

Parabrachial Complex: A Hub for Pain and Aversion

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The parabrachial nucleus (PBN) has long been recognized as a sensory relay receiving an array of interoceptive and exteroceptive inputs relevant to taste and ingestive behavior, pain, and multiple aspects of autonomic control, including respiration, blood pressure, water balance, and thermoregulation. Outputs are known to be similarly widespread and complex. How sensory information is handled in PBN and used to inform different outputs to maintain homeostasis and promote survival is only now being elucidated. With a focus on taste and ingestive behaviors, pain, and thermoregulation, this review is intended to provide a context for analysis of PBN circuits involved in aversion and avoidance, and consider how information of various modalities, interoceptive and exteroceptive, is processed within PBN and transmitted to distinct targets to signal challenge, and to engage appropriate behavioral and physiological responses to maintain homeostasis.

Key words: alarm; defense; thermoregulation; taste; nociception; brainstem

PBN as a sensory hub for pain and aversion

Interest in brain circuits mediating reward goes back decades, stimulated by the discovery that animals would work to activate specific brain pathways, a recognition of the adaptive value of positive affect in motivating adaptive behaviors, such as feeding or mating, and increasing appreciation of the role of these pathways in drug abuse (White and Franklin, 1989; Koob and Le Moal, 2001). By contrast, central circuits mediating aversion and avoidance have lacked a central focus, although these defensive behaviors have equal adaptive value. Damaging or potentially damaging stimuli require behavioral and physiological responses that minimize exposure to the noxious event and support learning that allows avoidance of future encounters. Regardless of the modality of the noxious stimulus, hardwired neural connections permit appropriate physiological responses that begin with adaptive behavioral and autonomic changes within the acute setting, followed by the emergence of learned avoidance behavior. A growing body of work points to the parabrachial complex (PBN) as an evolutionarily conserved hindbrain structure that allows a variety of threats to be linked to an appropriate configuration of behavioral and physiological responses (Fulwiler and Saper, 1984; Bernard and Bandler, 1998; Fuller et al., 2011; Nakamura and Morrison, 2011; Kaur et al., 2013). The present review con-

siders PBN as a “hub” for pain and aversion, with a focus on contributions to pain, bad taste and regulation of ingestive behaviors, and thermoregulatory challenge.

The PBN is a cell grouping that surrounds the superior cerebellar peduncles in the dorsolateral pons. In rodent, PBN can be divided into more than a dozen subnuclei on the basis of cytoarchitecture (Fulwiler and Saper, 1984). Medial PBN (mPBN) comprises populations of neurons heterogeneous in size and morphology, whereas lateral PBN (lPBN) includes several homogeneous groups. The cytoarchitecturally defined subdivisions within mPBN and lPBN are also marked by differential connectivity and neurochemistry. Figure 1 provides a schematic of major subnuclei and some important inputs and output of PBN. The majority of PBN neurons are glutamatergic, although a significant population is GABAergic (Geerling et al., 2017). There are numerous peptides colocalized with both populations, including calcitonin gene-related peptide (CGRP), substance P, neurotensin, and dynorphin. Cytoarchitectural organization in primates, including humans, is similar, although fewer subnuclei have been delineated (Kitamura et al., 2001; Paxinos et al., 2009).

The PBN receives input from sensory systems (Fig. 1), as well as from higher brain areas. Sensory input relevant to taste and other viscerosensory modalities, respiratory control, fluid balance, and cardiovascular function is derived primarily from the nucleus of the solitary tract (Herbert et al., 1990). Additional inputs relevant to respiratory control arise from brainstem chemosensory neurons (Rosin et al., 2006). Nociceptive, pruritic, and thermal information is directed to lPBN via the spinoparabrachial tract from the trigeminal and spinal dorsal horns (Hylden et al., 1985; Craig, 1995; Cameron et al., 2015; Rodriguez et al., 2017; Morrison and Nakamura, 2019). PBN also has reciprocal connections with structures throughout the brain, consis-

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tent with a role in integrating sensory information with behavior and autonomic function. For example, PBN is reciprocally connected with CeA, BNST, and multiple hypothalamic nuclei, including the preoptic area. Other major outputs from PBN include the paraventricular and gustatory thalamus, and the insular and infralimbic/prelimbic cortex (Tokita et al., 2010; Saper and Loewy, 2016; Morrison and Nakamura, 2019). Projections within the brainstem include reticular motor areas (Geerling et al., 2017; Barik et al., 2018) and the rostral ventromedial medulla (RVM), the latter an area implicated in both pain modulation and thermogenesis (Roeder et al., 2016; Chen et al., 2017; Morrison and Nakamura, 2019). Recent technical advances are allowing increasingly detailed delineation of the function(s) of distinct inputs to and outputs from PBN, some of which will be considered below.

Role of PBN in taste-guided behavior

Although health and survival depend upon eating and drinking, these acts carry inherent risks, such as poisoning, food allergy, and nutrient intolerance. To cope with these threats, the mammalian gustatory system has evolved specialized chemoreceptors (or taste receptors) that act as the ultimate guardians of the gastrointestinal tract. Upon binding their respective ligands, these receptors elicit a signal that is channeled into appropriate response outputs. For instance, one family of taste receptors (the T2Rs) bind a vast array of bitter ligands, which tend to be toxic. Activation of the T2Rs unconditionally drives rejective behaviors and deters further ingestion (Adler et al., 2000; Chandrashekar et al., 2000; Matsunami et al., 2000; Schier and Spector, 2019). While these hardwired circuits linked to the sensory properties of food offer a great deal of protection, they are not failsafe. Noxious chemicals can be cloaked in an otherwise palatable food, whereas essential nutrients or medicinal substances are sometimes packaged with a nonlethal bitterant (e.g., cruciferous vegetables). The body's ability to associate the orosensory properties of a food or fluid with its actual postingestive consequences, and to adjust behavioral and physiological responses in ways that maximize the benefit while minimizing the risks, are therefore critical for health and survival.

A key feature of the gustatory and viscerosensitive systems facilitates the link between taste and postingestive consequences. Viscerosensitive events, such as food poisoning or nutrient malabsorption, have privileged access to the gustatory system. This was demonstrated >50 years ago with a series of experiments from Garcia, Koelling, and others (Garcia et al., 1955; Garcia and Koelling, 1966). These experiments showed that rats rapidly learned to avoid a flavor that had been paired with certain negative gastrointestinal events, such as the emetic agent lithium chloride (LiCl) or irradiation. This phenomenon is now called conditioned taste aversion. The association is selective in that rats do not display similar expediency in learning to avoid a flavor paired with a negative exteroceptive event, such as foot shock.

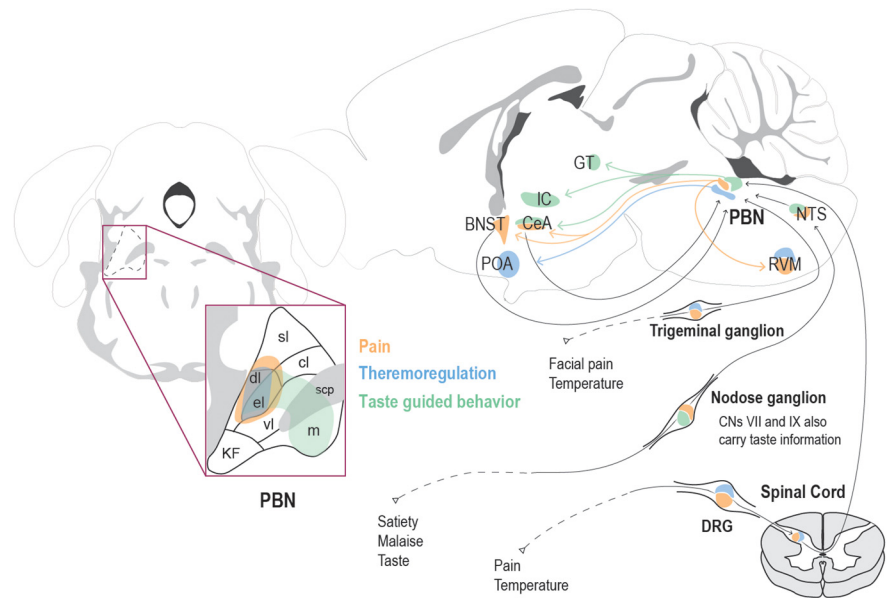


Figure 1. Pathways to and from the parabrachial complex that mediate taste-guided behavior, and contribute to pain and thermal defense. The PBN is located in the dorsal pons and surrounds the superior cerebellar peduncle (scp). Sensory information encoding taste, temperature, and noxious stimulation travels from primary sensory neurons in the nodose, trigeminal, or DRGs onto different intermediary structures within the CNS, where the input ultimately reaches distinct but functionally overlapping subnuclei within the PBN. The mPBN, through its connections with the CeA, insular cortex (IC), and gustatory thalamus (GT), primarily mediates taste-guided behavior (green). The external lateral nucleus responds to a diverse range of interoceptive and exteroceptive signals that may be painful or potentially painful (orange), and these neurons project to forebrain structures, including CeA and BNST, as well as RVM in the brainstem. The IPBN also contains populations of neurons (blue) that direct temperature information to the preoptic area of the hypothalamus to drive thermoregulatory responses. Subnuclei comprising the parabrachial complex are as follows: dl, Dorsal lateral; el, external lateral; sl, superior lateral; cl, central lateral; vl, ventral lateral; m, medial; BNST; CeA; IC, insular cortex; GT; KF, Kölliker Fuse; POA, preoptic area; RVM; scp, superior cerebellar peduncle.

Conversely, rats can readily learn to pair a tone or light with foot shock, but are less susceptible to associations between these exteroceptive cues (tone, light) and negative internal gastrointestinal events. Collectively, these studies imply an underlying organization that facilitates integration of specific sensory inputs with each other (e.g., taste, smell, viscerosensitive), and links those to specific motor outputs (e.g., rejection).

Lesions of PBN attenuate various aspects of taste-guided behavior, including conditioned taste aversion, salt appetite, and preference (Hill and Almli, 1983; Flynn et al., 1991; Spector, 1995; Grigson et al., 2015), pointing to PBN as a link between taste and ingestive behavior. PBN has also been implicated in suppression of feeding based on postingestive signals. The region is thought to contribute to satiety as part of a negative feedback system with excitatory input from nucleus of the solitary tract neurons that relay interoceptive signals, including gastric distension and postprandial peptides (e.g., cholecystokinin), both of which activate vagal afferent neurons innervating the alimentary canal. The output from PBN is presumed to suppress appetitive drive by relaying a negative valence signal to the forebrain, where it both counteracts the hedonic value of the food and suppresses motivational drive to consume (Chambers et al., 2013). This negative feedback signal is normally activated only transiently, as a homeostatic mechanism following a meal.

PBN can also be recruited in malaise, as an adaptive component of the sickness response (Kent et al., 1996; Kelley et al., 2003; Chaskiel et al., 2016). A recent series of studies demonstrated that a subpopulation of IPBN neurons that respond to negative visceral stimuli, such as LiCl, project to CeA and the BNST (Carter et al., 2013, 2015; Roman et al., 2017), and that manipulation of

external lateral PBN (eLPBN) neurons projecting to the CeA greatly diminished the effect of these negative stimuli on food intake. By contrast, manipulation of the connection with the BNST pathway had no effect on intake (Carter et al., 2013).

One shortcoming of the above findings is that most studies were limited to measures of intake. Such measures do not allow us to discern whether a particular food is aversive, meaning that it has a negative hedonic valence, or merely avoided, meaning that it elicits a motor repertoire that allows the organism to steer clear of a potentially harmful substance (Davis and Levine, 1977; Spector and Glendinning, 2009; Schier and Spector, 2019). In nonverbal experimental animals, like the rat, we must depend on a complement of behavioral procedures to differentiate aversion from avoidance and to uncover the motivational bases and neural circuitry involved. One approach is the taste reactivity test, which measures the stereotypic oromotor reflexes elicited by stimulation of the taste receptors, and is a more useful readout of potentially aversive qualities of a given taste than consumption per se (Grill and Norgren, 1978). Studies using this behavioral assay demonstrate that taste avoidance is not necessarily accompanied by taste aversion (Pelchat et al., 1983; Schier et al., 2019). Given this distinction, it will be useful to determine whether and how PBN contributes to aversion versus avoidance of specific taste-related and postingestive signals.

PBN and pain

PBN, particularly lPBN, has an important role in receiving, processing, and relaying somatic and visceral nociceptive signals (Gauriau and Bernard, 2002). It is the primary supraspinal target of nociceptive transmission neurons with cell bodies in the superficial dorsal horn. It also receives projections from deep dorsal horn (Bernard et al., 1995; Feil and Herbert, 1995; Bester et al., 2000; Polgár et al., 2010). Nociceptive neurons have been identified in lPBN using electrophysiological recording, calcium imaging, and cell activity markers (Bernard and Besson, 1990; Bernard et al., 1994; Hermanson and Blomqvist, 1996; Bourgeais et al., 2001; Campos et al., 2018; Uddin et al., 2018). Interestingly, nociceptive neurons are concentrated in the external lateral subnucleus, although ascending spinoparabrachial neurons avoid the subnucleus. This mismatch led to the suggestion that intra-PBN interactions are responsible for at least some of the noxious-evoked activations observed in lPBN (Saper, 1995; Bourgeais et al., 2003). This idea was confirmed in a recent analysis showing that dynorphin-expressing neurons in the dorsal lateral subnucleus (dLPBN) with extensive dendritic fields are activated by noxious stimuli and send axons to eLPBN (Chiang et al., 2019). In turn, eLPBN projects directly to the CeA and BNST and, through a thalamic relay, to the insula, implicating eLPBN in both emotional and autonomic aspects of pain (Fulwiler and Saper, 1984; Yasui et al., 1989; Jasmin et al., 1997; Bourgeais et al., 2001). lPBN also projects to the midbrain periaqueductal gray (Gauriau and Bernard, 2002) and to the RVM (Roeder et al., 2016; Chen et al., 2017), both of which are implicated in descending modulation of pain.

PBN and the affective dimension of pain

It has long been recognized that pain is not simply a sensory-discriminative phenomenon. Indeed, by definition, the experience of pain has a significant element of unpleasantness and distress. Given the central position of PBN as a sensory relay to a host of forebrain structures important for motivation and emotion, an important question is how PBN contributes to the affective dimension of pain (Gauriau and Bernard, 2002; Neugebauer,

2015). Han et al. (2010) have shown that CGRP-expressing inputs to the CeA from lPBN enhance excitability of neurons in the nociceptive amygdala, and that focal application of exogenous CGRP in CeA to mimic lPBN input produces behavioral hyperalgesia and ultrasonic vocalization, the latter taken as a measure of distress. Recent complementary work in mice shows that stimulation of nociceptive sensory axons activates lPBN neurons and induces aversive behaviors, including stress vocalization and avoidance of the location where stimulation occurred (Rodriguez et al., 2017). Consistent with this body of evidence, CGRP-expressing neurons have also been shown to be necessary for the affective component of aversive learning, where a painful stimulus is paired with a specific contextual cue (Han et al., 2015). Viewed as a whole, these data point to lPBN as having an important role in the affective dimension of pain.

Contributions to hyperalgesia and persistent pain

lPBN makes a relatively limited contribution to acute pain responses, but there is significant evidence for a role for this region in hyperalgesia and persistent pain. This includes the fact that lPBN receives its primary nociceptive input from neurokinin 1-expressing neurons in the superficial dorsal horn, a population associated with hyperalgesia in persistent pain due to inflammation or nerve injury (Nichols et al., 1999; Todd et al., 2000; Suzuki et al., 2002; Khasabov et al., 2005; Rivat et al., 2009). More important, there is evidence for reorganization of the connection between lPBN and descending control systems in persistent inflammatory pain models, and blocking lPBN reverses behavioral hypersensitivity under these conditions (Chen and Heinricher, 2019). In addition, lPBN neurons display increased excitability in rodent models of arthritic and neuropathic pain (Matsumoto et al., 1996; Uddin et al., 2018). Interestingly, some mechanically responsive lPBN neurons develop a form of amplified activity known as after-discharges in animals subjected to nerve injury. After-discharges refer to neural responses that far outlast the evoking stimulus, by at least half a second. The proportion of neurons exhibiting after-discharges is increased, and after-discharges are longer-lasting in nerve-injured animals (Uddin et al., 2018). This hyperexcitability appears in part to reflect a loss of recurrent inhibition from the CeA. CeA not only receives a significant projection from lPBN, but also sends a dense inhibitory reciprocal connection back to lPBN. This inhibitory connection from CeA to lPBN is specifically suppressed in slices taken from nerve-injured animals. These electrophysiological observations suggest that loss of inhibition from CeA back to PBN underlies PBN hyperexcitability, and raise the possibility that restoration of this inhibitory connection could reverse behavioral hypersensitivity in persistent pain states.

Distinct outputs from PBN contribute to different aspects of pain

The widespread distribution of outputs from the PBN suggests that distinct outputs contribute to different aspects of behavioral and physiological responses evoked by the interoceptive and exteroceptive inputs to this complex region. The functions of specific pathways are becoming increasingly tractable with optogenetic tools that allow differential manipulation of specific terminal projections arising from PBN. Using this approach, Barik et al. (2018) provided evidence that projections to the caudal-dorsal medullary reticular formation, an area long implicated in motor function (Peterson, 1979), arise from tachykinin1-positive neurons in lPBN. Activation of this projection facilitated motor responses evoked by noxious stimulation, particularly

during inflammation. In another series of studies, Chiang et al. (2019) analyzed PBN projections to ventromedial hypothalamus and lateral periaqueductal gray, and to CeA and BNST. The former arose primarily from dIPBN, and the latter from eIPBN. Stimulation of the projections to ventromedial hypothalamus and periaqueductal gray elicited running and jumping. Activation of the projection to the periaqueductal gray also produced analgesia. In contrast, stimulation of the connections with CeA and BNST drove avoidance behavior (real-time place aversion) and aversive learning. Each of these effects is consistent with the known effect of stimulating the target structure directly. These findings further reinforce the idea of PBN as a “hub” linking interoceptive and exteroceptive sensory information to appropriate responses.

PBN has also been described as linking ascending pain-transmission pathways with descending pain-modulation pathways, including the periaqueductal gray-RVM circuit that has been implicated in both analgesia (including opioid analgesia) and hyperalgesia and persistent pain states (Heinricher and Fields, 2013; Chen and Heinricher, 2018). As already noted, IPBN projects densely to the periaqueductal gray, and stimulation of IPBN terminals in the periaqueductal gray produces analgesia (Chiang et al., 2019), as does direct stimulation of periaqueductal gray itself (Heinricher and Fields, 2013). By contrast, the IPBN output to the RVM exerts a net pronociceptive effect, which is most pronounced in persistent pain states (Chen and Heinricher, 2019).

PBN and cold defense

Just as pain serves as a warning signal for preserving bodily integrity, and taste serves as a signal for potentially noxious foods, thermosensory information informs behavioral and autonomic thermoregulatory mechanisms that maintain core body temperature within a narrow acceptable range. This sensory input is conveyed from the skin by primary afferent thermoreceptors, and relayed through the superficial dorsal horn to higher structures, including PBN. PBN contributes to both thermoregulatory behaviors and autonomic responses to skin warming or cooling (Morrison and Nakamura, 2019).

PBN outputs for behavioral thermoregulation are not fully understood, but projections to hypothalamic centers, particularly the preoptic area, mediate autonomic components of thermoregulation. Cold thermal information is relayed through the eIPBN to recruit shivering and nonshivering thermogenesis, whereas warm information is conveyed by dIPBN neurons and inhibits thermogenesis, presumably via dynorphinergic outputs (Geerling et al., 2016; Morrison and Nakamura, 2019).

In mammals, behavioral thermoregulation is one of the main mechanisms for coping with a thermally challenging environment, whether cooler or warmer than optimal. When behavioral coping is not sufficient, autonomic circuits also help regulate and maintain core body temperature within an acceptable range. However, there are situations where these two mechanisms are insufficient. One such challenge is extreme cold combined with lack of food, a situation in which the sustained thermogenesis that would be required to maintain normal body temperature would drain energy reserves, potentially resulting in death. Some mammals have developed the ability to escape this dangerous situation by entering a state of hibernation (Nedergaard and Cannon, 1990). By reducing metabolism and allowing core body temperature to fall, hibernation allows these animals to survive a harsh winter. Hibernation is marked by an inverted thermoregulatory response in which cold exposure suppresses, rather than promotes, thermogenesis (Tupone et al., 2017). Development of an experimen-

tal model of thermoregulatory inversion in rat, a nonhibernating species, has allowed investigation of the neural circuits underlying this thermoregulatory switch (Tupone et al., 2013).

Studies using selective inactivation suggest that, while dIPBN is essential for cold-induced inhibition of thermogenesis, the relevant cell population and projection target are distinct from those involved under normal conditions in which cold elicits thermogenesis (Tupone et al., 2018). Although how the choice of normal versus inverted thermoregulation is made at the level of PBN remains unclear, it is evident that a need to align thermoregulatory output with other homeostatic functions, particularly energy metabolism, is a key driver of the switch between the two circuits. Delineation of PBN circuits contributing to normal and inverted thermoregulation could therefore help elucidate integrative principles within the PBN. It is nonetheless reasonable to suggest that the convergence of cardiovascular, respiratory, metabolic, and nociceptive information in PBN enables integration of multiple sources of information that determines whether a behavioral strategy, autonomic thermoregulation, or hibernation is chosen as the appropriate response in a given environment and state of the body.

PBN as a contributor to general alarm, with a specific role for CGRP-expressing neurons in eIPBN

The recognition that PBN plays a role in a range of defensive responses to potential threats of various modalities was recently brought together with a proposal that a subpopulation of CGRP-expressing neurons in eIPBN functions as a general alarm (Palmiter, 2018). This conceptual framework was inspired by the finding that CGRP-expressing IPBN neurons are required for the starvation phenotype resulting from ablation of hypothalamic neurons expressing agouti-related peptide (Wu et al., 2012). Inhibition of CGRP-expressing neurons in eIPBN restored food intake in these animals (Carter et al., 2013) and also prevented anorexia in visceral illness, malaise, and cancer cachexia (Carter et al., 2013; Campos et al., 2017). Together with evidence that CGRP-expressing IPBN neurons projecting to CeA have a significant role in the affective dimension of pain and contribute to hyperalgesia in persistent pain states (Neugebauer et al., 2004), and that these neurons have a role in other protective responses (Mu et al., 2017), for example, chemosensory arousal and itch (Kaur et al., 2017), it has been proposed that CGRP-expressing neurons in eIPBN generate a multimodal threat signal that engages defensive behaviors (Palmiter, 2018).

In conclusion, as should be apparent from this brief review, even when considered within the relatively limited confines of ingestive behavior, pain, and thermoregulation, PBN receives multiple inputs, plays a role in multiple functions relevant to homeostasis and the state of the body, and contributes to distinct behavioral and motivational outputs. Investigators are now taking a more holistic view of PBN, and starting to seek organizing principles with which to understand the function of this complex region. The idea of a specific subset of IPBN neurons serving as a general alarm is an important step in this direction, with the idea that sensory signals related to threat generate a scalable, intermodal intensity signal that engages appropriate circuits to elicit defensive responding. Despite recent advances, a host of questions remain. First, PBN is by no means limited to processing only information related to aversive and painful stimuli. For example, PBN has long been known to play a role in taste preference as well as taste aversion (Yamamoto et al., 1994; Han et al., 2018; Fu et al., 2019), and understanding when and how positive hedonic valence is processed in PBN remains much less explored. It

would be interesting, for example, to determine whether this region has a role in pleasurable touch. Second, PBN is embedded within a complex web of connections spanning lower medulla to neocortex. Whether different projections have distinct sources and functions is only now starting to be considered, a task that is greatly facilitated by modern circuit analytical tools that allow dissection of specific populations within PBN as well as inputs and outputs. Indeed, the identification of neurochemical markers and neuropeptides within distinct PBN subnuclei is providing increasing insights into the organization of PBN circuitry. However, caution is warranted when making the assumption that all neurons expressing a given marker share a common function. Third, it must be acknowledged that our knowledge of PBN derives primarily from studies in rodent, although spinoparabrachial projections have been identified in primate (Craig, 1995), and functional imaging reveals activation of the PBN region during activation of viscerosensory and nociceptive systems (Topolovec et al., 2004; Dunckley et al., 2005; Youssef et al., 2016). Finally, almost nothing is known of the internal organization of PBN. How, or even whether, sensory information is integrated within PBN to contribute to the coordinated behavioral and physiological responses required in challenging environments is only beginning to be explored (Alhadeff et al., 2018). Individual neurons within PBN apparently receive multimodal information (see, e.g., Fu et al., 2019 or Campos et al., 2018) but contribute to coordinated and differentiated behavioral and autonomic outputs. This convergence raises the possibility that different populations of PBN neurons integrate multiple forms of sensory information to determine the appropriate physiological adjustments and behavioral strategies.

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