.1002/ar.1092370111
Kleckner, I. R., Zhang, J., Touroutoglou, A., Chanes, L., Xia, C., Simmons, W. K., Quigley, K. S., Dickerson, B. C., & Barrett, L. F. (2017). Evidence for a large-scale brain system supporting allostasis and interoception in humans. *Nature Human Behaviour, 1*. https://doi.org/10.1038/s41562-017-0069
Kota, S., Rugg, M. D., & Lega, B. C. (2020). Hippocampal theta oscillations support successful associative memory function. *Journal of Neuroscience, 40*(49), 9507–9518. https://doi.org/10.1523/JNEUROSCI.0767-20.2020
Kucyi, A., & Davis, K. D. (2015). The dynamic pain connectome. *Trends in Neurosciences, 38*(2), 86–95. https://doi.org/10.1016/j.tins.2014.11.006
Kumaran, D., Hassabis, D., & McClelland, J. L. (2016). What learning systems do intelligent agents need? Complementary learning systems theory updated. *Trends in Cognitive Sciences, 20*(7), 512–534. https://doi.org/10.1016/j.tics.2016.05.004
Kurian, S. M., Naressi, R. G., Manoel, D., Barwich, A.-S., Malnic, B., & Saraiva, L. R. (2021). Odor coding in the mammalian olfactory epithelium. *Cell and Tissue Research, 383*(1), 445–456. https://doi.org/10.1007/s00441-020-03327-1
Lamme, V. A., & Roelfsema, P. R. (2000). The distinct modes of vision offered by feedforward and recurrent processing. *Trends in Neurosciences, 23*(11), 571–579. https://doi.org/10.1016/s0166-2236(00)01657-x
Leslie, R. A., & Gwyn, D. G. (1984). Neuronal connections of the area postrema. *Federation Proceedings, 43*(15), 2941–2943.
Leslie, R. A., Gwyn, D. G., & Hopkins, D. A. (1982). The central distribution of the cervical vagus nerve and gastric afferent and efferent projections in the rat. *Brain Research Bulletin, 8*(1), 37–43. https://doi.org/10.1016/0361-9230(82)90025-9
Levinthal, D. J., & Strick, P. L. (2012). The motor cortex communicates with the kidney. *Journal of Neuroscience, 32*(19), 6726–6731. https://doi.org/10.1523/JNEUROSCI.0406-12.2012
Levinthal, D. J., & Strick, P. L. (2020). Multiple areas of the cerebral cortex influence the stomach. *Proceedings of the National Academy of Sciences, 117*(23), 13078–13083. https://doi.org/10.1073/pnas.2002737117
Lisman, J., & Redish, A. D. (2009). Prediction, sequences and the hippocampus. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences, 364*(1521), 1193–1201. https://doi.org/10.1098/rstb.2008.0316
Llewellyn-Smith, I. J., & Verberne, A. J. M. (2011). *Central Regulation of Autonomic Functions*. Oxford University Press.
Lochmann, T., & Deneve, S. (2011). Neural processing as causal inference. *Current Opinion in Neurobiology, 21*(5), 774–781. https://doi.org/10.1016/j.conb.2011.05.018
Loewy, A. D. (1990). Central autonomic pathways. In K. M. Spyer (Ed.), *Central Regulation of Autonomic Functions* (pp. 88–103). New York: Oxford University Press.
Loewy, A. D., & Spyer, K. M. (Eds.). (1990). *Central Regulation of Autonomic Functions*. Oxford University Press.
Luo, L., & Flanagan, J. G. (2007). Development of continuous and discrete neural maps. *Neuron, 56*(2), 284–300. https://doi.org/10.1016/j.neuron.2007.10.014
Luxem, K., Mocellin, P., Fuhrmann, F., Kürsch, J., Miller, S. R., Palop, J. J., Remy, S., & Bauer, P. (2022). Identifying behavioral structure from deep variational embeddings of animal motion. *Communications Biology, 5*(1), 1267. https://doi.org/10.1038/s42003-022-04080-7
MacIver, M. A., & Finlay, B. L. (2022). The neuroecology of the water-to-land transition and the evolution of the vertebrate brain. *Philosophical Transactions of the Royal Society B: Biological Sciences, 377*(1844), Article 20200523. https://doi.org/10.1098/rstb.2020.0523
Malnic, B., Hirono, J., Sato, T., & Buck, L. B. (1999). Combinatorial receptor codes for odors. *Cell, 96*(5), 713–723. https://doi.org/10.1016/s0092-8674(00)80581-4
Manzini, I., Schild, D., & Di Natale, C. (2022). Principles of odor coding in vertebrates and artificial chemosensory systems. *Physiological Reviews, 102*(1), 61–154. https://doi.org/10.1152/physrev.00036.2020
Margulies, D. S., Ghosh, S. S., Goulas, A., Falkiewicz, M., Huntenburg, J. M., Langs, G., Bezgin, G., Eickhoff, S. B., Castellanos, F. X., Petrides, M., Jefferies, E., & Smallwood, J. (2016). Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proceedings of the National Academy of Sciences, 113*(44), 12574–12579. https://doi.org/10.1073/pnas.1608282113
Markov, N. T., Ercsey-Ravasz, M., Van Essen, D. C., Knoblauch, K., Toroczkai, Z., & Kennedy, H. (2013). Cortical high-density counterstream architectures. *Science, 342*(6158), Article 1238406. https://doi.org/10.1126/science.1238406
Marrazzi, A. S., & de No, R. L. (1944). Interaction of neighboring fibers in myelinated nerves. *Journal of Neurophysiology, 7*(2), 83–101. https://doi.org/10.1152/jn.1944.7.2.83
Massari, V. J., Johnson, T. A., & Gatti, P. J. (1995). Cardiotopic organization of the nucleus ambiguus? An anatomical and physiological analysis of neurons regulating atrioventricular conduction. *Brain Research, 679*(2), 227–240. https://doi.org/10.1016/0006-8993(95)00227-H
McAllen, R. M., & Spyer, K. M. (1978). Two types of vagal preganglionic motoneurones projecting to the heart and lungs. *The Journal of Physiology, 282*(1), 353–364. https://doi.org/10.1113/jphysiol.1978.sp012468
McLean, J. H., & Hopkins, D. A. (1985a). Ultrastructure of the dorsal motor nucleus of the vagus nerve in monkey with a comparison of synaptology in monkey and cat. *The Journal of Comparative Neurology, 231*(2), 162–174. https://doi.org/10.1002/cne.902310204
McLean, J. H., & Hopkins, D. A. (1985b). Ultrastructural studies of the nucleus ambiguus in cat and monkey following injection of HRP into the vagus nerve. *Journal of Neurocytology, 14*(6), 961–979. https://doi.org/10.1007/BF01224807
McRitchie, D. A., & Törk, I. (1993). The internal organization of the human solitary nucleus. *Brain Research Bulletin, 31*(1–2), 171–193. https://doi.org/10.1016/0361-9230(93)90024-6
Meister, M. (2015). On the dimensionality of odor space. *ELife, 4*, Article e07865. https://doi.org/10.7554/eLife.07865
Mesik, J., Kay, K. N., & Oxenham, A. J. (2022). Distinct representations of tonotopy and pitch in human auditory cortex. *Journal of Neuroscience, 42*(3), 416–434. https://doi.org/10.1523/JNEUROSCI.0960-21.2021
Milardi, D., Cacciola, A., Calamuneri, A., Ghilardi, M. F., Caminiti, F., Cascio, F., Andronaco, V., Anastasi, G., Mormina, E., Arrigo, A., Bruschetta, D., & Quartarone, A. (2017). The olfactory system revealed: Non-invasive mapping by using constrained spherical deconvolution tractography in healthy humans. *Frontiers in Neuroanatomy, 11*. https://doi.org/10.3389/fnana.2017.00032
Min, D. K., Tuor, U. I., & Chelikani, P. K. (2011). Gastric distention induced functional magnetic resonance signal changes in the rodent brain. *Neuroscience, 179*, 151–158. https://doi.org/10.1016/j.neuroscience.2011.01.051
Min, D. K., Tuor, U. I., Koopmans, H. S., & Chelikani, P. K. (2011). Changes in differential functional magnetic resonance signals in the rodent brain elicited by mixed-nutrient or protein-enriched meals. *Gastroenterology, 141*(5), 1832–1841. https://doi.org/10.1053/j.gastro.2011.07.034
Miselis, R., & Shapiro, R. (1983). Dorsal motor nucleus neurons have extensive dendrites penetrating the nucleus of the solitary tract. *Federation Proceedings, 42*(4).
Morgan, J. L., Berger, D. R., Wetzel, A. W., & Lichtman, J. W. (2016). The fuzzy logic of network connectivity in mouse visual thalamus. *Cell, 165*(1), 192–206. https://doi.org/10.1016/j.cell.2016.02.033
Mussa, B. M., & Verberne, A. J. M. (2013). The dorsal motor nucleus of the vagus and regulation of pancreatic secretory function. *Experimental Physiology, 98*(1), 25–37. https://doi.org/10.1113/expphysiol.2012.066472
Mussa-Ivaldi, F. A., & Bizzi, E. (2000). Motor learning through the combination of primitives. *Philosophical Transactions of the Royal Society B: Biological Sciences, 355*(1404), 1755–1769.

Nara, K., Saraiva, L. R., Ye, X., & Buck, L. B. (2011). A large-scale analysis of odor coding in the olfactory epithelim. *Journal of Neuroscience, 31*(25), 9179–9191. https://doi.org/10.1523/JNEUROSCI.1282-11.2011

Nassenstein, C., Taylor-Clark, T. E., Myers, A. C., Ru, F., Nandigama, R., Bettner, W., & Undem, B. J. (2010). Phenotypic distinctions between neural crest and placodal derived vagal C-fibres in mouse lungs. *The Journal of Physiology, 588*(Pt 23), 4769–4783. https://doi.org/10.1113/jphysiol.2010.195339

Nemeroff, C. B., Mayberg, H. S., Krahl, S. E., McNamara, J., Frazer, A., Henry, T. R., George, M. S., Charney, D. S., & Brannan, S. K. (2006). VNS therapy in treatment-resistant depression: Clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology, 31*(7), Article 7. https://doi.org/10.1038/sj.npp.1301082

Neuhuber, W. L. (1987). Sensory vagal innervation of the rat esophagus and cardia: A light and electron microscopic anterograde tracing study. *Journal of the Autonomic Nervous System, 20*(3), 243–255. https://doi.org/10.1016/0165-1838(87)90153-6

Neuhuber, W. L., & Berthoud, H.-R. (2022). Functional anatomy of the vagus system: How does the polyvagal theory comply? *Biological Psychology, 174*, Article 108425. https://doi.org/10.1016/j.biopsycho.2022.108425

Neuhuber, W. L., & Sandoz, P. A. (1986). Vagal primary afferent terminals in the dorsal motor nucleus of the rat: Are they making monosynaptic contacts on preganglionic efferent neurons? *Neuroscience Letters, 69*(2), 126–130. https://doi.org/10.1016/0304-3940(86)90590-2

Niimura, Y., Matsui, A., & Touhara, K. (2014). Extreme expansion of the olfactory receptor gene repertoire in African elephants and evolutionary dynamics of orthologous gene groups in 13 placental mammals. *Genome Research, 24*(9), 1485–1496. https://doi.org/10.1101/gr.169532.113

Niimura, Y., & Nei, M. (2005). Comparative evolutionary analysis of olfactory receptor gene clusters between humans and mice. *Gene, 346*, 13–21. https://doi.org/10.1016/j.gene.2004.09.025

Niven, J. E., & Laughlin, S. B. (2008). Energy limitation as a selective pressure on the evolution of sensory systems. *The Journal of Experimental Biology, 211*(Pt 11), 1792–1804. https://doi.org/10.1242/jeb.017574

Noble, E. E., Billington, C. J., Kotz, C. M., & Wang, C. (2011). The lighter side of BDNF. *American Journal of Physiology Regulatory, Integrative and Comparative Physiology, 300*(5), R1053–1069. https://doi.org/10.1152/ajpregu.00776.2010

Norgren, R., & Smith, G. P. (1988). Central distribution of subdiaphragmatic vagal branches in the rat. *Journal of Comparative Neurology, 273*(2), 207–223. https://doi.org/10.1002/cne.902730206

Oh, E. J., & Weinreich, D. (2002). Chemical communication between vagal afferent somata in nodose ganglia of the rat and the guinea pig in vitro. *Journal of Neurophysiology, 87*(6), 2801–2807. https://doi.org/10.1152/jn.2002.87.6.2801

Öngür, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys, and humans. *Cerebral Cortex, 10*(3), 206–219. https://doi.org/10.1093/cercor/10.3.206

Ottaviani, M. M., Wright, L., Dawood, T., & Macefield, V. G. (2020). In vivo recordings from the human vagus nerve using ultrasound-guided microneurography. *The Journal of Physiology, 598*(17), 3569–3576. https://doi.org/10.1113/JP280077

Owens, A. P., Allen, M., Ondobaka, S., & Friston, K. J. (2018). Interoceptive inference: From computational neuroscience to clinic. *Neuroscience and Biobehavioral Reviews, 90*, 174–183. https://doi.org/10.1016/j.neubiorev.2018.04.017

Paquola, C., Wael, R. V. D., Wagstyl, K., Bethlehem, R. A. I., Hong, S.-J., Seidlitz, J., Bullmore, E. T., Evans, A. C., Misic, B., Margulies, D. S., Smallwood, J., & Bernhardt, B. C. (2019). Microstructural and functional gradients are increasingly dissociated in transmodal cortices. *PLOS Biology, 17*(5), Article e3000284. https://doi.org/10.1371/journal.pbio.3000284

Parr, T., & Friston, K. J. (2019). Attention or salience? *Current Opinion in Psychology, 29*, 1–5. https://doi.org/10.1016/j.copsyc.2018.10.006

Paton, J. F. R. (1999). Nucleus tractus solitarii: Integrating structures. *Experimental Physiology, 84*(5), 815–833. https://doi.org/10.1111/j.1469-445X.1999.01912.x

Paulus, M. P., Feinstein, J. S., & Khalsa, S. S. (2019). An active inference approach to interoceptive psychopathology. *Annual Review of Clinical Psychology, 15*(1), 97–122. https://doi.org/10.1146/annurev-clinpsy-050718-095617

Paulus, M. P., & Stein, M. B. (2010). Interoception in anxiety and depression. *Brain Structure and Function, 214*(5–6), 451–463. https://doi.org/10.1007/s00429-010-0258-9

Pearson, K., & Gordon, J. (2014). Spinal Reflexes (Book, Section). In *Principles of Neural Science, Fifth Edition* (Vol. 1). McGraw-Hill Education,.

Pelot, N. A., Goldhagen, G. B., Cariello, J. E., Musselman, E. D., Clissold, K. A., Ezzell, J. A., & Grill, W. M. (2020). Quantified morphology of the cervical and subdiaphragmatic vagus nerves of human, pig, and rat. *Frontiers in Neuroscience, 14*, Article 601479. https://doi.org/10.3389/fnins.2020.601479

Pezzulo, G., Kemere, C., & van der Meer, M. A. A. (2017). Internally generated hippocampal sequences as a vantage point to probe future-oriented cognition: Hippocampal sequences and future-oriented cognition. *Annals of the New York Academy of Sciences, 1396*(1), 144–165. https://doi.org/10.1111/nyas.13329

Pezzulo, G., Rigoli, F., & Friston, K. (2015). Active Inference, homeostatic regulation and adaptive behavioural control. *Progress in Neurobiology, 134*, 17–35. https://doi.org/10.1016/j.pneurobio.2015.09.001

Pfister, P., Smith, B. C., Evans, B. J., Brann, J. H., Trimmer, C., Sheikh, M., Arroyave, R., Reddy, G., Jeong, H.-Y., Raps, D. A., Peterlin, Z., Vergassola, M., & Rogers, M. E. (2020). Odorant receptor inhibition is fundamental to odor encoding. *Current Biology, 30*(13), 2574–2587.e6. https://doi.org/10.1016/j.cub.2020.04.086

Porges, S. W. (1995). Orienting in a defensive world: Mammalian modifications of our evolutionary heritage. A Polyvagal Theory. *Psychophysiology, 32*(4), 301–318. https://doi.org/10.1111/j.1469-8986.1995.tb01213.x

Porges, S. W. (2021). Polyvagal Theory: A biobehavioral journey to sociality. *Comprehensive Psychoneuroendocrinology, 7*, Article 100069. https://doi.org/10.1016/j.cpnec.2021.100069

Powley, T. L., & Philips, R. J. (2002). Musings on the wanderer: What's new in our understanding of vago-vagal reflexes? I. Morphology and topography of vagal afferents innervating the GI tract. *American Journal OfPhysiology Gastrointestinal and Liver Physiology 283(6): G1217-G1225, 283*(6), G1217–G1225. https://doi.org/10.1152/ajpgi.00249.2002

Price, B. H., & Gavornik, J. P. (2022). Efficient temporal coding in the early visual system: Existing evidence and future directions. *Frontiers in Computational Neuroscience, 16*. https://doi.org/10.3389/fncom.2022.929348

Price, C. J., Hoyda, T. D., & Ferguson, A. V. (2008). The area postrema: A brain monitor and integrator of systemic autonomic state. *The Neuroscientist, 14*(2), 182–194. https://doi.org/10.1177/1073858407311100

Przeździk, I., Faber, M., Fernández, G., Beckmann, C. F., & Haak, K. V. (2019). The functional organization of the hippocampus along its long axis is gradual and predicts recollection. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior, 119*, 324–335. https://doi.org/10.1016/j.cortex.2019.04.015

Qiu, C., Shivacharan, R. S., Zhang, M., & Durand, D. M. (2015). Can neural activity propagate by endogenous electrical field? *Journal of Neuroscience, 35*(48), 15800–15811. https://doi.org/10.1523/JNEUROSCI.1045-15.2015

Raedt, R., Clinckers, R., Mollet, L., Vonck, K., El Tahry, R., Wyckhuys, T., De Herdt, V., Carrette, E., Wadman, W., Michotte, Y., Smolders, I., Boon, P., & Meurs, A. (2011). Increased hippocampal noradrenaline is a biomarker for efficacy of vagus nerve stimulation in a limbic seizure model. *Journal of Neurochemistry, 117*(3), 461–469. https://doi.org/10.1111/j.1471-4159.2011.07214.x

Ramon, F., & Moore, J. W. (1978). Ephaptic transmission in squid giant axons. *American Journal of Physiology-Cell Physiology, 234*(5), C162–C169. https://doi.org/10.1152/ajpcell.1978.234.5.C162

Ran, C., Boettcher, J. C., Kaye, J. A., Gallori, C. E., & Liberles, S. D. (2022). A brainstem map for visceral sensations. *Nature, 609*(7926), Article 7926. https://doi.org/10.1038/s41586-022-05139-5

Rao, R. P., & Ballard, D. H. (1999). Predictive coding in the visual cortex: A functional interpretation of some extra-classical receptive-field effects. *Nature Neuroscience, 2*(1), 79–87. https://doi.org/10.1038/4580

Reddy, G., Murthy, V. N., & Vergassola, M. (2022). Olfactory sensing and navigation in turbulent environments. *Annual Review of Condensed Matter Physics, 13*(1), 191–213. https://doi.org/10.1146/annurev-conmatphys-031720-032754

Reese, B. E. (1987). The distribution of axons according to diameter in the optic nerve and optic tract of the rat. *Neuroscience, 22*(3), 1015–1024. https://doi.org/10.1016/0306-4522(87)92977-0

Reese, B. E. (1993). Clinical implications of the fibre order in the optic pathway of primates. *Neurological Research, 15*(2), 83–86. https://doi.org/10.1080/01616412.1993.11740114

Reese, B. E. (1996). The chronotopic reordering of optic axons. *Perspectives on Developmental Neurobiology, 3*(3), 233–242.

Reese, B. E. (2011). Development of the retina and optic pathway. *Vision Research, 51*(7), 613–632. https://doi.org/10.1016/j.visres.2010.07.010

Reese, B. E., & Cowey, A. (1988). Segregation of functionally distinct axons in the monkey's optic tract. *Nature, 331*(6154), 350–351. https://doi.org/10.1038/331350a0

Reese, B. E., Guillery, R. W., Marzi, C. A., & Tassinari, G. (1991). Position of axons in the cat's optic tract in relation to their retinal origin and chiasmatic pathway. *The Journal of Comparative Neurology, 306*(4), 539–553. https://doi.org/10.1002/cne.903060402

Rennaker, R. L., Chen, C.-F. F., Ruyle, A. M., Sloan, A. M., & Wilson, D. A. (2007). Spatial and temporal distribution of odorant-evoked activity in the piriform cortex. *The Journal of Neuroscience, 27*(7), 1534–1542. https://doi.org/10.1523/JNEUROSCI.4072-06.2007

Rinaman, L. (2003). Postnatal development of hypothalamic inputs to the dorsal vagal complex in rats. *Physiology & Behavior, 79*(1), 65–70. https://doi.org/10.1016/S0031-9384(03)00105-7

Rinaman, L. (2010). Ascending projections from the caudal visceral nucleus of the solitary tract to brain regions involved in food intake and energy expenditure. *Brain Research, 1350*, 18–34. https://doi.org/10.1016/j.brainres.2010.03.059

Rinaman, L., & Schwartz, G. (2004). Anterograde transneuronal viral tracing of central viscerosensory pathways in rats. *Journal of Neuroscience, 24*(11), 2782–2786. https://doi.org/10.1523/JNEUROSCI.5329-03.2004

Rizzolatti, G., & Kalaska, J. (2013). Voluntary movement: The parietal and premotor cortex. *Principles of Neural Science, 5*, 865–893.

Rizzolatti, G., Strick, P., et al. (2013). Cognitive functions of the premotor systems. *Principles of Neural Science*, 412–425.

Robie, A. A., Hirokawa, J., Edwards, A. W., Umayam, L. A., Lee, A., Phillips, M. L., Card, G. M., Korff, W., Rubin, G. M., Simpson, J. H., Reiser, M. B., & Branson, K. (2017). Mapping the neural substrates of behavior. *Cell, 170*(2), 393–406.e28. https://doi.org/10.1016/j.cell.2017.06.032

Roosevelt, R. W., Smith, D. C., Clough, R. W., Jensen, R. A., & Browning, R. A. (2006). Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat. *Brain Research, 1119*(1), 124–132. https://doi.org/10.1016/j.brainres.2006.08.048

Rottenberg, J., Gross, J. J., & Gotlib, I. H. (2005). Emotion context insensitivity in major depressive disorder. *Journal of Abnormal Psychology, 114*(4), 627–639. https://doi.org/10.1037/0021-843X.114.4.627

Rucci, M., Ahissar, E., & Burr, D. (2018). Temporal coding of visual space. *Trends in Cognitive Sciences, 22*(10), 883–895. https://doi.org/10.1016/j.tics.2018.07.009

Saadon-Grosman, N., Arzy, S., & Loewenstein, Y. (2020). Hierarchical cortical gradients in somatosensory processing. *NeuroImage, 222*, Article 117257. https://doi.org/10.1016/j.neuroimage.2020.117257

Saenz, M., & Langers, D. R. M. (2014). Tonotopic mapping of human auditory cortex. *Hearing Research, 307*, 42–52. https://doi.org/10.1016/j.heares.2013.07.016

Sanchez-Panchuelo, R. M., Francis, S., Bowtell, R., & Schluppeck, D. (2010). Mapping human somatosensory cortex in individual subjects with 7T functional MRI. *Journal of Neurophysiology, 103*(5), 2544–2556. https://doi.org/10.1152/jn.01017.2009

Saper, C. B. (2002). The central autonomic nervous system: Conscious visceral perception and autonomic pattern generation. *Annual Review of Neuroscience, 25*(1), 433–469. https://doi.org/10.1146/annurev.neuro.25.032502.111311

Saper, C. B., & Stornetta, R. L. (2015). Chapter 23—Central Autonomic System. In G. Paxinos (Ed.), *The Rat Nervous System* (*Fourth edition.*,, pp. 629–673). Academic Press. https://doi.org/10.1016/B978-0-12-374245-2.00023-1.

Saraiva, L. R., Ibarra-Soria, X., Khan, M., Omura, M., Scialdone, A., Mombaerts, P., Marioni, J. C., & Logan, D. W. (2015). Hierarchical deconstruction of mouse olfactory sensory neurons: From whole mucosa to single-cell RNA-seq. *Scientific Reports, 5*(1), 18178. https://doi.org/10.1038/srep18178

Schapiro, A. C., Kustner, L. V., & Turk-Browne, N. B. (2012). Shaping of object representations in the human medial temporal lobe based on temporal regularities. *Current Biology: CB, 22*(17), 1622–1627. https://doi.org/10.1016/j.cub.2012.06.056

Schapiro, A. C., Turk-Browne, N. B., Botvinick, M. M., & Norman, K. A. (2017). Complementary learning systems within the hippocampus: A neural network modelling approach to reconciling episodic memory with statistical learning. *Philosophical Transactions of the Royal Society B: Biological Sciences, 372*(1711), Article 20160049. https://doi.org/10.1098/rstb.2016.0049

Schmidt, H., & Knösche, T. R. (2022). Modelling the effect of ephaptic coupling on spike propagation in peripheral nerve fibres. *Biological Cybernetics, 116*(4), 461–473. https://doi.org/10.1007/s00422-022-00934-9

Schulkin, J., & Sterling, P. (2019). Allostasis: A brain-centered, predictive model of physiological regulation. *Trends in Neurosciences, 42*(10), 740–752. https://doi.org/10.1016/j.tins.2019.07.010

Sepulcre, J., Sabuncu, M. R., Yeo, T. B., Liu, H., & Johnson, K. A. (2012). Stepwise connectivity of the modal cortex reveals the multimodal organization of the human brain. *Journal of Neuroscience, 32*(31), 10649–10661. https://doi.org/10.1523/JNEUROSCI.0759-12.2012

Servos, P., Zacks, J., Rumelhart, D. E., & Glover, G. H. (1998). Somatotopy of the human arm using fMRI. *NeuroReport, 9*(4), 605.

Seth, A. K. (2013). Interoceptive inference, emotion, and the embodied self. *Trends in Cognitive Sciences, 17*(11), 565–573. https://doi.org/10.1016/j.tics.2013.09.007

Seth, A. K., & Friston, K. J. (2016). Active interoceptive inference and the emotional brain. *Philosophical Transactions of the Royal Society of London Series B, Biological Sciences, 371*(1708). https://doi.org/10.1098/rstb.2016.0007

Seth, A. K., Suzuki, K., & Critchley, H. D. (2012). An interoceptive predictive coding model of conscious presence. *Frontiers in Psychology, 2*. https://doi.org/10.3389/fpsyg.2011.00395

Settell, M. L., Pelot, N. A., Knudsen, B. E., Dingle, A. M., McConico, A. L., Nicolai, E. N., Trevathan, J. K., Ezzell, J. A., Ross, E. K., Gustafson, K. J., Shoffstall, A. J., Williams, J. C., Zeng, W., Poore, S. O., Populin, L. C., Suminski, A. J., Grill, W. M., & Ludwig, K. A. (2020). Functional vagotopy in the cervical vagus nerve of the domestic pig: Implications for the study of vagus nerve stimulation. *Journal of Neural Engineering, 17*(2), Article 026022. https://doi.org/10.1088/1741-2552/ab7ad4

Shadmehr, R., Smith, M. A., & Krakauer, J. W. (2010). Error correction, sensory prediction, and adaptation in motor control. *Annual Review of Neuroscience, 33*, 89–108. https://doi.org/10.1146/annurev-neuro-060909-153135

Shaffer, C., Westlin, C., Quigley, K. S., Whitfield-Gabrieli, S., & Barrett, L. F. (2022). Allostasis, action, and affect in depression: Insights from the theory of constructed emotion. *Annual Review of Clinical Psychology, 18*(1), 553–580. https://doi.org/10.1146/annurev-clinpsy-081219-115627

Shannon, C. E., & Weaver, W. (1964/1949). *The mathematical theory of communication.* University of Illinois Press.

Shapiro, R. E., & Miselis, R. R. (1985a). The central organization of the vagus nerve innervating the stomach of the rat. *Journal of Comparative Neurology, 238*(4), 473–488. https://doi.org/10.1002/cne.902380411

Shapiro, R. E., & Miselis, R. R. (1985b). The central neural connections of the area postrema of the rat. *The Journal of Comparative Neurology, 234*(3), 344–364. https://doi.org/10.1002/cne.902340306

Shen, M. J., Shinohara, T., Park, H.-W., Frick, K., Ice, D. S., Choi, E.-K., Han, S., Maruyama, M., Sharma, R., Shen, C., Fishbein, M. C., Chen, L. S., Lopshire, J. C., Zipes, D. P., Lin, S.-F., & Chen, P.-S. (2011). Continuous low-level vagus nerve stimulation reduces stellate ganglion nerve activity and paroxysmal atrial tachyarrhythmias in ambulatory canines. *Circulation, 123*(20), 2204–2212. https://doi.org/10.1161/CIRCULATIONAHA.111.018028

Sherman, B. E., & Turk-Browne, N. B. (2020). Statistical prediction of the future impairs episodic encoding of the present. *Proceedings of the National Academy of Sciences, 117*(37), 22760–22770. https://doi.org/10.1073/pnas.2013291117

Silverman, H. A., Stiegler, A., Tsaava, T., Newman, J., Steinberg, B. E., Masi, E. B., Robbiati, S., Bouton, C., Huerta, P. T., Chavan, S. S., & Tracey, K. J. (2018). Standardization of methods to record Vagus nerve activity in mice. *Bioelectronic Medicine, 4*(1), 3. https://doi.org/10.1186/s42234-018-0002-y

Sirota, A., & Buzsáki, G. (2005). Interaction between neocortical and hippocampal networks via slow oscillations. *Thalamus & Related Systems, 3*(4), 245–259.

Smith, R., Badcock, P., & Friston, K. J. (2021). Recent advances in the application of predictive coding and active inference models within clinical neuroscience. *Psychiatry and Clinical Neurosciences, 75*(1), 3–13. https://doi.org/10.1111/pcn.13138

Smith, R., Thayer, J. F., Khalsa, S. S., & Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. *Neuroscience & Biobehavioral Reviews, 75*, 274–296. https://doi.org/10.1016/j.neubiorev.2017.02.003

Spors, H., Wachowiak, M., Cohen, L. B., & Friedrich, R. W. (2006). Temporal dynamics and latency patterns of receptor neuron input to the olfactory bulb. *Journal of Neuroscience, 26*(4), 1247–1259. https://doi.org/10.1523/JNEUROSCI.3100-05.2006

Steinberg, B. E., Silverman, H. A., Robbiati, S., Gunasekaran, M. K., Tsaava, T., Battinelli, E., Stiegler, A., Bouton, C. E., Chavan, S. S., Tracey, K. J., & Huerta, P. T. (2016). Cytokine-specific neurograms in the sensory vagus nerve. *Bioelectronic Medicine, 3*(1), 7–17. https://doi.org/10.15424/bioelectronmed.2016.00007

Stephan, K. E., Manjaly, Z. M., Mathys, C. D., Weber, L. A. E., Paliwal, S., Gard, T., Tittgemeyer, M., Fleming, S. M., Haker, H., Seth, A. K., & Petzschner, F. H. (2016). Allostatic self-efficacy: A metacognitive theory of dyshomeostasis-induced fatigue and depression. *Frontiers in Human Neuroscience, 10*. https://doi.org/10.3389/fnhum.2016.00550

Sterling, P. (2004). Principles of Allostasis: Optimal design, predictive regulation, pathophysiology, and rational therapeutics. *Allostasis, homeostasis, and the costs of physiological adaptation* (pp. 17–64). Cambridge University Press,. https://doi.org/10.1017/CBO9781316257081.004

Sterling, P. (2012). Allostasis: A model of predictive regulation. *Physiology & Behavior, 106*(1), 5–15. https://doi.org/10.1016/j.physbeh.2011.06.004

Sterling, P., & Laughlin, S. (2015). *Principles of Neural Design.* MIT Press.

Stettler, D. D., & Axel, R. (2009). Representations of odor in the piriform cortex. *Neuron, 63*(6), 854–864. https://doi.org/10.1016/j.neuron.2009.09.005

Stiles, J. (2008). *The Fundamentals of Brain Development: Integrating Nature and Nurture.* Harvard University Press.

Stuesse, S. L., & Fish, S. E. (1984). Projections to the cardioinhibitory region of the nucleus ambiguus of rat. *The Journal of Comparative Neurology, 229*(2), 271–278. https://doi.org/10.1002/cne.902290211

Suarez, A. N., Hsu, T. M., Liu, C. M., Noble, E. E., Cortella, A. M., Nakamoto, E. M., Hahn, J. D., de Lartigue, G., & Kanoski, S. E. (2018). Gut vagal sensory signaling regulates hippocampus function through multi-order pathways. *Nature Communications, 9*(1), 2181. https://doi.org/10.1038/s41467-018-04639-1

Szinte, M., & Knapen, T. (2020). Visual organization of the Default Network. *Cerebral Cortex, 30*(6), 3518–3527. https://doi.org/10.1093/cercor/bhz323

Takeuchi, Y., Nagy, A. J., Barcsai, L., Li, Q., Ohsawa, M., Mizuseki, K., & Berényi, A. (2021). The medial septum as a potential target for treating brain disorders associated with oscillopathies. *Frontiers in Neural Circuits, 15*. https://doi.org/10.3389/fncir.2021.701080

Tan, L., Li, Q., & Xie, X. S. (2015). Olfactory sensory neurons transiently express multiple olfactory receptors during development. *Molecular Systems Biology, 11*(12), 844. https://doi.org/10.15252/msb.20156639

Tao, J., Campbell, J. N., Tsai, L. T., Wu, C., Liberles, S. D., & Lowell, B. B. (2021). Highly selective brain-to-gut communication via genetically defined vagus neurons. *Neuron, 109*(13), 2106–2115.e4. https://doi.org/10.1016/j.neuron.2021.05.004

Taylor, C. P., & Dudek, F. E. (1982). Synchronous neural afterdischarges in rat hippocampal slices without active chemical synapses. *Science, 218*(4574), 810–812. https://doi.org/10.1126/science.7134978

Taylor, E. W., Wang, T., & Leite, C. A. C. (2022). An overview of the phylogeny of cardiorespiratory control in vertebrates with some reflections on the 'Polyvagal Theory. *Biological Psychology, 172*, Article 108382. https://doi.org/10.1016/j.biopsycho.2022.108382

Thayer, J. F., Loerbroks, A., & Sternberg, E. M. (2011). Inflammation and cardiorespiratory control: The role of the vagus nerve. *Respiratory Physiology & Neurobiology, 178*(3), 387–394. https://doi.org/10.1016/j.resp.2011.05.016

Thomas, J. M., Huber, E., Stecker, G. C., Boynton, G. M., Saenz, M., & Fine, I. (2015). Population receptive field estimates of human auditory cortex. *NeuroImage, 105*, 428–439. https://doi.org/10.1016/j.neuroimage.2014.10.060

Traynelis, S. F., & Jaramillo, F. (1998). Getting the most out of noise in the central nervous system. *Trends in Neurosciences, 21*(4), 137–145. https://doi.org/10.1016/s0166-2236(98)01238-7

Triplett, J. W., Phan, A., Yamada, J., & Feldheim, D. A. (2012). Alignment of multimodal sensory input in the superior colliculus through a gradient-matching mechanism. *The Journal of Neuroscience, 32*(15), 5264–5271. https://doi.org/10.1523/JNEUROSCI.0240-12.2012

Tsanov, M. (2018). Differential and complementary roles of medial and lateral septum in the orchestration of limbic oscillations and signal integration. *European Journal of Neuroscience, 48*(8), 2783–2794. https://doi.org/10.1111/ejn.13746

Upadhye, A. R., Kolluru, C., Druschel, L., Al Lababidi, L., Ahmad, S. S., Menendez, D. M., Buyukcelik, O. N., Settell, M. L., Blanz, S. L., Jenkins, M. W., Wilson, D. L., Zhang, J., Tatsuoka, C., Grill, W. M., Pelot, N. A., Ludwig, K. A., Gustafson, K. J., & Shoffstall, A. J. (2022). Fascicles split or merge every ~560 microns within the human cervical vagus nerve. *Journal of Neural Engineering, 19*(5). https://doi.org/10.1088/1741-2552/ac9643

Ura, H., Sugaya, Y., Ohata, H., Takumi, I., Sadamoto, K., Shibasaki, T., & Maru, E. (2013). Vagus nerve stimulation induced long-lasting enhancement of synaptic transmission and decreased granule cell discharge in the hippocampal dentate gyrus of urethane-anesthetized rats. *Brain Research, 1492*, 63–71. https://doi.org/10.1016/j.brainres.2012.11.024

Valenza, G., Sclocco, R., Duggento, A., Passamonti, L., Napadow, V., Barbieri, R., & Toschi, N. (2019). The central autonomic network at rest: Uncovering functional MRI correlates of time-varying autonomic outflow. *NeuroImage, 197*, 383–390. https://doi.org/10.1016/j.neuroimage.2019.04.075

van Hartevelt, T. J., & Kringelbach, M. L. (2012). The Olfactory System (Third). In J. K. Mai, & G. Paxinos (Eds.), *The Human Nervous System* (pp. 1219–1238). Elsevier, Academic Press. https://doi.org/10.1016/B978-0-12-374236-0.10034-3 (Third).

Veerakumar, A., Yung, A. R., Liu, Y., & Krasnow, M. A. (2022). Molecularly defined circuits for cardiovascular and cardiopulmonary control. *Nature, 606*(7915), Article 7915. https://doi.org/10.1038/s41586-022-04760-8

Vivekananda, U., Bush, D., Bisby, J. A., Baxendale, S., Rodionov, R., Diehl, B., Chowdhury, F. A., McEvoy, A. W., Miserocchi, A., Walker, M. C., & Burgess, N. (2021). Theta power and theta-gamma coupling support long-term spatial memory retrieval. *Hippocampus, 31*(2), 213–220. https://doi.org/10.1002/hipo.23284

Vogt, B. A. (2016). Midcingulate cortex: Structure, connections, homologies, functions and diseases. *Journal of Chemical Neuroanatomy, 74*, 28–46. https://doi.org/10.1016/j.jchemneu.2016.01.010

Vogt, B. A., Berger, G. R., & Derbyshire, S. W. G. (2003). Structural and functional dichotomy of human midcingulate cortex. *European Journal of Neuroscience, 18*(11), 3134–3144. https://doi.org/10.1111/j.1460-9568.2003.03034.x

Vos de Wael, R., Larivière, S., Caldairou, B., Hong, S.-J., Margulies, D. S., Jefferies, E., Bernasconi, A., Smallwood, J., Bernasconi, N., & Bernhardt, B. C. (2018). Anatomical and microstructural determinants of hippocampal subfield functional connectome embedding. *Proceedings of the National Academy of Sciences, 115*(40), 10154–10159. https://doi.org/10.1073/pnas.1803667115

Wang, G.-J., Yang, J., Volkow, N. D., Telang, F., Ma, Y., Zhu, W., Wong, C. T., Tomasi, D., Thanos, P. K., & Fowler, J. S. (2006). Gastric stimulation in obese subjects activates the hippocampus and other regions involved in brain reward circuitry. *Proceedings of the National Academy of Sciences of the United States of America, 103*(42), 15641–15645. https://doi.org/10.1073/pnas.0601977103

Wehrwein, E. A., Orer, H. S., & Barman, S. M. (2016). Overview of the anatomy, physiology, and pharmacology of the autonomic nervous system. *Comprehensive Physiology* (pp. 1239–1278). John Wiley & Sons, Ltd.. https://doi.org/10.1002/cphy.c150037

Williams, E. K., Chang, R. B., Strochlic, D. E., Umans, B. D., Lowell, B. B., & Liberles, S. D. (2016). Sensory neurons that detect stretch and nutrients in the digestive system. *Cell, 166*(1), 209–221. https://doi.org/10.1016/j.cell.2016.05.011

Wilson, C. D., Serrano, G. O., Koulakov, A. A., & Rinberg, D. (2017). A primacy code for odor identity. *Nature Communications, 8*(1), Article 1. https://doi.org/10.1038/s41467-017-01432-4

Wilson, D. A., & Sullivan, R. M. (2011). Cortical processing of odor objects. *Neuron, 72*(4), 506–519. https://doi.org/10.1016/j.neuron.2011.10.027

Wolff, J. G. (2016). Information compression, multiple alignment, and the representation and processing of knowledge in the brain. *Frontiers in Psychology, 7*. https://doi.org/10.3389/fpsyg.2016.01584

Wolpert, D., Pearson, K., & Ghez, C. (2013). The organization and planning of movement. In E. Kandel (Ed.), *Principles of Neural Science* (pp. 743–752). New York: McGraw-Hill Medical.

Wolpert, D. M., Miall, R. C., & Kawato, M. (1998). Internal models in the cerebellum. *Trends in Cognitive Sciences, 2*(9), 338–347. https://doi.org/10.1016/S1364-6613(98)01221-2

Xu, L., Li, W., Voleti, V., Zou, D.-J., Hillman, E. M. C., & Firestein, S. (2020). Widespread receptor-driven modulation in peripheral olfactory coding. *Science, 368*(6487), eaaz5390. https://doi.org/10.1126/science.aaz5390

Yeshurun, Y., & Sobel, N. (2010). An odor is not worth a thousand words: From multidimensional odors to unidimensional odor objects. *Annual Review of Psychology, 61*(219–241), C1–5. https://doi.org/10.1146/annurev.psych.60.110707.163639

Yip, Z. C., & Heiman, M. G. (2018). Ordered arrangement of dendrites within a C. elegans sensory nerve bundle. *ELife, 7*, Article e35825. https://doi.org/10.7554/eLife.35825

Zak, J. D., Reddy, G., Vergassola, M., & Murthy, V. N. (2020). Antagonistic odor interactions in olfactory sensory neurons are widespread in freely breathing mice. *Nature Communications, 11*(1), 3350. https://doi.org/10.1038/s41467-020-17124-5

Zanos, T. P. (2019). Recording and decoding of vagal neural signals related to changes in physiological parameters and biomarkers of disease. *Cold Spring Harbor Perspectives in Medicine, 9*(12), Article a034157. https://doi.org/10.1101/cshperspect.a034157

Zanos, T. P., Silverman, H. A., Levy, T., Tsaava, T., Battinelli, E., Lorraine, P. W., Ashe, J. M., Chavan, S. S., Tracey, K. J., & Bouton, C. E. (2018). Identification of cytokine-specific sensory neural signals by decoding murine vagus nerve activity. *Proceedings of the National Academy of Sciences, 115*(21), E4843–E4852. https://doi.org/10.1073/pnas.1719083115

Zhang, X., & Firestein, S. (2002). The olfactory receptor gene superfamily of the mouse. *Nature Neuroscience, 5*(2), Article 2. https://doi.org/10.1038/nn800

Zhao, Q., Yu, C. D., Wang, R., Xu, Q. J., Dai Pra, R., Zhang, L., & Chang, R. B. (2022). A multidimensional coding architecture of the vagal interoceptive system. *Nature, 603*(7903), 878–884. https://doi.org/10.1038/s41586-022-04515-5

Zhuo, H. (1997). Neurochemistry of the nodose ganglion. *Progress in Neurobiology, 52*(2), 79–107. https://doi.org/10.1016/S0301-0082(97)00003-8