Neuroscience and Biobehavioral Reviews 161 (2024) 105667

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Neural cell-types and circuits linking thermoregulation and social behavior

Joseph F. Rogers [a,b], Morgane Vandendoren [a,b], Jonathan F. Prather [a], Jason G. Landen [a,b], Nicole L. Bedford [a], Adam C. Nelson [a,b,*]

[a] Department of Zoology & Physiology, University of Wyoming, Laramie, WY, USA
[b] University of Wyoming Sensory Biology Center, USA

ARTICLE INFO

Keywords:
Thermoregulation
Social behavior
Neuropsychiatric disorders
Autonomic nervous system
Hypothalamus
Fever
Psychosocial fever
Social thermoregulation
Brown adipose tissue
Blushing
Huddling
Paraventricular nucleus of the hypothalamus
Raphe nuclei
Ventromedial hypothalamus
Preoptic area
Insular cortex
Schizophrenia
Major depressive disorder
Autism spectrum disorder

ABSTRACT

Understanding how social and affective behavioral states are controlled by neural circuits is a fundamental challenge in neurobiology. Despite increasing understanding of central circuits governing prosocial and agonistic interactions, how bodily autonomic processes regulate these behaviors is less resolved. Thermoregulation is vital for maintaining homeostasis, but also associated with cognitive, physical, affective, and behavioral states. Here, we posit that adjusting body temperature may be integral to the appropriate expression of social behavior and argue that understanding neural links between behavior and thermoregulation is timely. First, changes in behavioral states—including social interaction—often accompany changes in body temperature. Second, recent work has uncovered neural populations controlling both thermoregulatory and social behavioral pathways. We identify additional neural populations that, in separate studies, control social behavior and thermoregulation, and highlight their relevance to human and animal studies. Third, dysregulation of body temperature is linked to human neuropsychiatric disorders. Although body temperature is a "hidden state" in many neurobiological studies, it likely plays an underappreciated role in regulating social and affective states.

1. Introduction

A major goal of behavioral neurobiology is to understand the neural circuits underlying behaviors essential for survival, reproduction, and well-being – including social interaction. While the central circuits involved in social behaviors ranging from aggression to parental care are increasingly well known (Chen and Hong, 2018; Wei et al., 2021), how bodily states interact with these circuits remains less clear. Autonomic processes such as sympathetic regulation of thermal and cardiovascular responses may regulate diverse social and affective behaviors. Yet, without knowledge of how information flows between the brain and body, our mechanistic understanding of social behavior will remain incomplete.

A causal link between body and brain states was proposed over a century ago when William James hypothesized that emotional and affective states come after, not before, bodily reactions (James, 1884). Rather than emotional states causing bodily changes, James argued that physiological changes themselves give rise to emotions. In support of this notion, recent neurobiological studies have shown that fearful states cannot be separated from cardiac processes and that the insula integrates perceptual and cardiac information to elicit emotional responses (Hsueh et al., 2023; Klein et al., 2021; Signoret-Genest et al., 2023). Understanding how autonomic processes regulate behavior will shed light on the central and peripheral processes involved in generating social and affective states and may offer new insight into the study and treatment of neuropsychiatric conditions.

Regulation of body temperature is a fundamental autonomic process that can influence behavioral states. While internal temperature is often a "hidden variable" in behavioral neurobiological studies, it can nevertheless have significant explanatory power in describing behavior

* Corresponding author at: Department of Zoology & Physiology, University of Wyoming, Laramie, WY, USA.
E-mail address: anelso74@uwyo.edu (A.C. Nelson).

https://doi.org/10.1016/j.neubiorev.2024.105667
Received 3 January 2024; Received in revised form 5 April 2024; Accepted 7 April 2024
Available online 9 April 2024

(Aronov and Fee, 2012; Blumberg et al., 1987; Butler-Struben et al., 2022; Harshaw et al., 2017). Maintaining core body temperature (Tb) within a narrow physiological range is essential for homeostasis: hypo- and hyperthermia present dangerous or even deadly challenges to key physiological processes (Nixdorf-Miller et al., 2006). Most mammals maintain a Tb of approximately 37℃ – the "set point" defended by the hypothalamus. Yet, Tb fluctuates across circadian and behavioral states by approximately 0.5℃, indicating that Tb has multiple balance points optimized for specific times of day or behaviors (Romanovsky, 2007; Škop et al., 2020). Moreover, fine-tuning of Tb can enhance cognitive function (Kleitman, 1963; Wright et al., 2002), physical performance (Grahn et al., 2005; Marino, 2002) competitive performance (Gilbert et al., 2007a), and affective state (Hanusch et al., 2013; Hanusch and Janssen, 2019; Lowry et al., 2018). The details of how neural circuits adjust Tb to enhance social and affective behavior remain unclear.

In mammals, thermoregulation is controlled by central hypothalamic circuits that integrate both internal and external signals to regulate downstream autonomic and behavioral processes controlling heat production and loss (Fukushima et al., 2022; Nakamura, 2011; Nakamura and Morrison, 2022; Tan and Knight, 2018). Autonomic mechanisms driving defense against cold include 1) vasoconstriction of cutaneous blood vessels, 2) brown adipose tissue (BAT) thermogenesis, and 3) shivering of skeletal muscle, while defense against heat can be controlled by 1) vasodilation, 2) suppression of BAT thermogenesis, and 3) sweating. In contrast to autonomic thermoregulation, behavioral thermoregulation is a motivated behavior characterized by temperature seeking, nest building, and social thermoregulation (Terrien et al., 2011).

Here, we identify three primary reasons why investigation of neural circuits linking thermoregulatory processes and social behavior warrants further attention. First, social behavior and thermoregulation are sometimes reciprocally connected. Changes in Tb leading to changes in social behavior is of interest as it would suggest that Tb plays a functional role in the expression of behavior, supporting the Jamesian notion that bodily states are required to give rise to emotional states. Alternatively, changes in behavioral state leading to changes in Tb raises the hypothesis that neural circuits may co-regulate both behavior and Tb.

Second, specific neural cell-types, circuits, and regions controlling aspects of Tb have been implicated in the regulation of social behavior. These findings suggest the existence of dedicated circuits for coordinating or fine-tuning Tb, perhaps to facilitate or enhance behavior. Here, we discuss serotonergic neurons of the brainstem raphe nuclei, oxytocin neurons of the paraventricular hypothalamus, and Cckar-expressing neurons in the ventral lateral portion of the ventral medial hypothalamus as examples of neuronal cell-types that can regulate both Tb and social behavior. In addition, a neural pathway from the dorsal peduncular cortex and dorsal tenia tecta to the dorsomedial hypothalamus integrates stressful psychosocial stimuli to drive a thermoregulatory response necessary for the expression of social avoidance behavior (Kataoka et al., 2020) – compelling evidence of a circuit linking autonomic and behavioral outputs into a single integrated state. Moreover, brain regions including the insular cortex, preoptic area, and dorsomedial hypothalamus, all known for their role in Tb regulation, also contribute to social behavior. Yet, whether the same or different cell-types and circuits within these regions govern Tb and social behavior is poorly understood.

Third, dysregulation of Tb is observed in several human neuropsychiatric disorders. For example, major depressive disorder, schizophrenia, and autism spectrum disorder are all linked to disrupted thermoregulation and thermosensation. These observations prompt a renewed examination of the evidence supporting a functional role for thermoregulation in social and affective deficits in neuropsychiatric disorders.

In this review we briefly overview mechanisms of thermoregulation (Section 2), then examine the relationship between thermoregulation and social interaction in mammals (Section 3). We focus on humans and rodents, particularly rodent models where manipulation-based experiments shed light on neural mechanisms. Next, we examine neural cell-types and circuits that link thermoregulation and social behavior either in the same or separate studies (Section 4). Because the connection between afferent thermosensory pathways and social behavioral states are poorly understood, our synthesis primarily draws from a comparatively large literature examining efferent thermogenic pathways. We then examine the relationship between disrupted thermal biology and neuropsychiatric disorders in the human population (Section 5). Finally, we critically evaluate why Tb adjustment might be useful for fine-tuning behavior and evaluate approaches to test this idea (Sections 6 and 7). A conceptual overview of this review is shown in Fig. 1.

Although there are compelling reasons to speculate that brain temperature can also regulate social and affective states, this topic is beyond the scope of this review. As reviewed elsewhere, brain temperature is generally higher than that of the body, shows regional specificity, and is a major determinant of channel kinetics and neuronal firing rates (Sela et al., 2021; Wang et al., 2014), suggesting regional brain temperature regulation could be a determinant of behavior. Indeed, fluctuations in brain temperature (1–3℃) have been associated with the function of neural circuits controlling social behaviors such as bird song (Aronov and Fee, 2012; Long and Fee, 2008; Wang et al., 2014). However, there is currently limited experimental data in which to assess hypotheses about the circuit-level relationship between intracranial temperature and social behavior.

2. Mechanisms of thermoregulation

Tb is regulated by a combination of autonomic and behavioral pathways. For endotherms, behavioral mechanisms are more energy-efficient than autonomic pathways and are the preferred mode of thermoregulation (Terrien et al., 2011). The neural circuit mechanisms controlling autonomic thermoregulation have been reviewed extensively (Morrison and Nakamura, 2019; Nakamura, 2011; Nakamura and Morrison, 2022; Tan and Knight, 2018) and are better understood than behavioral thermoregulation. Here, we briefly describe key autonomic and behavioral thermoregulatory mechanisms as a foundation for understanding their association with social and affective states (Sections 4 – 7).

2.1. Vasoconstriction and dilation

Autonomic control of thermoregulation, including vasomotor processes, is ubiquitous in mammals and is regulated by central circuits in the preoptic area of the hypothalamus (POA), dorsomedial hypothalamus (DMH), and the rostral medullary region (rMR) of the brainstem. This hypothalamo-medullary network communicates to sympathetic premotor neurons and motor neurons in the spinal cord (Nakamura and Morrison, 2022). These sympathetic nerve terminals release noradrenaline that binds to α-adrenergic receptors on cutaneous vascular smooth muscle, causing cutaneous vasoconstriction and blood redistribution, thereby conserving heat during cold challenge (Ootsuka and Tanaka, 2015). Conversely, heat loss during warm challenge is facilitated by vasodilation. In humans, active heat loss is achieved *via* sympathetic cholinergic cutaneous vasodilation (Charkoudian, 2010), whereas, in rodents, vasodilation is often mediated by release of tonic sympathetic vasoconstriction (O'Leary et al., 1985; Wanner et al., 2007).

2.2. Brown adipose tissue

BAT is a specialized tissue that plays a unique role in thermoregulation and energy expenditure. Unlike white adipose tissue, which stores energy in the form of fat (Emont et al., 2022), BAT is rich in mitochondria and contains a high density of iron-rich proteins that give it its characteristic brown color. A primary function of BAT is to generate heat

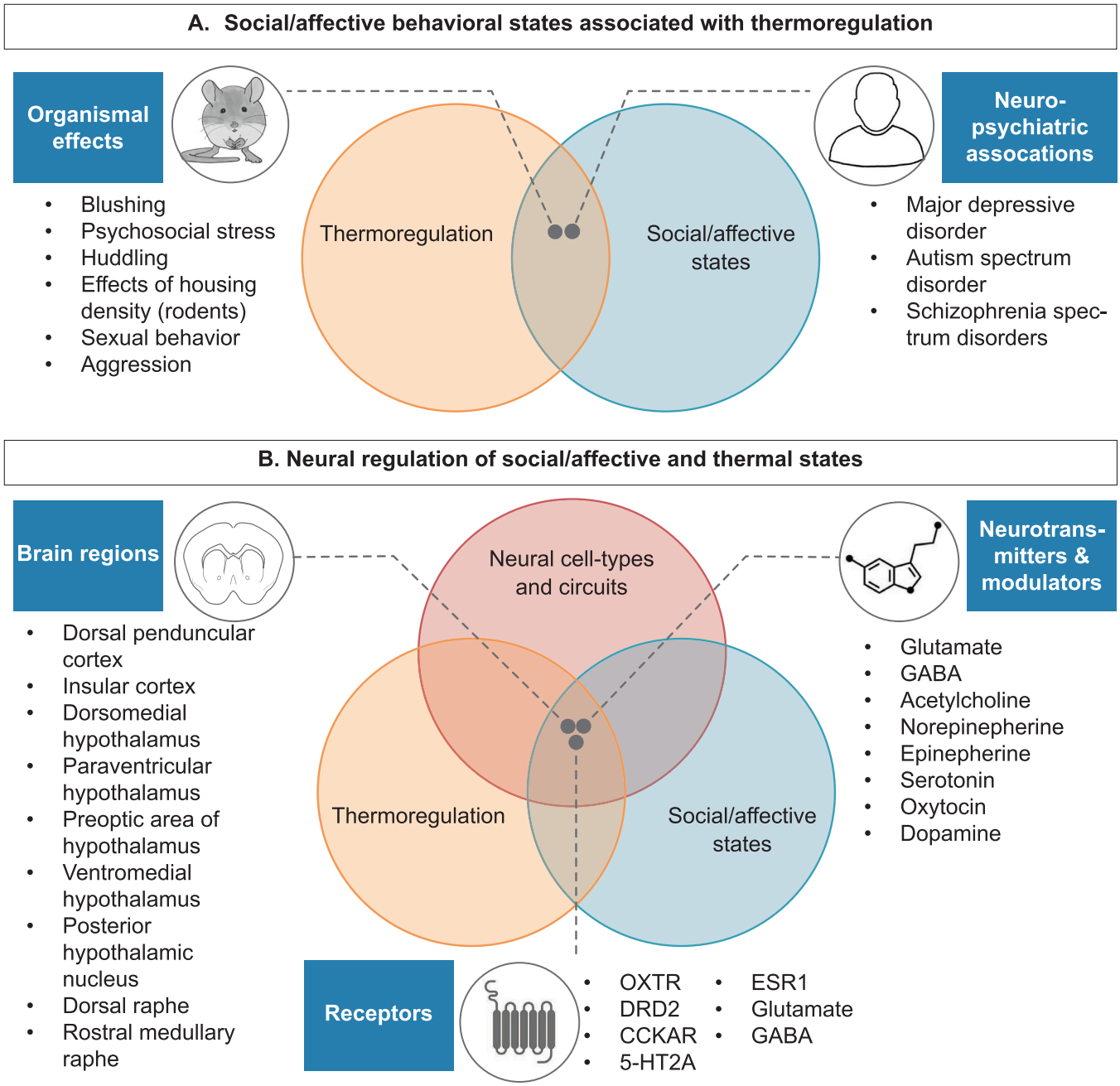


Fig. 1. Conceptual framework illustrating the intersection of social behavior, thermoregulation, and the underlying neural mechanisms. A. We examine social and affective behavioral states that are linked to internal thermal states. We primarily focus on efferent thermoregulatory pathways—as opposed to afferent thermosensory pathways—because less is known about the latter topic. Subtle changes in body temperature are associated with a variety of organismal responses, including social behavioral processes (left). Several neuropsychiatric disorders characterized by disrupted social interactions are also associated with dysregulation of autonomic processes, including thermoregulation (right). B. The identity of brain regions, cell types, neurotransmitters, and receptors that affect social behavior and efferent regulators of body temperature are becoming increasingly understood. We review the literature surrounding several brain regions, with a focus on hypothalamic efferent pathways involved in homeostasis and innate social behaviors such as aggression, prosocial behavior, and sexual behavior. We highlight neuromodulatory pathways that include serotonin, oxytocin, and dopamine.

through non-shivering thermogenesis. This is achieved by uncoupling oxidative phosphorylation from ATP production in mitochondria, resulting in the dissipation of energy as heat rather than ATP synthesis (Cannon and Nedergaard, 2004). BAT is especially abundant in newborn humans and hibernating mammals (Hunstiger et al., 2023; Urisarri et al., 2021), where its role in maintaining Tb is critical. BAT thermogenesis can be activated by cold exposure in diverse species, including humans (Saito et al., 2009; Wang et al., 2020). During cold exposure, BAT increases heat production – a process that can be harnessed to regulate core Tb and metabolic rate. Uncoupling protein 1 (UCP1) is essential for activating BAT thermogenesis by uncoupling electron transport from ATP synthesis, which results in increased substrate flux through the electron transport chain and increased respiration, resulting in heat generation (Roesler and Kazak, 2020). Research in rodents has provided further mechanistic insight into BAT activation, including the roles of interferon regulatory factor 4 (IRF4) (Kong et al., 2014) and certain microRNAs (Ng et al., 2017). Intriguingly, BAT is also innervated by brain regions that influence social behavior (Fukushima et al., 2022).

2.3. Shivering thermogenesis

Shivering is a physiological response that aids in maintaining Tb by generating heat through rapid muscle contractions. During cold exposure, the POA can trigger the activation of skeletal muscle motor neurons, producing heat and protecting against hypothermia (Conceição et al., 2019). Moreover, Nakamura and Morrison (2011) suggest a model where descending excitatory signals from the DMH and rMR drive shivering, sympathetic responses for cold defense, and fever, all under inhibitory control of a POA circuit (Nakamura and Morrison, 2011; Y. Nakamura et al., 2022).

2.4. Inflammatory Fever

In response to inflammatory stimuli, the body may induce fever – a regulated increase in Tb that is beneficial for fighting infection. Heat generated during the febrile response enhances performance of immune cells, induces stress on pathogens and infected cells, and combines with other stressors to provide general immune defense (Nakamura, 2011). Fever is triggered by pathogenic lipids and other molecules that induce the production of the pyrogenic mediator prostaglandin E_2 (PGE_2) (Morrison and Nakamura, 2019). PGE_2 production occurs in endothelial cells lining the medial POA (mPOA) and is specifically driven *via* an increase in COX2 expression (Matsumura et al., 1998; Tan and Knight, 2018). In a landmark paper, Y.Nakamura et al. (2022) identified prostaglandin EP3 receptor-expressing neurons in the POA (POA^{EP3R}) as bidirectional regulators of Tb and fever. In response to warm ambient temperatures, or when chemogenetically stimulated, these neurons promote heat dissipation. Conversely, in response to cool ambient temperatures, PGE_2, or chemogenetic inhibition, POA^{EP3R} neurons elicit fever-like hyperthermia *via* BAT thermogenesis. This work suggests a model in which tonic inhibitory signaling from POA^{EP3R} neurons to the DMH regulates thermal homeostasis. POA^{EP3R} neurons were also found to project to social behavior-related brain areas (notably, the basolateral amygdala and mammillary body) suggesting possible ties to social and affective states.

2.5. Behavioral thermoregulation

Behavioral thermoregulation involves activities like seeking out warmer or cooler environments, adjusting body posture, and modifying activity levels to achieve a preferred temperature range (Terrien et al., 2011). The balance between behavioral and autonomic thermoregulation enables endotherms to thrive in a wide range of environmental conditions while optimizing energy expenditure. Recently, Yahiro et al. (2023) described two thermosensory pathways from the lateral parabrachial nucleus (LPB) that mediate both behavioral and autonomic thermoregulation. They identify a role for LPB projections to the median preoptic nucleus (MnPO) in heat avoidance behavior and projections to the central amygdala (CeA) in cold avoidance (Yahiro et al., 2023). The cold avoidance LPB → CeA pathway is noteworthy because the CeA is involved in aversive memory, suggesting the involvement of emotional processing in cold avoidance. Notably, both pathways were necessary to produce BAT thermogenesis in response to skin cooling – an autonomic process. Last, recent work has uncovered GABAergic neurons of the lateral hypothalamus that specifically control aspects of thermal seeking and avoidance during operant conditioning (Jung et al., 2022).

3. Associations between body temperature and social behavior in mammals

In this section, we review the reciprocal connections between Tb and social behavior, with a focus on how thermal states can enhance or diminish social interaction (Fig. 1A). First, blushing in humans is a component of emotional expression that involves vasodilation of blood vessels in the face (Drummond and Lance, 1987). Second, social thermoregulation, including huddling and skin-to-skin contact between mothers and newborns, are cooperative behaviors where individuals pay the cost of heat production but share the benefits (Alberts, 2007; Gilbert et al., 2007a; Haig, 2008). Third, housing density in rodents affects both social behavior and thermoregulation (Kappel et al., 2017; Škop et al., 2021). Fourth, inflammatory and psychosocial fever have distinct etiologies and impact social/affective behavior in unique ways (Oka, 2015).

While our understanding of how Tb affects the expression of social behavior is incomplete, the observations that Tb can affect cognitive functions like memory, attention, and decision-making (Coleshaw and Van Someren, 1983; Hadi and Block, 2019; Wright et al., 2002), as well as physical activity, mood, and complex behaviors (Kleitman, 1963; Wright et al., 2002), suggests that thermal states could enhance social behavior. Indeed, temperature cues can influence bond formation, group dynamics, and willingness to participate in social activities (Batchelder et al., 1983; Canals et al., 1989; Harshaw et al., 2018). Understanding how thermal states affect social interactions will provide an entry point for determining the underlying neural mechanisms.

3.1. Blushing

Charles Darwin described blushing as the "*most peculiar and most human of all expressions*". An involuntary phenomenon characterized by reddening of the face, blushing is regulated by autonomic vasodilation of facial blood vessels, resulting in increased blood flow to the skin. Blushing is often triggered by feelings of embarrassment, shame, or self-consciousness, reflecting the profound connection between our internal emotional states and outward expressions (Thorstenson et al., 2020). The evolution of blushing in humans raises questions about its adaptive value in social groups. Blushing may have evolved as a social signal to communicate sincerity, trustworthiness, or submission. It has also been suggested that blushing may be a mechanism for displaying remorse – indicating recognition of social norms and willingness to conform (Thorstenson et al., 2020).

The sympathetic nervous system plays a crucial role in the regulation of blushing (Drummond and Lance, 1987). When triggered by emotional or social stimuli, facial blushing is likely controlled by cholinergic fibers (Drummond et al., 2020) from the stellate ganglia (or cervicothoracic ganglia) that promote vasodilation (Drummond and Finch, 1989). While the precise signaling pathway responsible for blushing is not fully understood, it appears to be independent of both α- and ß-adrenergic receptor signaling in facial blood vessels (Drummond, 1997). Although emotional blushing is triggered by social stimuli, it appears to be driven by the same pathways controlling thermoregulatory flushing (i.e., sweating and active heat loss), which are distinct from those controlling gustatory flushing (e.g., response to hot chili peppers (Drummond and Lance, 1987)). Although poorly understood, a possible physiological benefit of blushing may be to induce rapid heat loss and limit blood pressure increase during socially stressful events (Drummond, 1999).

The dorsal hypothalamic area (DHA), a dorsal subregion of the dorsomedial hypothalamic nucleus (DMH), has been proposed as a potential central regulator of blushing (Machado et al., 2018; Mathis and Kenny, 2018). In mice, DHA glutamatergic projections to the raphe pallidus (RPa) of the rMR were activated during cage-exchange – a type of social stress (Machado et al., 2018). Stress-induced sympathetic pathways in rodents are generally thought to increase BAT thermogenesis and cutaneous vasoconstriction (Kataoka et al., 2020). Similar to a previous finding in the DMH (Kataoka et al., 2014), chemogenetic activation of glutamatergic DHA neurons resulted in BAT thermogenesis. Unexpectedly, and in contrast to expectations, activation of these DHA neurons also triggered tail vasodilation (Machado et al., 2018). Because the DHA receives inputs from brain areas related to social behavior and stress, it was speculated that glutamatergic DHA→RPa projections may also activate a unique sympathetic pathway that integrates social stimuli to trigger blushing in humans (Machado et al.,

2018; Mathis and Kenny, 2018). However, the effects of targeted manipulations of glutamatergic DHA → RPa neurons are not known. Moreover, it should be noted that while blushing is likely controlled by cholinergic vasodilator activity, tail vasodilation is likely mediated by release of adrenergic vasoconstrictor activity (Häbler et al., 1999; O'Leary et al., 1985; Wanner et al., 2007). Thus, central circuits controlling blushing – a social and thermal behavior – remain an exciting area of research.

3.2. Huddling

Huddling, or sustained physical contact between individuals, can serve two primary functions in vertebrates: thermoregulation and social reward. Aggregation behaviors like huddling are hypothesized to be driven by homeostatic differences among individuals or as responses to the thermal environment (Harshaw et al., 2014; Moss and While, 2021; Seebacher and Krause, 2017). This framework suggests that thermoregulation and social behavior co-evolved and may share some mechanisms. For example, the neuropeptide oxytocin (OT) may have first evolved for homeostatic functions such as thermoregulation and later been co-opted for social behavior that facilitates maintenance of Tb (Harshaw et al., 2018; Moss and While, 2021).

Thermoregulatory huddling is widespread among animals and is an effective means of regulating homeostatic Tb and conserving energy; see Gilbert et al. (2010) for a comprehensive review. Huddling can alter Tb and energy budgets by increasing the ambient temperature surrounding individuals in close contact, by reducing cold-exposed surface area, or by augmenting insulation (Gilbert et al., 2010). Most endotherms with the ability to huddle maintain a higher and more stable Tb than their isolated counterparts. However, depending on the species, developmental stage, and environmental conditions, huddling can be either warming or cooling (Gilbert et al., 2010). In some species such as snow goose goslings (Fortin et al., 2000) and adult penguins (Gilbert et al., 2007b), huddling results in reduced metabolic heat production, lower Tb, and therefore energy savings. In contrast, huddling in rabbit pups results in higher Tb as well as thermoregulatory energy savings (Gilbert et al., 2007a).

Rodents, including adult mice, display huddling behavior in the wild (Crowcroft, 1967) and in the laboratory (Batchelder et al., 1983; Bryant and Hails, 1975; Martin et al., 1980). While room temperature (~21°C) is thermoneutral (i.e., an ambient temperature where metabolic rate is at a minimum) for humans, it is well below thermoneutrality for mice, largely due to their high surface area to volume ratio (Gordon, 2012, 1993; Škop et al., 2020). At room temperature, individually-housed adult mice are thermally stressed and devote around a third of their energy to cold-induced thermogenesis (Škop et al., 2023); in contrast, group-housed mice display lower thermal conductance and energy expenditure, an effect thought to be due to energy-saving benefits of huddling (Škop et al., 2021). In support of this idea, group-housed animals huddle more at lower temperatures (Batchelder et al., 1983). Precisely how diurnal patterns of huddling across sleep and wake states affect Tb is poorly understood.

In rodent neonates, the relationship between social thermoregulation and Tb is different compared to adults due to their small size, poor insulation, and immature thermogenic systems (Harshaw et al., 2014). Mouse pups three to four days of age display increased O_2 consumption and higher core Tb when huddling compared to non-huddling pups, specifically in cool temperatures (Bryant and Hails, 1975). At greater than nine days old, a more adult-like pattern of social thermoregulation emerges, where group-housed pups show reduced metabolic rates. In a more recent thermography study, it was found that as mouse pups develop from postnatal day four to eight, they form progressively more cohesive huddles and reduced rates of heat loss, suggesting precocious refinement of behavioral thermoregulation (Harshaw and Alberts, 2012).

Huddling in human adults can protect against cold stress (Hayward et al., 1975), but more commonly, maternal-neonate interactions provide thermoregulatory benefits to newborns (Asakura, 2004). For the first two days after birth, neonates in contact with their mother's skin have 2.3 times less heat loss than those wrapped in a blanket (Fransson et al., 2005). Moreover, as the ambient temperature around the neonate increases as a result of physical touch, metabolic output decreases (Adamson et al., 1965). Thus, physical contact is a conserved means of saving energy.

The molecular and genetic mechanisms regulating social thermoregulation are becoming better understood. BAT thermogenesis is a central component of huddling because it is a means by which individuals supply heat to the huddle. Inhibition of BAT thermogenesis results in imbalanced huddling interactions and decreases in time spent huddling (Sokoloff and Blumberg, 2001). OT also plays a role in huddling: administration of exogenous OT to mice substantially increased huddling and decreased aggression among group members, while OT antagonists drastically decreased huddling behavior (Arakawa et al., 2015). Compared to wildtype mice, OT knockout (OTKO) mice display reduced levels of BAT thermogenesis when huddling, form less cohesive huddles, and display deficits in thermotaxis, suggesting a role for OT in both thermogenesis and thermosensation (Harshaw et al., 2018). Taken together, these studies show that huddling draws upon cooperative physical contact to share heat and reduce energy expenditure. Although the neural mechanisms regulating this process are not known, research in this domain presents an opportunity to understand circuit-level mechanisms controlling social and homeostatic needs.

In addition to thermal benefits, the close physical contact experienced during huddling can also reduce stress or be intrinsically rewarding. Intriguingly, the neural circuits regulating huddling as social reward in rodent models are better understood than those controlling the thermoregulatory components. For example, individuals often display preferences for social contact or for contexts associated with social contact, and this behavior relies on neuromodulation of the nucleus accumbens by OT and serotonin (Barletti and Negulescu, 2018; Dölen et al., 2013). Similarly, social contact can buffer the effects of stress through amylin-calcitonin signaling in the MPOA (Denommé and Mason, 2022; Fukumitsu et al., 2022; Kikusui et al., 2006). In contrast, isolation and removal from physical contact can be aversive (Pietropaolo et al., 2008) and can disrupt group-level behaviors such as huddling (Endo et al., 2018). This aversive state thought to be mediated by dopamine neurons of the dorsal raphe nucleus (Matthews et al., 2016). Since these studies were performed below thermoneutrality and did not record Tb, a crucial question is whether positive-valence associations with huddling are dependent upon heat exchange by conduction during physical contact.

3.3. Housing density

Housing density, and individual housing in particular, have been shown to have pervasive effects on both the thermal (Škop et al., 2021) and social (Kappel et al., 2017) biology of laboratory rodents. Here, we examine these effects on the premise that, although individual housing appears to trigger coordinated changes in thermoregulation and social behavior (particularly aggression), the underlying mechanisms are poorly understood. We suggest these changes could be a fruitful area for identifying neural circuits that coordinate changes in thermoregulation and social/affective behavior.

The thermoneutral zone for a clothed adult human is 14.8–24.5°C (Kingma et al., 2012, 2014), whereas that of standard laboratory mice, depending on light cycle, is estimated to be 29–33°C (Gordon, 2012; Škop et al., 2020). As a result, room temperature (~22°C) is stressful for mice (Gordon, 2012, 1993; Škop et al., 2020). As discussed in Section 3.2, single housing (compared to group housing) amplifies the thermal stress of living below the thermoneutral zone, as indicated by changes in core Tb, thermal conductance, and energy expenditure (Škop et al., 2021). Housing density also affects thermal preferences, with

individually housed mice preferring warmer temperatures (Gordon et al., 1998).

Individual housing also affects the social and affective behavior of laboratory rodents, often in negative ways (Kappel et al., 2017; Lee et al., 2021; Matthews and Tye, 2019; Olsson and Westlund, 2007). Compared to group housed males, individually housed males show increased anxiety and depressive-like behaviors, along with higher levels of corticosterone and reduced brain-derived neurotrophic factor (BDNF) (Kappel et al., 2017). Chronic social isolation (on the order of weeks or longer) increases aggression in rodents, which serves as the premise for the isolation-induced aggression paradigm. Intriguingly, isolation-induced aggression is associated with the serotonergic system – a key thermoregulatory system discussed in Section 4.2 (Sánchez et al., 1993). Chronic isolation is also used as a model of schizophrenia due to its effects on schizophrenia-relevant behaviors like pre-pulse inhibition, mating, anhedonia, and anxiety (Geyer et al., 1993; Jiang et al., 2013). On the other hand, acute social isolation (on the order of 24 h) is associated with a rebound in prosocial interaction, suggesting the presence of an innate drive for social interaction (Matthews and Tye, 2019).

Because thermal stress below the thermoneutral zone is compounded during individual housing, and because social isolation itself can also be stressful (Lee et al., 2021), there is a critical need to better understand the interplay between thermal and social stressors on the biology of laboratory rodents. One prediction is that individually housed animals at room temperature would be motivated to physically interact with conspecifics to promote heat transfer by conduction and to reduce surface area to volume ratio (and therefore heat loss) (Gilbert et al., 2010). Conversely, at a thermoneutral temperature, this thermal motivation could be reduced. Thus, manipulating ambient temperature can be used to address the role of social vs. thermoregulatory drives, for example, in tests of the social homeostasis model (Lee et al., 2021; Matthews and Tye, 2019). Taken together, individual housing affects both the thermal and social biology of laboratory rodents. However, it remains unclear whether these processes are coordinated responses at the level of neural circuits. This knowledge gap could be addressed in neurobiological studies examining social behaviors at varied ambient temperatures.

3.4. *Inflammatory fever and sickness*

In humans, there are many behavioral changes associated with inflammatory fever, including fatigue, decreased interest in activities, social withdrawal, malaise, hyperalgesia, sleep disturbances, anorexia, and cognitive dysfunction (Harden et al., 2015). These are often referred to collectively as sickness behavior. Recent neurobiological studies have demonstrated that components of sickness behavior are controlled by ADCYAP1-positive neurons in the brainstem (Ilanges et al., 2022) and by a subpopulation of neurons and non-neuronal cells of the ventral medial POA (Osterhout et al., 2022). Social behavior is often acutely diminished during sickness behavior, the benefit of which could be conserving energy resources for fighting infection and limiting the risk of disease transmission (Hennessy et al., 2014). Although the circuits controlling fever are increasingly well understood (Y. Nakamura et al., 2022), the cell-types and circuits controlling fever-induced changes in social interaction are not known.

3.5. *Psychosocial stress and psychogenic fever*

Most stressful experiences and stimuli, including social stress, result in elevated Tb. If extreme enough, stress also causes hyperthermia (Adriaan Bouwknecht et al., 2007). Psychogenic fever refers to a stress-induced rise in Tb (reaching as high as 41°C) which is ameliorated by psychotropic drugs that display anxiolytic and sedative properties, but not by antipyretic (i.e., fever-reducing) drugs (Lkhagvasuren et al., 2011; Oka, 2015). Unlike inflammatory fever, which triggers a PGE_2--dependent rise in Tb, psychogenic fever appears to rely on a different set of effectors and circuits (Oka, 2015; Olivier, 2015).

Social stress in rodents induces a spectrum of behavioral and physiological responses that are consistent with changes observed in human affective disorders, including fever (Keeney et al., 2001; Keeney and Hogg, 1999; Krishnan et al., 2007). As such, the social defeat stress (SDS) paradigm has been widely used as a biomedical model of psychogenic stress. In this paradigm, a male mouse or rat is defeated by an aggressive conspecific male either repeatedly or in a singular interaction to induce chronic or acute stress, respectively. While social defeat reliably induces hyperthermia, social avoidance, and depression-like behavior, there exists a subpopulation of individuals, even in inbred rodents, who are much less susceptible to these outcomes. In an early investigation of neural circuits underlying SDS, it was found that BDNF signaling in the mesolimbic dopamine circuit was necessary for the expression of social avoidance (Krishnan et al., 2007), highlighting a potential treatment mechanism.

Pharmacological studies have begun to investigate the role of oxytocin-related neuromodulatory mechanisms underlying the avoidance seen in socially defeated animals. During social interaction tests (SIT) in mice, social avoidance is associated with hyperthermia, and this hyperthermia is blocked with systemic administration of an oxytocin receptor (OXTR) antagonist. In contrast, OXTR antagonism also resulted in reduced initiation of social interaction, suggesting a complex relationship between social and thermal states (Harshaw et al., 2021). In California mice (*Peromyscus californicus*), OXTR agonism in the nucleus accumbens promotes social interaction during SIT *via* Gq-specific signaling (Williams et al., 2020). Together, these results suggest that oxytocin could regulate aspects of social avoidance and Tb – an idea further explored in Section 4.3.

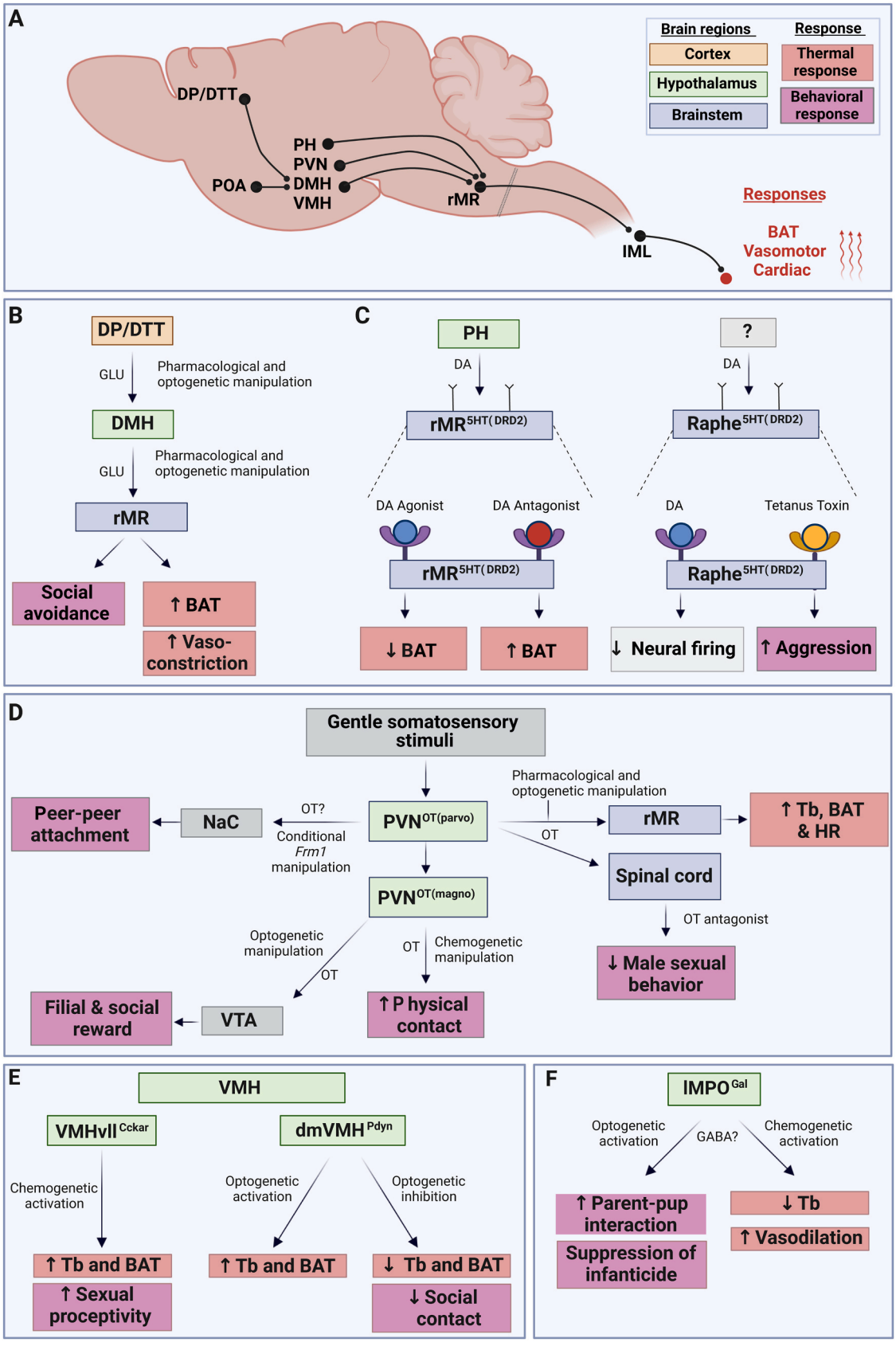
More recently, the neural circuits underlying the social avoidance and psychogenic hyperthermia aspects of SDS in rats have been clearly elucidated. This cortical-hypothalamic-brainstem pathway controls aspects of both social avoidance and psychogenic hyperthermia (Kataoka et al., 2020) and is discussed in Section 4.1. This landmark study demonstrates that optogenetic inhibition of this pathway attenuates both the thermogenic and social avoidance responses, suggesting that bodily states are required to generate a fear response, supporting William James' hypothesis that physiological changes themselves can give rise to emotional experience.

4. Neural circuits linking social behavior and thermoregulation

Our understanding of the neural circuit basis of thermoregulation and social behavior comes from a few studies, central to this review, showing that anatomically discrete, cell-type specific populations of neurons are capable of simultaneously controlling aspects of thermoregulation and social/affective behavior. However, our review also identifies additional neural populations that, through separate studies, suggest a link between social behavior and thermoregulation (Fig. 1B). These neuronal populations are summarized in Fig. 2 and in Table 1. The identification of neurons with such dual control suggests dedicated circuits might optimize Tb for the implementation of behavioral outputs, raising the question of whether there are more such populations, and what their roles might be. Elucidating these circuits could enhance our understanding of integrated states and provide a foundation for therapeutic approaches.

4.1. *DP/DTT → DMH → rMR pathway*

The best description of a neural circuit regulating social behavior and thermoregulation is a cortical-hypothalamic-brainstem pathway. In a rat model, genetic ablation, pharmacology, and optogenetic studies revealed that the dorsal peduncular (DP) and dorsal tenia tecta (DTT) in the prefrontal cortex can drive thermogenic, hyperthermic, and cardiovascular sympathetic responses to psychosocial stress (Kataoka et al., 2020) (Fig. 2 A-B). In the context of SDS, these cortical regions activate VGLUT1-positive projections to the DMH and, in turn, neurons that



(caption on next page)

Fig. 2. Neural pathways contributing to both thermoregulation and social behavior. A. Brain regions associated with social behavior and thermoregulation. Diverse hypothalamic areas, and the DP/DTT region of the prefrontal cortex, can generate changes in affective, behavioral, and thermal state. Sympathetic premotor neurons in the rMR control thermogenesis via projections to the IML spinal cord, including BAT thermogenic, vasomotor, and cardiac responses. B. The DP/DTT-DMH-rMR pathway regulates psychosocial fever and social avoidance in a social defeat model. Glutamatergic transmission from DP/DTT to the DMH activates DMH to rMR projections, which in turn activates BAT thermogenesis and cardiovascular responses. C. Left: Serotonergic (5HT) rMR neurons expressing the DRD2 dopamine receptor (i.e. $rMR^{5HT(DRD2)}$) control BAT thermogenesis in a dopamine-dependent fashion. The PH is at least one input of dopamine into the rMR. Right: Serotonergic neurons of the raphe nuclei expressing DRD2 regulate aggression. TTX-ablation of these neurons increases aggression, and application of dopamine suppresses neural firing D. Parvocellular and magnocellular oxytocin neurons of the PVN ($PVN^{OT(parvo)}$ and $PVN^{OT(magno)}$) control aspects of prosocial interaction and thermogenesis. Parvocellular neurons are activated by gentle somatosensory stimuli and relay information to magnocellular neurons. In turn, activation or inhibition of PVN^{OT} magnocellular neurons can increase or decrease close social contact, respectively. Magnocellular neurons can also trigger social reward via projections to the VTA and subsequent activation of dopaminergic neurons. Parvocellular neurons can promote peer-peer attachment, activation of sympathetic thermogenic pathways, and male sexual behavior, specifically ejaculation. E. In subregions of the ventromedial hypothalamus, $vlVMH^{Cckar}$ and $dmVMH^{Pdyn}$ neurons are cell-type and region-specific populations that promote thermogenesis as well as sexual and social behavior. Left: $vlVMH^{Cckar}$ neurons control female sexual receptivity and thermogenesis. Inactivation of these neurons diminishes female sexual receptivity and interest in males, whereas activation has the opposite effect. Activation of $VMHvll^{Cckar}$ increases Tb to the maximum of the normal circadian range, whereas inhibition decreases Tb to the minimum of the normal range. Right: $dmVMH^{Pdyn}$ neurons are activated by cold temperature, and this activation results in a rapid increase in both Tb and brown adipose tissue (BAT) temperature. Inhibition of these neurons has the opposite effect. $dmVMH^{Pdyn}$ neurons exhibit increased calcium activity during social interaction, and inhibition results in shorter social interaction times. **F.** Galanin-positive neurons of the lMPO (i.e., $lMPO^{Gal}$) promote pup interaction and increased heat loss, potentially through cutaneous vasodilation. Conversely, activation of $lMPO^{Gal}$ results in hypothermia, and activation promotes close physical contact with pups. **Abbreviations**. 5HT: serotonin; Cckar: cholecystokinin A receptor, DA: dopamine, DP/DTT: dorsal peduncular/dorsal tenia tecta, DMH: dorsomedial hypothalamus, DRD2: dopamine receptor 2, Esr-1: estrogen receptor alpha, Gal: galanin; GLU: glutamate, lMPO: lateral-medial preoptic area, NaC: nucleus accumbens, OT: oxytocin, PH: posterior hypothalamus, Pdyn: prodynorphin, PVN: paraventricular nucleus of the hypothalamus, rMR: rostral medullary raphe, rRPa: raphe pallidus nucleus, VMH: ventral medial hypothalamus (vl = ventrolateral, vm = ventromedial), VTA: ventral tegmental area.

project to sympathetic premotor neurons in the rMR (Kataoka et al., 2014) – a region controlling BAT thermogenesis. While several subregions of the prefrontal cortex displayed both connectivity to the DMH and elevated FOS expression during SDS, only inhibition of DP/DTT → DMH projections blunted SDS-induced increases in BAT thermogenesis and Tb. The DT/DTT receives inputs from thalamic, cortical, and amygdala brain areas, suggesting it integrates signals from these regions to drive sympathetic and behavioral responses.

Optogenetic inhibition of DP/DTT → DMH transmission abolished fear responses in the presence of a dominant rat, evidenced by increased social interaction. Furthermore, tail skin vasoconstriction, a typical stress response (Nakamura, 2011), was absent upon photoinhibition of the DP/DTT → DMH pathway, suggesting disruption of stress-induced autonomic responses. These results align with the concept of stress-induced sympathetic stimulation as an adaptive mechanism to enhance fight-or-flight readiness (Nakamura and Morrison, 2022). It could be speculated that increased Tb aids survival by enhancing cognitive sharpness (Wright et al., 2002), muscle performance (James, 2013), and improved oxygen delivery to muscles *via* enhanced blood circulation (Heinonen et al., 2011).

The DP/DTT → DMH → rMR pathway is unlikely to be the only one activated by social stress. SDS also strongly induces post-stress sleep (Sanford et al., 2014; Yu et al., 2022), provided the defeated animal is returned to its home-cage away from the victor. One possibility is that the elevated body temperature induced by SDS could promote slow-wave sleep; indeed, under certain conditions, warm skin may activate POA hypothalamic nitrergic neurons, thereby initiating both NREM sleep and subsequent body cooling (Harding et al., 2018).

4.2. Serotonergic neurons of the raphe nuclei

Serotonin (5-HT) is a monoamine neurotransmitter that, in the central nervous system, is produced by neurons of the raphe nuclei (i.e., $raphe^{5\text{-}HT}$ neurons). Raphe nuclei can be divided into two anatomical subregions: rostral nuclei of the pons and midbrain (including the dorsal raphe (DR) and median raphe), and caudal nuclei of the medulla (including rMR) (Okaty et al., 2019). Pioneering studies using 5-HT pharmacology and raphe lesions placed the serotonergic system as a regulator of thermoregulatory processes. The effects of 5-HT administration are contrasting: depending on the conditions, it can promote hyperthermia or hypothermia (Voronova, 2021). In a separate literature, the observation that cerebrospinal fluid levels of serotonin are lower in aggressive men (L.Brown et al., 1979) led to ongoing research on this relationship (L.Brown, 1982; Olivier, 2006). Finally, accumulating evidence suggests that $raphe^{5\text{-}HT}$ neurons play a role in maternal/neonatal interactions, including huddling (Lerch-Haner et al., 2008). This diversity of 5-HT-mediated responses stems from the neuroanatomical heterogeneity of the raphe nuclei, the brain-wide diversity of $raphe^{5\text{-}HT}$ projection targets, and the diversity of post-synaptic 5-HT receptor types found throughout the brain (Okaty et al., 2019). Given its complex organization, a central challenge to understanding the serotonergic system is to identify functionally specific $raphe^{5\text{-}HT}$ neural populations and their associated post-synaptic receptors. Indeed, converging evidence suggests specific functions of the serotonergic system stem from distinct serotonergic modules (Okaty et al., 2019).

Fourteen 5-HT receptor types and subtypes have been identified. While the precise relationships between 5-HT receptors and aggression remain unclear (Da Cunha-Bang and Knudsen, 2021), dozens of studies show that certain 5-HT receptors can increase or decrease Tb (reviewed by Voronova, 2021). Depending on where it is expressed, the same receptor may even have contrasting effects on Tb. For example, pharmacological activation of 5-HT1A in the raphe triggers decreased heat production and increased heat loss (Nakamura and Morrison, 2007), suggesting a body-cooling pathway; however, activation of this receptor in the spinal cord triggers the opposite effect (Madden and Morrison, 2008), underscoring the importance of circuit-specificity in manipulation-based studies. In contrast to 5-HT1A, activation of 5-HT2 receptors routinely causes hyperthermia (Voronova, 2021). Among the three 5-HT2 subtypes, 5-HT2A is strongly associated with an increase in core Tb and peripheral vasoconstriction, suggesting a body-warming pathway (Ootsuka et al., 2004). One study examining the intersection of 5-HT2A pharmacology and social behavior found that hyperthermia (but not heart rate or arterial pressure) induced by social stress was specifically blocked by the antagonist SR-46349B (Beig et al., 2009). This result is consistent with the notion that thermal and behavioral responses to social stress can be 5-HT dependent.

Thermoregulation circuity studies of the serotonergic system point towards regional specificity within the raphe. Sympathetic premotor neurons of the rMR controlling BAT thermogenesis, vasoconstriction, and fever have been primarily identified by tracing studies and by virtue of their projections to the spinal cord, and are generally composed of neurons expressing either 5-HT, vesicular glutamate transporter 3 (VGLUT3), or both (K. Nakamura et al., 2022; Nakamura et al., 2004). These neurons can likely be further subdivided according to projection targets or molecular profile.

Recently, two genetically distinct rMR populations with relevance to

Table 1
Neural populations that contribute to both thermoregulatory and behavioral phenotypes.

Brain region	Sub-region	Projection or cell type	Thermoregulatory effect	Behavioral effect
Hypothalamus	Paraventricular nucleus (PVN)	Parvocellular OT projections to rMR.	Activation of putative parvocellular neurons drives thermogenic, iBAT and cardiac responses (Fukushima et al. 2022). Some PVN^{OT} neurons project to the IML (which then innervates iBAT), and likely descend through rMR (Sutton et al. 2014, Fukushima et al. 2022).	–
		Parvocellular OT modulation of magnocellular OT	–	Social touch activates parvo-OT which synapse onto magno-OT neurons to promote interfemale communication (Tang et al. 2020).
		Parvocellular OT projections to NaC.	–	NaC uniquely receives parvo-OT projections which are involved in peer-peer social attachment (Lewis et al. 2020).
		Magnocellular and parvocellular OT projections to VTA.	–	Optogenetic stimulation of PVN^{OT} neurons activates VTA DA neurons that likely project to the NaC to enhance sociability (Hung et al. 2017).
	Dorsomedial hypothalamic nucleus (DMH)	GLU projections to rMR.	Neuronal activation required for iBAT thermogenesis and core Tb increase (Kataoka et al. 2014).	Optogenetic inhibition of cortical projections in the DMH is essential for cessation of sympathetic fear response and driving social-avoidance of dominant male (Kataoka et al. 2020).
	Ventromedial hypothalamic nucleus (VMH)	*Pdyn* expressing dmVMH neurons ($dmVMH^{Pdyn}$).	Optogenetic activation increases iBAT and core Tb (Feng et al. 2022).	Optogenetic inhibition reduces the number of social physical contacts made (Feng et al. 2022).
		$VMHvll^{Esr1}$ neurons expressing the cholecystokinin A receptor (Cckar; i.e., $VMHvll^{Cckar}$.	Activation results in increases Tb to the maximum of the normal range, inhibition results in decreased Tb to the minimum of normal range (Yin et al. 2022).	Regulate female proceptivity during mating: inactivation diminished interest in males and sexual receptivity, activating these cells has the opposite effect (Yin et al. 2022).
	Posterior hypothalamic nucleus (PH)	DA projection to the RPa.	Dopaminergic input from PH to *DRDD2* receptors in the RPa inhibits BAT thermogenesis (Conceição Furber et al. 2021).	Inhibition of either $raphe^{5\text{-}HT(DRD1a)}$ or $raphe^{5\text{-}HT(DRD2)}$ causes an increase in aggression, as measured by attack bites (Niederkofler et al. 2016).
	Lateral medial preoptic area (lMPO)	Galanin expressing neurons ($lMPO^{Gal}$).	Chemogenetic activation of $lMPO^{Gal}$ neurons causes decreased Tb at or below ambient thermoneutral temperatures, but not above thermoneutrality (Kroeger et al. 2018), possibly due to vasodilation of glabrous skin (Tanaka et al., 2011).	Ablation enhances infanticide; activation suppresses infanticidal attacks and enhanced pup grooming (Wu et al. 2014). Activation of gal-positive projections to ventral tegmental area and periaqueductal grey enhance motivation to interact with pups and pup grooming, respectively (Kohl et al. 2018).
Cortex	Dorsal peduncular/ dorsal tenia tecta	Glutamatergic projections to DMH.	Activation triggers iBAT thermogenesis and increased Tb via multi-synaptic pathway to DMH and rMR (Kataoka et al. 2020).	Activation of DMH^{VGLUT1} neurons is essential for fear response and social-avoidance behaviour to dominant male intruder (Kataoka et al. 2020).
	Insular cortex (IC)	Posterior Insular Cortex (pIC).	Cool and warm stimuli are distinctly encoded in the pIC (Vestergaard et al. 2023).	Fear balance (Klein et al. 2021) and social avoidance (Rogers-Carter et al. 2018) are regulated by insular cortex. Implication of pIC in neuropsychiatric disorders (Ebisch et al. 2011).
Brainstem	Rostral medullary raphe (rMR)	5-HT and *Drd2*	$rMR^{5\text{-}HT}$ neurons expressing DRD2 ($rMR^{5\text{-}HT(DRD2)}$) are capable of DA-dependent suppression of BAT thermogenesis (Conceição Furber et al. 2021).	Inhibition of $raphe^{5\text{-}HT(DRD1a)}$ or $raphe^{5\text{-}HT(DRD2)}$ throughout the raphe, including the rMR, promotes aggression (Niederkofler et al. 2016).
		Oxtr expressing 5-HT and/or *Vglut3* neurons.	Raphe neurons expressing OTR and serotonin ($raphe^{5\text{-}HT(OTR)}$), or Vglut3 ($raphe^{Vglut3(OTR)}$), or both, are capable of OT-dependent stimulation of BAT thermogenic responses (Fukushima, Kataoka, and Nakamura, 2022).	$Raphe^{5\text{-}HT(OTR)}$ neurons have been implicated in the control of aggression (Pagani, 2015) and maternal behaviour (Grieb et al. 2021).
Pons & Midbrain	Dorsal raphe (DR)	5-HT	5-HT neurons of the dorsal raphe are implicated in thermosensation of warm temperatures and in body cooling (Hale et al. 2011).	Cre-dependent knockdown of Tph2 in the DR of $Tph2^{flox/flox}$ mothers causes an alteration in crouching behavior (Muzerelle et al. 2021).

"–" Indicates there is currently no study to support this.

thermoregulation and social/affective behavior have been identified. First, rMR neurons expressing OXTR ($rMR^{5\text{-}HT(OXTR)}$) in rats are capable of OT-dependent stimulation of BAT thermogenic and cardiac sympathetic responses, in line with a thermogenic role of the rMR (Fukushima et al., 2022). It should be noted, however, that it was not conclusively determined whether $rMR^{5\text{-}HT(OXTR)}$ or VGLUT3-positive neurons expressing oxytocin receptor (i.e., $rMR^{Vglut-3(OXTR)}$) were driving the thermogenic response.

In contrast to the warming effect of $rMR^{5\text{-}HT(OXTR)}$ neurons, serotonergic neurons of the rMR expressing the dopamine (DA) receptor subtype D2 ($rMR^{5\text{-}HT(DRD2)}$) play a role in body cooling. This population is capable of DA-dependent suppression of BAT thermogenesis in rats; the release of DA in the rMR is driven, at least in part, by dopaminergic neurons of the posterior hypothalamic nucleus (PH; Fig. 2 A and C) (Conceição Furber et al., 2021). These observations underscore the diversity of thermoregulatory roles of serotonergic modules within the raphe. Intriguingly, $raphe^{5\text{-}HT(OXTR)}$ neurons have been implicated in the control of aggression (Pagani, 2015) and maternal behavior (Grieb et al., 2021) and, as discussed below, $rMR^{5\text{-}HT(DRD2)}$ neurons play a direct role in regulating aggression.

Given the developmental, regional, molecular, and projection heterogeneity of $raphe^{5\text{-}HT}$ neurons, traditional genetic approaches using knockout alleles or driver-genes have limited ability to address mechanisms of action. Intersectional genetic approaches, however, have allowed for greater specificity and elucidated functional roles in thermoregulation and aggression. In an early study using a double-transgenic approach, $raphe^{5\text{-}HT}$ neurons were targeted with either the *Slc6a4*-Cre or *Pet1*-Cre crossed to the RC::FPDi line, allowing for

conditional chemogenetic silencing. Inhibition of these raphe$^{5\text{-HT}}$ neurons resulted in an immediate and lasting hypothermia (Ray et al., 2011), confirming a direct role of raphe$^{5\text{-HT}}$ neurons in thermogenesis. However, the regional and cell-type specificity of the neurons controlling this response was not further investigated.

More recent approaches using triple-transgenic, dual-recombinase mouse lines have targeted cell-type specific populations of raphe$^{5\text{-HT}}$ neurons, including those expressing DA receptors. Raphe$^{5\text{-HT}}$ neurons expressing DA receptor 1a (raphe$^{5\text{-HT(DRD1a)}}$) are expressed from an early embryonic stage and are found throughout the raphe, particularly along the midline. In contrast, raphe$^{5\text{-HT(DRD2)}}$ neurons begin expressing DRD2 during adolescence and are located in the rostral-most DR, especially the lateral wings, and sparsely distributed in caudal DR, median, and medullary raphe (Niederkofler et al., 2016). Although these populations have markedly different projection patterns, inhibition of either raphe$^{5\text{-HT(DRD1a)}}$ or raphe$^{5\text{-HT(DRD2)}}$ caused an increase in aggression. Although DA stimulation generally induced excitatory currents in raphe$^{5\text{-HT}}$ neurons, it caused inhibitory currents in the raphe$^{5\text{-HT(DRD2)}}$ module. Because other cell-type specific populations of raphe$^{5\text{-HT}}$ neurons were not found to be involved in aggression, these results suggest that DA receptor expressing raphe$^{5\text{-HT}}$ neurons might have a conserved role in aggression (Niederkofler et al., 2016) (Fig. 2C). When viewed in light of the observation that DA input to rMR$^{5\text{-HT(DRD2)}}$ suppresses thermogenesis (Conceição Furber et al., 2021), the finding that dopaminergic silencing of raphe$^{5\text{-HT(DRD2)}}$ triggers aggression yields a potential circuity linking thermoregulation and aggression. One possibility is that activation of the raphe$^{5\text{-HT(DRD2)}}$ module simultaneously causes 1) body cooling *via* projections to the POA and sympathetic outflow regions of the rMR and spinal cord, and 2) aggression *via* projections to the hypothalamus. Tests of whether body cooling primes an individual to succeed in an aggressive encounter will further our understanding of neural circuity linking social behavior and thermoregulation.

Maternal-neonate interactions contribute to neonatal thermoregulation (Asakura, 2004), and might be regulated by dedicated raphe$^{5\text{-HT}}$ cell-types or circuits in the DR (i.e., DR$^{5\text{-HT}}$). Several studies have demonstrated that 5-HT depletion alters maternal-to-pup behaviors in mice, including nesting, pup retrieval, huddling, and nursing (Angoa-Pérez et al., 2014; Lerch-Haner et al., 2008; Trowbridge et al., 2011). However, because many of these studies were done on mothers with a complete knockout of serotonergic neurons, it is unclear whether effects were attributable to developmental defects. One recent study addressed this limitation by performing a Cre-dependent knockdown of *Tph2* in the DR of Tph2$^{\text{flox/flox}}$ mothers that had previously mothered a litter (Muzerelle et al., 2021). This manipulation caused an alteration in maternal crouching behavior, but not nest building, pup retrieval, or nursing time, and therefore recapitulated only a subset of the behaviors seen in complete knockout of 5-HT. Notably, the 5-HT neurons in the DR have also been found to have thermosensitive and thermoregulatory properties in rodents (Hale et al., 2011). Because crouching is a way for the mother to create warmth around the pup, this finding provides a means for understanding how DR$^{5\text{-HT}}$ modules regulate maternal-neonate thermoregulation.

In summary, the serotonergic system regulates thermoregulation, aggression, and maternal/neonate interactions. Recent developments have provided tools for understanding how serotonergic modules can control specific functions. Intriguingly, separate studies have identified a role of the raphe$^{5\text{-HT(DRD2)}}$ module in thermoregulation (Conceição Furber et al., 2021) and in aggression (Niederkofler et al., 2016), providing a framework for understanding neuromodulation of Tb and fighting.

4.3. Oxytocin neurons of the paraventricular nucleus of the hypothalamus

The paraventricular nucleus (PVN) plays essential roles in neuroendocrine and autonomic regulation through its extensive hypothalamic and hindbrain connections. Here, we focus on OT neurons of the PVN (PVN$^{\text{OT}}$) as they have been studied extensively and are linked to functional circuits associated with both thermoregulation and social behaviors, though most studies investigated these roles separately. OT neurons are classified into magnocellular or parvocellular subpopulations, with distinct differences in size, circuitry, spatial orientation, and electrophysiology. However, our understanding of the projections and phenotypes of these distinct subpopulations remains incomplete.

As a neuromodulator, OT has a well-established role in regulating social, sexual, and maternal behavior in mammals (Froemke and Young, 2021). PVN$^{\text{OT}}$ modulation of the female auditory cortex is required for mouse parenting responses to pup vocalization (Schiavo et al., 2020). In male rats, oxytocin receptors in spinal ejaculation generator (SEG) and gastrin-releasing peptide (GRP) neurons of the lumbar spinal cord are directly activated by OT signaling from PVN$^{\text{OT}}$ to promote ejaculation (Oti et al., 2021). Furthermore, OT signaling is required for components of social recognition and empathy-like behaviors in mice and prairie voles, respectively (Froemke and Young, 2021). Social salience, a term used to describe a prominent awareness of social cues, is enhanced by PVN$^{\text{OT}}$ activation and projections, suggesting that the function of OT signaling goes beyond well simply promoting prosocial behavior (Froemke and Young, 2021).

OT can also modulate thermoregulation by producing metabolic heat and regulating energy homeostasis (Kasahara et al., 2013). OT and OXTR have been implicated in the regulation of energy homeostasis, but the precise mechanisms are still unclear. OXTR is expressed throughout the mouse brain as well as in adipose tissue and is required for proper thermogenic responses (Kasahara et al., 2013; Son et al., 2022; Yi et al., 2015). OXTR knock-out (*Oxtr*$^{-/-}$) male mice are unable to maintain body temperature during cold challenges and show increased c-Fos expression in PVN$^{\text{OT}}$ neurons at 5° C and imbalanced expression of β3 and α2A adrenergic receptors in BAT (Kasahara et al., 2013). Restoration of *Oxtr* in the DMH and ventromedial hypothalamus using viral vectors rescued this diminished thermoregulation, suggesting the sufficiency of OT/OXTR pathways for cold-defense (Kasahara et al., 2013). These observations suggest that more circuit-level studies of oxytocin signaling in hypothalamic areas controlling thermoregulation and social behavior are warranted.

The close association between the oxytocinergic system and cardiovascular functions have been revealed in investigations of fear, aggression, and psychosocial stress. Intranasal administration of OT increases heart rate variability (HRV), a measurement that is often positively correlated with cardiovascular health in humans; notably, individuals with elevated levels of perceived loneliness were more resistant to the effects of OT on HRV (Norman et al., 2011). In agreement with this finding, socially isolated prairie voles experience increased resting heart rate and reduced HRV, and these psychosocial responses were prevented with OT administration (Grippo et al., 2009). Since OT is largely synthesized in the PVN and PVN$^{\text{OT}}$ neurons influence cardiac responses, these effects in humans and prairie voles may be mediated by PVN$^{\text{OT}}$ neurons (Fukushima et al., 2022).

The above studies suggest that PVN$^{\text{OT}}$ circuitry jointly modulates social behavior and cardiovascular processes, which are often co-regulated with Tb. Intriguingly, PVN$^{\text{OT}}$ neurons were recently demonstrated to play a role in synchronizing Tb and cardiac responses. The release of OT by rMR-projecting PVN$^{\text{OT}}$ neurons drives intrascapular BAT (iBAT) thermogenesis and cardiac responses independent of glutamatergic input in anesthetized rats (Fukushima et al., 2022). OT release is likely responsible for this process as administration of OXTR antagonist in the rMR lead to the cessation of these responses (Fukushima et al., 2022) (Fig. 2D). Thus, the PVN$^{\text{OT}}$ → rMR pathway is a candidate circuit integrating social and thermal responses.

Neuronal sub-populations of the PVN are capable of controlling energy balance and thermoregulation through distinct projection pathways. Chemogenetic activation of PVN nitric oxide synthase 1 neurons (i.e., PVN$^{\text{NOS1}}$) promotes increased physical activity and thermogenesis

in mice (Sutton et al., 2014). In contrast to two other studies (Fukushima et al., 2022; Tang et al., 2020), Sutton et al. (2014) suggest that PVN^{OT} neurons send dense projections to choline acetyltransferase (ChAT)--positive sympathetic preganglionic neurons of the intermediolateral nucleus (IML) of the thoracic spinal cord, but not the rMR. In this study, activation of PVN^{OT} neurons did not produce changes in iBAT temperature (Sutton et al., 2014), although temperature transponders were implanted into the subcutaneous tissue above the iBAT pad, a technique prone to lower or inaccurate temperature readings (Meyer et al., 2017). The existence of PVN^{OT} → IML projections may suggest that PVN^{OT} projections bypass the rMR in mice (but not rats), or that there is anatomical and/or functional variation among PVN^{OT} projection neurons. A related point is that transsynaptic retrograde tracing in various rodent models has shown that iBAT innervation can originate from or integrate with the PVN; however, the cell types, neuromodulators, and their mechanistic functions have not been fully elucidated (Bamshad et al., 1999; Bartness et al., 2010; Oldfield et al., 2002). Thus, further investigation of PVN cell-type specific pathways is needed to understand the role of this brain region in thermogenesis.

OT neurons can modulate the CNS and ANS through non-synaptic communication. Exocytotic release of OT from large dense core vesicles (also called volume transmission) has been documented in the hypothalamus and spinal cord, with effects on both thermogenesis and sexual behavior (Chini et al., 2017; Fukushima et al., 2022; Oti et al., 2021). Recent *in vivo* imaging using an OT GRAB sensor captured OT release (likely from non-synaptic exocytotic release) in the PVN during the sniffing and intromission phases—but not other phases—of male sexual behavior (Qian et al., 2023). Next, while investigating the neural circuitry responsible for male rat sexual behavior and penile reflexes, Oti et al. (2021) located varicosities originating from PVN^{OT} neurons (presumptively of the magnocellular population) near GRP neurons in the lumbar spinal cord. It was concluded that the driver of sexual behavior was *en passant* release of OT in the spinal cord as no synaptic microvesicles, contacts, or boutons were observed. PVN^{OT} *en passant* fibers with varicosities also closely localize with VGLUT3 sympathetic premotor neurons and serotonergic neurons in the rat rMR, suggesting volume transmission and diffusion of OT is a common mechanism in hindbrain (Fukushima et al., 2022). These studies highlight the role of non-canonical neuropeptide release in the control of thermoregulation and behavior.

Parvocellular and magnocellular PVN^{OT} neurons play exclusive roles in oxytocinergic signaling in the brain, behavior modulation (Grinevich and Ludwig, 2021; Hung et al., 2017; Lewis et al., 2020; Tang et al., 2020), and thermogenesis (Fukushima et al., 2022). Broadly, parvocellular subpopulations are known to project to the brain stem and spinal cord while magnocellular populations cross the blood brain barrier to the posterior pituitary. PVN^{OT} parvocellular cells uniquely send projections to the nucleus accumbens (NaC), mediating social reward signaling in mice *via* the peptide *Fmr1* (Lewis et al., 2020) (Fig. 2D). PVN^{OT} parvocellular neurons also project to the rMR where they likely activate thermogenesis (Fukushima et al., 2022). In addition, PVN^{OT} parvocellular neurons in female rats are activated during social touch, and these neurons subsequently activate neighboring magnocellular neurons, modulating inter-female communication and direct physical contact (Tang et al., 2020) (Fig. 2D). Thus, PVN^{OT} parvocellular neurons are a candidate mechanism for the simultaneous coordination of social behavior and thermoregulation (Fig. 2D and Table 1). One possibility is that the activation of these neurons reinforces rewarding aspects of social touch by triggering thermogenesis and heat transfer between individuals.

A combination of magnocellular and parvocellular OT neurons is speculated to project to dopamine neurons of the ventral tegmental area (VTA) to regulate social reward through the release of OT (Hung et al., 2017) (Fig. 2D). However, precisely distinguishing magno- vs. parvocellular OT function has been challenging. Recently, molecular-genetic approaches have been used to distinguish between these two cell types: calbindin (*Calb1*) and potassium channel subunit (*Kcnmb4*) are considered distinctive markers for magnocellular PVN^{OT} cells, while Reelin (*Reln*) and cannabinoid receptor 1 (*Cnr1*) genes are upregulated in parvocellular subpopulations (Lewis et al., 2020). It is important to note that it is unclear whether these markers can be fully relied upon for molecular analysis or immunohistochemistry, as they have not been reliably tested or standardized.

Though no studies to our knowledge have conducted simultaneous measurements of social and thermoregulatory biology in context with PVN^{OT} neurons, current evidence suggests that this might be possible. In particular, PVN^{OT} parvocellular neurons are poised to coordinate social and thermal processes through their projections to the NaC and rMR (Fig. 2D). More generally, the spatial proximity of PVN^{OT} projections to the hindbrain and spinal cord thermoregulatory centers (Fukushima et al., 2022; Hallbeck et al., 2001; Sutton et al., 2014; Tang et al., 2020), coupled with the neuromodulation of social behavior by parvo- and magno-PVN^{OT} neurons, indicate the possibility of dual coordination. As discussed in Section 7, the functional role of thermogenesis in regulating social and sexual behavior could be addressed in studies targeting uncoupling mechanisms of heat production in BAT.

4.4. Ventromedial hypothalamus

The ventromedial hypothalamus (VMH) has long been associated with regulation of sexual and aggressive behavior, and several cell-type and projection-type specific populations have been linked to specific behaviors (Anderson, 2016). While the VMH has been associated with the control of thermoregulation, for example in lesion studies (Mitchell et al., 1981), neuronal and circuit details have been far less understood. However, three recent studies using neurobiology tools along with temperature monitoring establish a link between sexual behavior and thermoregulation.

First, the dorsomedial region of the ventromedial hypothalamus (dmVMH) simultaneously coordinates thermoregulation and social behavior at the neuronal level. dmVMH neurons expressing prodynorphin ($dmVMH^{Pdyn}$) can initiate thermogenesis in response to cold environments (Feng et al., 2022) (Fig. 2E). $dmVMH^{Pdyn}$ neurons are activated by cold temperature, resulting in a rapid increase in both core Tb and BAT temperature, due in part to projections to the DMH, POA, and periaqueductal grey. In contrast, $dmVMH^{Pdyn}$ neurons are inhibited by warm temperature, resulting in reduced Tb. Of note, these neurons were not activated during inflammatory fever or fever driven by ectopic activation of the transient receptor channel TRPM8, suggesting they control thermogenesis independent of inflammation circuity. $dmVMH^{Pdyn}$ neurons receive diverse inputs from social- and cognitive-related brain regions, which may trigger their activation and consequent thermogenesis. Remarkably, $dmVMH^{Pdyn}$ neurons exhibited increased calcium activity during social interaction, and concurrent with this activity mice experienced social-induced hyperthermia. Inhibition of these neurons caused a decrease in social interaction, illustrating functional interplay between elevated Tb and social interaction. Bidirectional projections between $dmVMH^{Pdyn}$ neurons and regions such as the periaqueductal grey and POA area offer intriguing prospects for output signals regulating Tb and social behavior.

Second, the ventrolateral subdivision of the ventromedial hypothalamus (VMHvl) is well known for its importance in regulating sexual and aggressive behavior (Hashikawa et al., 2018; Lindenfors and S.S.S. Tullberg, 2011; Lonstein and Gammie, 2002; Martín-Sánchez et al., 2015). Within the VMHvl, neurons expressing the estrogen receptor-1 (Esr1, also known as Erα; i.e., $VMHvl^{Esr1}$) are particularly important for female proceptivity during mating as well as maternal aggression (Hashikawa et al., 2018; Lindenfors and S.S.S.Tullberg, 2011; Lonstein and Gammie, 2002; Martín-Sánchez et al., 2015). Because none of the aforementioned studies analyzed thermoregulation, links between $VMHvl^{Esr1}$-mediated regulation of behavior and thermoregulation have been poorly understood. However, a recent examination of $VMHvl^{Esr1}$

neurons in energy homeostasis and thermoregulation elucidated their role beyond social behavior (Van Veen et al., 2020): activation of these neurons led to a significant increase in BAT thermogenesis. This observation raises new questions about whether VMHvl^{Esr1} regulation of social and sexual behavior is dependent on, or enhanced by, concomitant modification of Tb.

Third, limitations of functional studies of VMHvl^{Esr1} neurons include the presence of neuronal sub-types and their organization into medial and lateral regions (i.e., VMHvlm and VMHvll) (Liu et al., 2022; Yin et al., 2022). To address these limitations, a recent study examined the functional role of the VMHvll^{Esr1} subpopulation expressing the cholecystokinin A receptor (Cckar; i.e., VMHvll^{Cckar}). Providing clarity to the sometimes-conflicting behavioral results associated with Esr1-positive neurons, VMHvll^{Cckar} neurons were found to regulate female proceptivity during mating: inactivation diminished interest in males and sexual receptivity, whereas activation had the opposite effect (Yin et al., 2022). Moreover, calcium activity in these neurons was dependent on the reproductive cycle and was highest during estrus. Given the association between estrus and Tb, this study also examined the role of VMHvll^{Cckar} neurons in thermoregulation. Remarkably, activation of VMHvll^{Cckar} resulted in Tb increase to the maximum of the normal diurnal range, while inhibition resulted in a decrease to the minimum of the normal range. These data suggest VMHvll^{Cckar} neurons simultaneously control social-sexual behavior and fine adjustments of Tb (Fig. 2E), and raise the question of whether the behavioral changes are dependent on the changes in Tb. Although the precise thermo-effector pathway that is activated by VMHvll^{Cckar} is not known, a prime candidate would be projections to the sympathetic premotor of neurons of rMR controlling thermogenesis.

Altogether, distinct VMH neuronal populations are capable of coordinating social behavior and thermoregulation and are in accordance with the hypothesis that fine-tuning of Tb could optimize performance during social interaction. A test of the temperature-dependency of VMH neurons controlling social or sexual behavior could inhibit BAT activation (see Section 7) during social interaction to address downstream effects on behavior.

4.5. Preoptic area and lateral medial preoptic area

The POA has an unequivocal role in both thermoregulation and innate social behavior. The POA is classically known as a "thermostat" of the brain because it is capable of integrating sensory information and executing command signals to thermoregulatory effectors to maintain homeostatic Tb (Harding et al., 2020; Morrison and Nakamura, 2019; Y. Nakamura et al., 2022). With respect to social behavior, the POA governs multiple aspects of parenting behavior in females and males (Tsuneoka and Funato, 2021). Because a core component of parental care in rodents is heat transfer to pups during huddling, one possibility is there are dedicated circuits that coordinate parental cutaneous vasodilation to facilitate heat transfer to young by conduction. However, the identity of such circuits remains obscure. Historically, characterization of POA circuity has been hampered by significant anatomical and molecular heterogeneity. But recent progress in single-cell molecular and spatial profiling techniques has provided a high-resolution framework for understanding the subdivisions and functional attributes of POA cell types (Moffitt et al., 2018).

Galanin neurons of the POA are associated with both thermoregulation and parental behavior and might be a neural population poised to integrate aspects of Tb and parental care (Fig. 2F). In mice, the anatomical intersection between the medial preoptic area (MPO) and the lateral preoptic area (lPOA), a region referred to as the lateral MPO (i.e., lMPO), contains galanin neurons whose activity can promote both heat loss and parental care. Evidence that galanin-positive lMPO neurons (i.e., lMPO^{Gal}) inhibit the thermogenic response comes from a chemogenetic study. Activation of lMPO^{Gal} neurons caused a profound decrease in core Tb at or below ambient thermoneutral temperatures, but not above thermoneutrality (Kroeger et al., 2018). Chemogenetic activation also caused an increase in non-REM sleep, consistent with the notion that non-REM sleep and body cooling are coupled. The effect of inhibiting lMPO^{Gal} neurons on Tb was not addressed. When viewed in light of other studies examining lMPO-adjacent projections to brainstem regions (Tanaka et al., 2011), it was concluded that lMPO^{Gal} activation causes an increase in blood flow to glabrous skin (i.e., vasodilation) and consequently heat loss. In support of the notion that galanin neurons in the vicinity of the lMPO promote body cooling in mice, lesions of these neurons cause chronic hyperthermia (Ma et al., 2019). Notably, animals with these lesions retain their usual diurnal variation in Tb, but mean Tb is shifted up by several degrees. However, the precise function of lMPO^{Gal} neurons is not yet clear. For example, in contrast to the chemogenetic study, ablation of lMPO^{Gal} neurons causes an increase in sleep (Ma et al., 2019). Given the molecular heterogeneity of galanin neurons of the preoptic area (Moffitt et al., 2018), it is speculated that the sleep- and thermal-regulating neurons may be separate populations (Harding et al., 2020). Thus, identification of the precise thermoregulatory subpopulation is necessary for a complete understanding of the function of lMPO^{Gal} neurons.

Galanin neurons in the vicinity of lMPO also control aspects of parental behavior. Manipulation of, and activity within, lMPO^{Gal} neurons is tightly linked with the execution of specific behavioral routines during parental care. First, Fos-expressing neurons around the lPOA during parental behavior are galanin-positive in both females and males. Ablation of these galanin-positive neurons enhanced infanticide, while activation suppressed infanticidal attacks and enhanced pup grooming (Wu et al., 2014). Examination of circuit-specific populations controlling these responses revealed that activation of galanin-positive projections to the periaqueductal grey in males and females specifically enhanced pup grooming. In contrast, activation of galanin-positive projections to the ventral tegmental area enhanced the motivation to interact with pups (Kohl et al., 2018).

Together, activating lMPO^{Gal} neurons causes suppression of infanticide and increased motivation to interact with pups, while other studies suggest these neurons control loss of body heat and enhance vasodilation. These observations are therefore congruent with the hypothesis that a function of lMPO^{Gal} neurons is to facilitate cutaneous vasodilation during parental-infant interactions to maintain homeostatic Tb in infants.

4.6. Insular cortex

Whereas social behavior is regulated by several neuroanatomical regions controlling thermoregulation, it is linked with very few thermosensory regions. The insular cortex appears to be a region where both thermosensation and social behavior could be coupled at the neuronal level. Brain regions controlling cutaneous sensation of external temperature have historically been a matter of debate; unlike other cutaneous modalities, the primary somatosensory cortex does not appear to be a master driver of thermosensation. Recently, a comprehensive analysis of calcium responses to thermal inputs identified the posterior insular cortex (pIC) as the primary location for the representation of cool and warm temperatures in humans, monkeys, and rodents (Vestergaard et al., 2023). Cool and warm stimuli have distinct encoding in the pIC: warm is encoded as absolute temperature, whereas cool is encoded as the magnitude of relative temperature change.

The finding that the pIC is the location of temperature perception adds to the variety of sensory, homeostatic, emotional, and behavioral processes integrated in this multi-functional region. The insular cortex's distributed role, along with its connections to sensory, emotional, and cognitive regions has led to the hypothesis it serves as a "salience network" to enhance the detection of homeostatically relevant inputs to enable the most appropriate response (Seeley, 2019). For example, the insular cortex has been shown in rats to regulate social avoidance and approach towards conspecifics that had previously experienced stress

(Rogers-Carter et al., 2018). Moreover, the insular cortex, including the pIC, has been implicated in neuropsychiatric disorders including ASD (Ebisch et al., 2011; Gutiérrez-Rojas et al., 2020).

The salience detection framework for understanding the pIC raises the question of whether this region might be important for detecting changes in the Tb of conspecifics, such as during periods of fever or stress. The avoidance of other individuals experiencing fever could serve as defense mechanism to prevent infection transmission (Kavaliers et al., 2022; Lopes et al., 2016). One study addressed this notion in rats by examining social interaction with other individuals experiencing fever and sickness (Rieger et al., 2022). Polyinosinic: polycytidylic acid (Poly I:C) is an immuno-stimulant that induces a potent fever along with other sickness behaviors such as lethargy and anorexia. In a social preference test using a three-chamber apparatus, male and female rats strongly avoided Poly I:C treated adult conspecifics (but not saline injected adults), and this avoidance was dependent on the insular cortex. When the pIC was inhibited with cannulated injections of muscimol, rats no longer displayed avoidance. On the other hand, rats did not show avoidance of Poly I:C treated juvenile rats, suggesting an age-dependence of social avoidance. Because Poly I:C triggers several immune responses, not just fever, it will be important to test whether fever itself is sufficient to elicit avoidance from conspecifics. If so, this would support the notion that changes in Tb could serve as a signal to regulate social interactions. Altogether, these studies indicate that the pIC is a site that could integrate afferent thermal information to guide social interactions, particularly in the context of pathogen transmission.

5. Dysregulation of thermal biology in neuropsychiatric disorders

Several major neuropsychiatric disorders affecting social behavior have been correlated with dysregulation of Tb. Here, we focus on schizophrenia, autism spectrum disorder (ASD), and major depressive disorder (MDD) as three conditions with well-documented thermoregulatory abnormalities. Given the clinical heterogeneity of these disorders (Moreno-De-Luca and Martin, 2021), there is a critical need to understand the precise relationship between components of thermoregulation (e.g., vasomotor patterns, brown fat thermogenesis, and behavioral thermoregulation) and specific affective symptoms. This correlative baseline data would then generate hypotheses that could be tested with functional and manipulation-based strategies using animal models. With such an approach, there is potential to develop new approaches to investigate neuropsychiatric disorders and provide non-invasive treatments that could ease strain on caregivers and healthcare institutions.

5.1. Major depressive disorder

MDD is a severe and persistent mental health condition characterized by profound and persistent feelings of sadness, emptiness, and a lack of interest or pleasure in most activities (Gutiérrez-Rojas et al., 2020). Individuals with MDD may experience a range of emotional, cognitive, physical, and behavioral symptoms that significantly impact their daily life and functioning. The association between MDD and altered thermoregulation is marked by increased night-time Tb in individuals with depression (Arbisi et al., 1994, 1989; Avery et al., 1982). More recently, a study of over 20,000 participants found that higher distal body temperature (measured using wearable sensors) is also positively correlated with depression severity (Mason et al., 2024).

Whole-body hyperthermia (WBH) is a therapeutic approach that exposes individuals to an acute increase in Tb followed by approximately five days of lowered Tb (Hanusch et al., 2013; Janssen et al., 2016). Participants who experienced a greater decline in Tb also experienced a greater reduction of depressive symptoms (Hanusch et al., 2013). Notably, the effectiveness of WBH was inversely correlated with core Tb measured before treatment: those with higher Tb before treatment were more likely to respond positively to WBH. Exposure to WBH has also been linked to a reduction in depression ratings among cancer patients (Koltyn et al., 1992). Thus, MDD is associated with, and treated by, changes in Tb.

In animal models, stimulation of midbrain serotonergic neurons produces antidepressant-like effects (Lowry et al., 2007) while simultaneously inducing thermoregulatory cooling (Hale et al., 2011). One interpretation could be that MDD disrupts warm-sensitive afferent spinoparabrachial pathways that project from the skin to midbrain serotonergic nuclei (Nakamura and Morrison, 2010). In accordance, animal studies have shown that WBH activates brainstem serotonergic neurons, as measured by increased immediate-early gene expression (Hale et al., 2011), suggesting these neurons could be further investigated for treatment of depressive disorders (Lowry et al., 2018). Another interpretation could be that MDD disrupts central efferent pathways with dual control over thermogenesis and affective behavioral states, such as the circuits reviewed here (Fig. 2 and Table 1). Relevant to these WBH studies is the observation that selective serotonin reuptake inhibitors (SSRI) affect Tb (Maswood et al., 2006). In rats, exposure to WBH potentiates the antidepressant-like effects of a subthreshold dose of the SSRI citalopram (Hale et al., 2017). However, in a follow-up study using a suprathreshold dose, WBH did not enhance the behavioral effects of the drug, but did enhance the short-term increase in core Tb (Hale et al., 2019). Thus, although the precise mechanistic details of how MDD and Tb are linked are not yet clear, this question warrants further attention and highlights the potential of bodily states to influence neuropsychiatric disorders.

5.2. Schizophrenia spectrum disorders

According to the World Health Organization, schizophrenia spectrum disorders (SSDs) affect approximately 24 million people worldwide (https://www.who.int). Those affected are characterized by disruptions in thought processing and perception, emotional responsiveness, and social interaction. Social behavior is thought to be disrupted through numerous psychotic symptoms such as delusion and reduced expression of emotions (Frith, 2000).

Clinicians have often observed that individuals with schizophrenia wear several layers of clothing, even in warm ambient temperatures. Individuals with SSD commonly exhibit disrupted Tb regulation, including variable baseline temperatures, abnormal daily temperature ranges, altered diurnal patterns, and difficulty adapting to hot and cold stress, suggesting impairments in both peripheral and central thermoregulatory mechanisms (Chong and Castle, 2004). These irregularities might be intrinsic to schizophrenia, but could also be influenced by neuroleptic medication (Gurrera and Chang, 1996; Zonnenberg et al., 2017).

Several candidate brain areas could be considered as potential sites of mechanistic overlap for thermoregulation and SSD. Notably, the mesolimbic dopamine system is implicated in both thermoregulation and psychosis, and some evidence suggests that disruptions in this system might be responsible for both temperature dysregulation and some symptoms of SSD. Dopamine transmission *via* DRD2 receptor subtypes is one such mechanism. Central DRD2 receptor density is higher in individuals with SSD (Webster, 2001), and, as discussed in Section 4.2, DRD2 is thought to play a major role in thermoregulation: dopaminergic input to raphe$^{5\text{-HT(DRD2)}}$ from the PH suppresses thermogenesis (Conceição Furber et al., 2021). Because the mesolimbic dopamine system is implicated in SSD (McCutcheon et al., 2018), DRD2 has also been investigated as a candidate gene in several studies. In a case-control study involving 101 cases and 145 controls, researchers found a significant difference in genotype distribution for the DRD2 *His313* polymorphism between SSD individuals and controls (Kukreti et al., 2006), leading to speculation that this variant leads to greater DRD2 expression. In a large genome-wide association study (GWAS) of 36,989 cases and 113,075 controls, DRD2 emerged prominently, corroborating its

role in schizophrenia pathology (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Follow-up studies showed that genetic variation in *Drd2* is associated with sociability, even in an undiagnosed population (Bralten et al., 2021), and *Drd2* mutations in mice and *Drosophila* disrupt social interactions (Ike et al., 2023).

Due to the heterogeneous nature of symptoms, the neurobiology of SSD has proven difficult to study. However, disruption of autonomic processes such as sleep and heart rate provides a potential avenue for a more comprehensive understanding (Horvath et al., 2015; Rogers et al., 2023), and *Drd2* presents a candidate gene underlying thermoregulatory and behavioral deficits that could be targeted with dopaminergic and antipsychotic pharmacological approaches.

5.3. Autism spectrum disorder

ASD is a neurodevelopmental disorder characterized by deficits in social communication and learning, along with repetitive behavior (Hodges et al., 2020). Consequently, quality of life can be highly restricted and autistic individuals may require significant care from an early age. While much is known about ASD as a social deficit disorder, it is also associated with autonomic dysregulation (Bujnakova et al., 2016; Owens et al., 2021), and associations with Tb have been made. Clinical studies have shown that ASD behavioral symptoms may improve with inflammatory fever (Curran et al., 2007). Clinically diagnosed ASD children (N = 30) were behaviorally scored *via* the Aberrant Behavior Checklist when febrile (Tb > 38ºC/100.4ºF), when fever had reduced to an asymptomatic state, and after seven days fever-free. Febrile children displayed reductions in irritability, hyperactivity, stereotypy, and inappropriate speech compared to afebrile children matched for age, gender, and language skills. Increased core Tb was correlated with less severe social behavioral phenotypes, which could not be attributed solely to the general effects of sickness. However, a caveat to this interpretation is that inflammation is capable of changing several brain functions, including arousal (Swardfager et al., 2016) and social interaction (Choi et al., 2016).

In a study conducted by the Simons Simplex Collection, parents of 2152 autistic children were asked to score which aspects of their child's behavior they believed improved during fever (Grzadzinski et al., 2018). Of the 17% of children with noted improvements during fever, parents reported significant improvement in temper, behavior, communication, socialization, and decreased repetitive behaviors. Overall, fever-induced blunting of ASD symptoms could support the notion of an underlying neural circuitry controlling both social behavior and thermoregulation.

The role of fever vs. inflammation ASD has been examined in a study of several different mouse models (Reed et al., 2020). Environmental models of ASD, but not genetic models, displayed increases in sociability during LPS-induced fever. In contrast, direct delivery of the pro-inflammatory cytokine interleukin-17a (IL-17a) into the primary somatosensory cortex dysgranular zone (S1DZ) was sufficient to promote sociability in both environmental and genetic models of ASD. This suggests the inflammatory response is sufficient to restore social behavior in ASD models (Reed et al., 2020). To further disentangle the effects of LPS-mediated inflammation vs. LPS-mediated fever, GABAergic neurons of the ventral part of the lateral preoptic nucleus were chemogenetically activated to induce fever, which notably did not affect social preference in the environmental model of ASD. However, one possible drawback of this experiment is that LPS-mediated fever is driven by EP3R-expressing neurons of the ventromedial preoptic nucleus (Y. Nakamura et al., 2022; Reed et al., 2020). Activation of this cell-type specific neuronal population would therefore serve as a more appropriate pathway to determine the effect of LPS on sociability.

At present, potential circuit-level mechanisms underlying the relationship between Tb and ASD in humans are not known. Thermal-based therapeutic approaches and pharmacology targeting body temperature could further evaluate the hypothesis that fever attenuates behavioral symptoms of ASD.

6. Adaptive value of fine-tuning Tb

Behavioral states can be associated with specific thermal states (Fig. 1), but how and when do alterations in Tb enhance survival or, in humans, athletic, cognitive, and affective states? Tb adjustments can be adaptive in a diversity of species, including in social contexts. For example, rabbit pups can alter their thermoregulatory state to outcompete their litter mates (Gilbert et al., 2007a). Specifically, pups in larger groups raise Tb before a nursing bout, which provides a suckling advantage. Pups are thermoregulatory inefficient in the first few days of their life, and female parents only visit their pups twice a day (Hudson and Distel, 1982), so optimizing Tb for nutrition can enhance competitive ability.

Human athletic performance can be influenced by thermal states, and manipulating circuitry driving these alterations could be useful for maximizing performance and limiting injury. Research has begun to explore the link between body-heat extraction and increased cardiovascular performance. Device-driven subatmospheric pressure applied to the entire hand (to increase blood flow) coupled with cooling of the palm improves cardiovascular function *via* an increased exercise duration (Grahn et al., 2005). Similarly, whole body cooling (WBC) can increase capacity for prolonged exercise at various ambient temperatures (Marino, 2002). Reviewing how thermal manipulations of Tb (*via* methods such as ice-vests, cold water baths, and cold air exposure) affect exercise performance, it was concluded that lowering core Tb can increase duration of exercise and decrease physiological and psychophysical strain and fatigue (Marino, 2002). Thus, cooling can enhance exercise performance, but the exact method and body area cooled are relevant to the overall effect (Douzi et al., 2019).

Thermal states also appear to affect cognitive performance in humans. Some studies suggest that memory registration and speed of reasoning decline with decreased Tb. For example, volunteer core Tb was lowered by immersion in 15°C water, and subsequent cognitive function tests were conducted upon rewarming in 41°C water. Memory registration and speed of calculation performance were impaired at lower body temperatures, particularly at 34–35°C, but notably also impaired at even a moderately low Tb (i.e., 36.7°C). However, recall of learned information and calculation accuracy were not affected at these lower temperatures (Coleshaw and Van Someren, 1983). In support of this, working memory, subjective alertness, and visual attention are all improved when Tb is elevated by approximately 0.15°C, even when controlling for circadian increases and decreases in Tb (Wright et al., 2002).

Elevated Tb is not always associated with improved cognitive performance, and age may be a critical factor. In older adults, lower median Tb has been associated with better cognitive function (Eggenberger et al., 2021). Moreover, individuals with mild cognitive impairments showed higher temperatures compared to cognitively healthy participants. Thus, Tb measurements could serve as early indicators of cognitive decline. One limitation of this latter study is it did not control for circadian fluctuations in Tb, which naturally have a ~1°C peak-to-trough span. Because both Tb and performance could covary with circadian phase, forced desynchrony manipulations, which experimentally separate circadian and sleep-wake homeostatic influences on neuro-behavioral function, can help identify the specific effect of Tb (as opposed to circadian phase).

Finally, human affective states can be altered by clinical manipulations of Tb. Some studies show that increasing physical warmth promotes prosocial behavior, and these changes are associated with activation of particular brain regions, including serotonergic modules in the raphe, the striatum, and the cortex (Raison et al., 2015). As discussed in Section 5.1, whole body heating has shown potential effects on treating MDD through the serotonin system. For treatment of neuropsychiatric disorders, there is a strong will to move away from drug-based treatments that carry several side effects (Tiwari et al., 2012) or are ineffective due to the heterogeneous nature of the disorder

(Moreno-De-Luca and Martin, 2021). Thermal-based therapeutic approaches that focus on patient thermoregulatory state might serve as non-invasive alternatives. The identification of conserved circuits that coregulate affective state and thermosensation or thermoregulation can provide the foundation for future research into neuropsychiatric disorders and human performance enhancement.

7. Testing the functional relationship between body temperature and social and affective states

In this review, we have described neural circuits linking thermoregulation with social behavior and propose that adjustments to Tb could enhance aspects of social, sexual, and affective states. Here, we consider research strategies to address the notion that dedicated circuits alter thermal states to enhance social and affective states. We focus on three aspects of research relevant to rodent models and manipulation-based strategies. First, ambient temperature is a major consideration because laboratory room temperature is cold for rodents. Second, studies employing simultaneous analysis of behavior and Tb during neural manipulation and recording are needed. Third, we envision tests of the hypothesis that a change in Tb is required for the optimal expression of certain behaviors.

Controlling ambient temperature can provide valuable context to whether a certain behavior is thermally motivated. At room temperature, a considerable amount of energy is spent on cold-induced thermogenesis, and in social animals such as rodents, huddling serves as means to save energy under these conditions (Batchelder et al., 1983; Prychodko, 1958; Škop et al., 2021; Stanier, 1975). We suggest PVN^{OT} parvocellular neurons are a candidate population co-regulating Tb (*via* projections to the rMR, spinal cord, or BAT) and prosocial interactions (*via* projections to the nucleus accumbens). One possibility is that in the relatively cool ambient temperatures of the laboratory, activation of these neurons generates motor pathways that promote both heat production and close physical interaction, thereby leading to a rewarding experience that is encoded in the nucleus accumbens (Fig. 2D). Alternatively, activation of this pathway would be less rewarding at thermoneutral temperatures.

Although we identify approximately seven populations of neurons that control aspects of Tb and social behavior (Fig. 2 and Table 1), most of this information comes from different studies. Only two of these populations have been investigated simultaneously: the DP/DTT→DMH→rMR pathway and $vlVMH^{Cckar}$ neurons simultaneously activate thermal and social behavioral responses. Activation of DP/DTT→DMH neurons results in a hyperthermic Tb and a psychosocial stress response (Kataoka et al., 2020), while activation of $vlVMH^{Cckar}$ neurons induces a subtle (i.e., not hyperthermic) increase in Tb while enhancing sexual behavior (Yin et al., 2022). For the other neuronal populations discussed in this review, it would be beneficial to know how activation/inhibition of these neurons precisely relates to changes in behavior and Tb.

How can we test whether certain circuits adjust Tb to enhance social or affective behavioral states? One experimental approach would be to combine neural manipulations of central circuits while simultaneously manipulating thermogenic effectors in the periphery. In practice, establishing this link could be accomplished by manipulating well defined pathways covered in this review. For example, activation of the DT/DTT → DMH → rMR pathway results in activation of sympathetic premotor neurons that activate iBAT thermogenesis, and this state is associated with social avoidance (Kataoka et al., 2020). A crucial next step in this paradigm would be to test whether iBAT thermogenesis is necessary or sufficient for the expression of social avoidance. Fortunately, thermogenic activity in brown fat can be specially manipulated. β3-adrenoceptor stimulation is required for the intracellular cascade of events that leads to UCP1 activation and subsequent BAT thermogenesis. Thus, administering a β3-adrenoceptor blocker such as SR59230A (Lkhagvasuren et al., 2011) into BAT deposits would curtail the thermogenic response independent of neural innervation; alternatively, treatment with β3-adrenoceptor agonists would selectively activate BAT thermogenesis (Lowell and Flier, 1997). There are also molecular and genetic tool to access UCP1, including a UCP1-Cre line that, when crossed to a floxed interferon regulatory factor 4 (IRF4) line, specifically reduces BAT thermogenesis (Kong et al., 2014). Finally, several microRNAs (miRNAs) can enhance or suppress BAT thermogenesis. For example, miR-32 is a BAT-specific super-enhancer-associated miRNA, and local overexpression and inhibition lead to enhanced and suppressed BAT thermogenesis, respectively (Ng et al., 2017).

By titrating these pharmacological and molecular tools to achieve a level of BAT thermogenesis that is comparable to that observed during psychosocial stress, this approach could enable a test of the hypothesis that the social avoidance triggered by activation of the DT/DTT → DMH → rMR pathway is dependent upon the heat generated by BAT. This approach could be used to examine the requirement of thermogenesis in other circuits characterized in this review, which often result in activation of BAT (Fig. 2). Ultimately, this line of research could improve our circuit-level understanding of William James' Theory of Emotion, whereby bodily states play a direct role in regulating social and affective behavior.

Acknowledgements

We thank University of Wyoming Sensory Biology Center and members of the Nelson and Bedford laboratory for their input. This work is funded by NIH COBRE Grant 5P20GM121310–07.

References

Adamson, K., Gandy, G.M., James, L.S., 1965. The influence of thermal factors upon oxygen consumption of the newborn human infant. J. Pediatr. 66, 495–508. https://doi.org/10.1016/S0022-3476(65)80114-7.

Adriaan Bouwknecht, J., Olivier, B., Paylor, R.E., 2007. The stress-induced hyperthermia paradigm as a physiological animal model for anxiety: a review of pharmacological and genetic studies in the mouse. Neurosci. Biobehav. Rev. 31, 41–59. https://doi.org/10.1016/j.neubiorev.2006.02.002.

Alberts, J.R., 2007. Huddling by rat pups: ontogeny of individual and group behavior. Dev. Psychobiol. 49, 22–32. https://doi.org/10.1002/dev.20190.

Anderson, D.J., 2016. Circuit modules linking internal states and social behaviour in flies and mice. Nat. Rev. Neurosci. 17, 692–704. https://doi.org/10.1038/nrn.2016.125.

Angoa-Pérez, M., Kane, M.J., Sykes, C.E., Perrine, S.A., Church, M.W., Kuhn, D.M., 2014. Brain serotonin determines maternal behavior and offspring survival. Genes Brain Behav. 13, 579–591. https://doi.org/10.1111/gbb.12159.

Arakawa, H., Blanchard, D.C., Blanchard, R.J., 2015. Central oxytocin regulates social familiarity and scent marking behavior that involves amicable odor signals between male mice. Physiol. Behav., A Special Issue in honour of Robert Blanchard 146, 36–46. https://doi.org/10.1016/j.physbeh.2015.04.016.

Arbisi, P.A., Depue, R.A., Krauss, S., Spoont, M.R., Leon, A., Ainsworth, B., Muir, R., 1994. Heat-loss response to a thermal challenge in seasonal affective disorder. Psychiatry Res 52, 199–214. https://doi.org/10.1016/0165-1781(94)90088-4.

Arbisi, P.A., Depue, R.A., Spoont, M.R., Leon, A., Ainsworth, B., 1989. Thermoregulatory response to thermal challenge in seasonal affective disorder: a preliminary report. Psychiatry Res 28, 323–334. https://doi.org/10.1016/0165-1781(89)90213-8.

Aronov, D., Fee, M.S., 2012. Natural changes in brain temperature underlie variations in song tempo during a mating behavior. PLoS One 7, e47856. https://doi.org/10.1371/journal.pone.0047856.

Asakura, H., 2004. Fetal and neonatal thermoregulation. J. Nippon Med. Sch. 71, 360–370. https://doi.org/10.1272/jnms.71.360.

Avery, D.H., Wildschiødtz, G., Rafaelsen, O.J., 1982. Nocturnal temperature in affective disorder. J. Affect. Disord. 4, 61–71. https://doi.org/10.1016/0165-0327(82)90020-9.

Bamshad, M., Song, C.K., Bartness, T.J., 1999. CNS origins of the sympathetic nervous system outflow to brown adipose tissue. Am. J. Physiol. Regul. Integr. Comp. Physiol. 276, R1569–R1578. https://doi.org/10.1152/ajpregu.1999.276.6.R1569.

Barletti, L., Negulescu, C., 2018. Quantum transmission conditions for diffusive transport in graphene with steep potentials. J. Stat. Phys. 171, 696–726. https://doi.org/10.1007/s10955-018-2032-y.

Bartness, T.J., Vaughan, C.H., Song, C.K., 2010. Sympathetic and sensory innervation of brown adipose tissue. Int. J. Obes. 34, S36–S42. https://doi.org/10.1038/ijo.2010.182.

Batchelder, P., Kinney, R.O., Demlow, L., Lynch, C.B., 1983. Effects of temperature and social interactions on huddling behavior in Mus musculus. Physiol. Behav. 31, 97–102. https://doi.org/10.1016/0031-9384(83)90102-6.

Beig, M.I., Baumert, M., Walker, F.R., Day, T.A., Nalivaiko, E., 2009. Blockade of 5-HT2A receptors suppresses hyperthermic but not cardiovascular responses to psychosocial

stress in rats. Neuroscience 159, 1185–1191. https://doi.org/10.1016/j.neuroscience.2009.01.038.
Blumberg, M.S., Mennella, J.A., Moltz, H., 1987. Hypothalamic temperature and deep body temperature during copulation in the male rat. Physiol. Behav. 39, 367–370. https://doi.org/10.1016/0031-9384(87)90236-8.
Bralten, J., Mota, N.R., Klemann, C.J.H.M., De Witte, W., Laing, E., Collier, D.A., de Kluiver, H., Bauduin, S.E.E.C., Arango, C., Ayuso-Mateos, J.L., Fabbri, C., Kas, M.J., van der Wee, N., Penninx, B.W.J.H., Serretti, A., Franke, B., Poelmans, G., 2021. Genetic underpinnings of sociability in the general population. Neuropsychopharmacol. Publ. Am. Coll. Neuropsychopharmacol. 46, 1627–1634. https://doi.org/10.1038/s41386-021-01044-z.
Bryant, D.M., Hails, C.J., 1975. Mechanisms of heat conservation in the litters of mice (Mus musculus L.). Comp. Biochem. Physiol. A Physiol. 50, 99–104. https://doi.org/10.1016/S0010-406X(75)80208-8.
Bujnakova, I., Ondrejka, I., Mestanik, M., Visnovcova, Z., Mestanikova, A., Hrtanek, I., Fleskova, D., Calkovska, A., Tonhajzerova, I., 2016. Autism spectrum disorder is associated with autonomic underarousal. Physiol. Res. S673–S682. https://doi.org/10.33549/physiolres.933528.
Butler-Struben, H.M., Kentner, A.C., Trainor, B.C., 2022. What's wrong with my experiment?: the impact of hidden variables on neuropsychopharmacology research. Neuropsychopharmacology 47, 1285–1291. https://doi.org/10.1038/s41386-022-01309-1.
Canals, M., Rosenmann, M., Bozinovic, F., 1989. Energetics and geometry of huddling in small mammals. J. Theor. Biol. 141, 181–189. https://doi.org/10.1016/S0022-5193(89)80016-5.
Cannon, B., Nedergaard, J., 2004. Brown adipose tissue: function and physiological significance. Physiol. Rev. 84, 277–359. https://doi.org/10.1152/physrev.00015.2003.
Charkoudian, N., 2010. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. J. Appl. Physiol. 109, 1221–1228. https://doi.org/10.1152/japplphysiol.00298.2010.
Chen, P., Hong, W., 2018. Neural circuit mechanisms of social behavior. Neuron 98, 16–30. https://doi.org/10.1016/j.neuron.2018.02.026.
Chini, B., Verhage, M., Grinevich, V., 2017. The action radius of oxytocin release in the mammalian CNS: from single vesicles to behavior. Trends Pharmacol. Sci. 38, 982–991. https://doi.org/10.1016/j.tips.2017.08.005.
Choi, G.B., Yim, Y.S., Wong, H., Kim, S., Kim, H., Kim, S.V., Hoeffer, C.A., Littman, D.R., Huh, J.R., 2016. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 351, 933–939. https://doi.org/10.1126/science.aad0314.
Chong, T.W.H., Castle, D.J., 2004. Layer upon layer: thermoregulation in schizophrenia. Schizophr. Res. 69, 149–157. https://doi.org/10.1016/S0920-9964(03)00222-6.
Coleshaw, S.R., Van Someren, N., 1983. Impaired memory registration and speed of reasoning caused by low body temperature. J. Appl. Physiol. 55, 27–31. https://doi.org/10.1152/jappl.1983.55.1.27.
Conceição, E.P.S., Madden, C.J., Morrison, S.F., 2019. Neurons in the rat ventral lateral preoptic area are essential for the warm-evoked inhibition of brown adipose tissue and shivering thermogenesis. Acta Physiol. 225, e13213 https://doi.org/10.1111/apha.13213.
Conceição Furber, E.P.S., Mota, C.M.D., Veytsman, E., Morrison, S.F., Madden, C.J., 2021. Dopaminergic input from the posterior hypothalamus to the raphe pallidus area inhibits brown adipose tissue thermogenesis. Am. J. Physiol. Regul. Integr. Comp. Physiol. 321, R938–R950. https://doi.org/10.1152/ajpregu.00149.2021.
Crowcroft, P., 1967. Mice all over. J. Mammal. 48, 500–502. https://doi.org/10.2307/1377806.
Curran, L.K., Newschaffer, C.J., Lee, L.-C., Crawford, S.O., Johnston, M.V., Zimmerman, A.W., 2007. Behaviors associated with fever in children with autism spectrum disorders. Pediatrics 120, e1386–e1392. https://doi.org/10.1542/peds.2007-0360.
Da Cunha-Bang, S., Knudsen, G.M., 2021. The modulatory role of serotonin on human impulsive aggression. Biol. Psychiatry 90, 447–457. https://doi.org/10.1016/j.biopsych.2021.05.016.
Denommé, M.R., Mason, G.J., 2022. Social buffering as a tool for Improving Rodent Welfare. J. Am. Assoc. Lab. Anim. Sci. 61, 5–14. https://doi.org/10.30802/AALAS-JAALAS-21-000006.
Dölen, G., Darvishzadeh, A., Huang, K.W., Malenka, R.C., 2013. Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. Nature 501, 179–184. https://doi.org/10.1038/nature12518.
Douzi, W., Dugué, B., Vinches, L., Al Sayed, C., Hallé, S., Bosquet, L., Dupuy, O., 2019. Cooling during exercise enhances performances, but the cooled body areas matter: a systematic review with meta-analyses. Scand. J. Med. Sci. Sports 29, 1660–1676. https://doi.org/10.1111/sms.13521.
Drummond, P.D., 1997. The effect of adrenergic blockade on blushing and facial flushing. Psychophysiology 34, 163–168. https://doi.org/10.1111/j.1469-8986.1997.tb02127.x.
Drummond, P.D., 1999. Facial flushing during provocation in women. Psychophysiology 36, 325–332. https://doi.org/10.1017/S0048577299980344.
Drummond, P.D., Finch, P.M., 1989. Reflex control of facial flushing during body heating in man. Brain 112, 1351–1358. https://doi.org/10.1093/brain/112.5.1351.
Drummond, P.D., Lance, J.W., 1987. Facial flushing and sweating mediated by the sympathetic nervous system. Brain 110, 793–803. https://doi.org/10.1093/brain/110.3.793.
Drummond, P.D., Shapiro, G.B., Nikolić, M., Bögels, S.M., 2020. Treatment options for fear of blushing. Curr. Psychiatry Rep. 22, 28. https://doi.org/10.1007/s11920-020-01152-5.
Ebisch, S.J.H., Gallese, V., Willems, R.M., Mantini, D., Groen, W.B., Romani, G.L., Buitelaar, J.K., Bekkering, H., 2011. Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. Hum. Brain Mapp. 32, 1013–1028. https://doi.org/10.1002/hbm.21085.
Eggenberger, P., Bürgisser, M., Rossi, R.M., Annaheim, S., 2021. Body temperature is associated with cognitive performance in older adults with and without mild cognitive impairment: a cross-sectional analysis. Front. Aging Neurosci. 13, 585904 https://doi.org/10.3389/fnagi.2021.585904.
Emont, M.P., Jacobs, C., Essene, A.L., Pant, D., Tenen, D., Colleluori, G., Di Vincenzo, A., Jørgensen, A.M., Dashti, H., Stefek, A., McGonagle, E., Strobel, S., Laber, S., Agrawal, S., Westcott, G.P., Kar, A., Veregge, M.L., Gulko, A., Srinivasan, H., Kramer, Z., De Filippis, E., Merkel, E., Ducie, J., Boyd, C.G., Gourash, W., Courcoulas, A., Lin, S.J., Lee, B.T., Morris, D., Tobias, A., Khera, A.V., Claussnitzer, M., Pers, T.H., Giordano, A., Ashenberg, O., Regev, A., Tsai, L.T., Rosen, E.D., 2022. A single-cell atlas of human and mouse white adipose tissue. Nature 603, 926–933. https://doi.org/10.1038/s41586-022-04518-2.
Endo, N., Ujita, W., Fujiwara, M., Miyauchi, H., Mishima, H., Makino, Y., Hashimoto, L., Oyama, H., Makinodan, M., Nishi, M., Tohyama, C., Kakeyama, M., 2018. Multiple animal positioning system shows that socially-reared mice influence the social proximity of isolation-reared cagemates. Commun. Biol. 1, 225. https://doi.org/10.1038/s42003-018-0213-5.
Feng, C., Wang, Y., Zha, X., Cao, H., Huang, S., Cao, D., Zhang, K., Xie, T., Xu, X., Liang, Z., Zhang, Z., 2022. Cold-sensitive ventromedial hypothalamic neurons control homeostatic thermogenesis and social interaction-associated hyperthermia. Cell Metab. 34, 888–901.e5. https://doi.org/10.1016/j.cmet.2022.05.002.
Fortin, D., Gauthier, G., Larochelle, J., 2000. Body temperature and resting behavior of greater snow goose goslings in the high arctic. Condor 102, 163–171. https://doi.org/10.1093/condor/102.1.163.
Fransson, A.-L., Karlsson, H., Nilsson, K., 2005. Temperature variation in newborn babies: importance of physical contact with the mother. Arch. Dis. Child. Fetal Neonatal Ed. 90, F500–F504. https://doi.org/10.1136/adc.2004.066589.
Frith, C., 2000. Explaining the symptoms of schizophrenia: abnormalities in the awareness of action. Brain Res. Rev. 31, 357–363. https://doi.org/10.1016/S0165-0173(99)00052-1.
Froemke, R.C., Young, L.J., 2021. Oxytocin, neural plasticity, and social behavior. Annu. Rev. Neurosci. 44, 359–381. https://doi.org/10.1146/annurev-neuro-102320-102847.
Fukumitsu, K., Kaneko, M., Maruyama, T., Yoshihara, C., Huang, A.J., McHugh, T.J., Itohara, S., Tanaka, M., Kuroda, K.O., 2022. Amylin-Calcitonin receptor signaling in the medial preoptic area mediates affiliative social behaviors in female mice. Nat. Commun. 13, 709. https://doi.org/10.1038/s41467-022-28131-z.
Fukushima, A., Kataoka, N., Nakamura, K., 2022. An oxytocinergic neural pathway that stimulates thermogenic and cardiac sympathetic outflow. Cell Rep. 40, 111380 https://doi.org/10.1016/j.celrep.2022.111380.
Geyer, M.A., Wilkinson, L.S., Humby, T., Robbins, T.W., 1993. Isolation rearing of rats produces a deficit in prepulse inhibition of acoustic startle similar to that in schizophrenia. Biol. Psychiatry 34, 361–372. https://doi.org/10.1016/0006-3223(93)90180-L.
Gilbert, C., Blanc, S., Giroud, S., Trabalon, M., Maho, Y.L., Perret, M., Ancel, A., 2007a. Role of huddling on the energetic of growth in a newborn altricial mammal. Am. J. Physiol. -Regul. Integr. Comp. Physiol. 293, R867–R876. https://doi.org/10.1152/ajpregu.00081.2007.
Gilbert, C., Maho, Y.L., Perret, M., Ancel, A., 2007b. Body temperature changes induced by huddling in breeding male emperor penguins. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R176–R185. https://doi.org/10.1152/ajpregu.00912.2005.
Gilbert, C., McCafferty, D., Le Maho, Y., Martrette, J.-M., Giroud, S., Blanc, S., Ancel, A., 2010. One for all and all for one: the energetic benefits of huddling in endotherms. Biol. Rev. 85, 545–569. https://doi.org/10.1111/j.1469-185X.2009.00115.x.
Gordon, C.J., 1993. Temperature Regulation in Laboratory Rodents. Camb. Camb. Univ. Press. https://doi.org/10.1017/CBO9780511565595.
Gordon, C.J., 2012. Thermal physiology of laboratory mice: defining thermoneutrality. J. Therm. Biol. 37, 654–685. https://doi.org/10.1016/j.jtherbio.2012.08.004.
Gordon, C.J., Becker, P., Ali, J.S., 1998. Behavioral thermoregulatory responses of single- and group-housed mice. Physiol. Behav. 65, 255–262. https://doi.org/10.1016/S0031-9384(98)00148-6.
Grahn, D.A., Cao, V.H., Heller, H.C., 2005. Heat extraction through the palm of one hand improves aerobic exercise endurance in a hot environment. J. Appl. Physiol. 99, 972–978. https://doi.org/10.1152/japplphysiol.00093.2005.
Grieb, Z.A., Ford, E.G., Yagan, M., Lau, B.Y.B., Manfredsson, F.P., Krishnan, K., Lonstein, J.S., 2021. Oxytocin receptors in the midbrain dorsal raphe are essential for postpartum maternal social and affective behaviors. Psychoneuroendocrinology 131, 105332. https://doi.org/10.1016/j.psyneuen.2021.105332.
Grinevich, V., Ludwig, M., 2021. The multiple faces of the oxytocin and vasopressin systems in the brain. J. Neuroendocrinol. 33, e13004 https://doi.org/10.1111/jne.13004.
Grippo, A.J., Trahanas, D.M., Zimmerman, R.R., Porges, S.W., Carter, C.S., 2009. Oxytocin protects against negative behavioral and autonomic consequences of long-term social isolation. Psychoneuroendocrinology 34, 1542–1553. https://doi.org/10.1016/j.psyneuen.2009.05.017.
Grzadzinski, R., Lord, C., Sanders, S.J., Werling, D., Bal, V.H., 2018. Children with autism spectrum disorder who improve with fever: Insights from the Simons Simplex Collection. Autism Res 11, 175–184. https://doi.org/10.1002/aur.1856.
Gurrera, R.J., Chang, S.S., 1996. Thermoregulatory dysfunction in neuroleptic malignant syndrome. Biol. Psychiatry 39, 207–212. https://doi.org/10.1016/0006-3223(95)00137-9.

Gutiérrez-Rojas, L., Porras-Segovia, A., Dunne, H., Andrade-González, N., Cervilla, J.A., 2020. Prevalence and correlates of major depressive disorder: a systematic review. Braz. J. Psychiatry 42, 657–672. https://doi.org/10.1590/1516-4446-2020-0650.
Häbler, H.-J., Bartsch, T., Jänig, W., 1999. Rhythmicity in single fiber postganglionic activity supplying the rat tail. J. Neurophysiol. 81, 2026–2036. https://doi.org/10.1152/jn.1999.81.5.2026.
Hadi, R., Block, L., 2019. Warm hearts and cool heads: uncomfortable temperature influences reliance on affect in decision-making. J. Assoc. Consum. Res. 4, 102–114. https://doi.org/10.1086/701820.
Haig, D., 2008. Huddling: brown fat, genomic imprinting and the warm inner glow. Curr. Biol. 18, R172–R174. https://doi.org/10.1016/j.cub.2007.12.040.
Hale, M.W., Dady, K.F., Evans, A.K., Lowry, C.A., 2011. Evidence for in vivo thermosensitivity of serotonergic neurons in the rat dorsal raphe nucleus and raphe pallidus nucleus implicated in thermoregulatory cooling. Exp. Neurol. 227, 264–278. https://doi.org/10.1016/j.expneurol.2010.11.012.
Hale, M.W., Lukkes, J.L., Dady, K.F., Kelly, K.J., Paul, E.D., Smith, D.G., Raison, C.L., Lowry, C.A., 2017. Whole-body hyperthermia and a subthreshold dose of citalopram act synergistically to induce antidepressant-like behavioral responses in adolescent rats. Prog. Neuropsychopharmacol. Biol. Psychiatry 79, 162–168. https://doi.org/10.1016/j.pnpbp.2017.06.006.
Hale, M.W., Lukkes, J.L., Dady, K.F., Kelly, K.J., Paul, E.D., Smith, D.G., Heinze, J.D., Raison, C.L., Lowry, C.A., 2019. Interactions between whole-body heating and citalopram on body temperature, antidepressant-like behaviour, and neurochemistry in adolescent male rats. Behav. Brain Res. 359, 428–439. https://doi.org/10.1016/j.bbr.2018.11.029.
Hallbeck, M., Larhammar, D., Blomqvist, A., 2001. Neuropeptide expression in rat paraventricular hypothalamic neurons that project to the spinal cord. J. Comp. Neurol. 433, 222–238. https://doi.org/10.1002/cne.1137.
Hanusch, K.-U., Janssen, C.W., 2019. The impact of whole-body hyperthermia interventions on mood and depression – are we ready for recommendations for clinical application? Int. J. Hyperth. 36, 572–580. https://doi.org/10.1080/02656736.2019.1612103.
Hanusch, K.-U., Janssen, C.H., Billheimer, D., Jenkins, I., Spurgeon, E., Lowry, C.A., Raison, C.L., 2013. Whole-Body Hyperthermia for the Treatment of Major Depression: associations With Thermoregulatory Cooling. Am. J. Psychiatry 170, 802–804. https://doi.org/10.1176/appi.ajp.2013.12111395.
Harden, L.M., Kent, S., Pittman, Q.J., Roth, J., 2015. Fever and sickness behavior: friend or foe? Brain. Behav. Immun. 50, 322–333. https://doi.org/10.1016/j.bbi.2015.07.012.
Harding, E.C., Franks, N.P., Wisden, W., 2020. Sleep and thermoregulation. Curr. Opin. Physiol. 15, 7–13. https://doi.org/10.1016/j.cophys.2019.11.008.
Harding, E.C., Yu, X., Miao, A., Andrews, N., Ma, Y., Ye, Z., Lignos, L., Miracca, G., Ba, W., Yustos, R., Vyssotski, A.L., Wisden, W., Franks, N.P., 2018. A neuronal hub binding sleep initiation and body cooling in response to a warm external stimulus. Curr. Biol. 28, 2263–2273.e4. https://doi.org/10.1016/j.cub.2018.05.054.
Harshaw, C., Alberts, J.R., 2012. Group and individual regulation of physiology and behavior: a behavioral, thermographic, and acoustic study of mouse development. Physiol. Behav. 106, 670–682. https://doi.org/10.1016/j.physbeh.2012.05.002.
Harshaw, C., Blumberg, M.S., Alberts, J.R., 2017. Thermoregulation, Energetics, and Behavior, in: APA Handbook of Comparative Psychology; Basic Concepts, Methods, Neural Substrate, and Behavior. American Psychological Association, Washington DC, pp. 931–952.
Harshaw, C., Culligan, J.J., Alberts, J.R., 2014. Sex differences in thermogenesis structure behavior and contact within huddles of infant mice. PLoS One 9, e87405. https://doi.org/10.1371/journal.pone.0087405.
Harshaw, C., Lanzkowsky, J., Tran, A.-Q.D., Bradley, A.R., Jaime, M., 2021. Oxytocin and 'social hyperthermia': interaction with β3-adrenergic receptor-mediated thermogenesis and significance for the expression of social behavior in male and female mice. Horm. Behav. 131, 104981 https://doi.org/10.1016/j.yhbeh.2021.104981.
Harshaw, C., Leffel, J.K., Alberts, J.R., 2018. Oxytocin and the warm outer glow: thermoregulatory deficits cause huddling abnormalities in oxytocin-deficient mouse pups. Horm. Behav. 98, 145–158. https://doi.org/10.1016/j.yhbeh.2017.12.007.
Hashikawa, K., Hashikawa, Y., Lischinsky, J., Lin, D., 2018. The neural mechanisms of sexually dimorphic aggressive behaviors. Trends Genet 34, 755–776. https://doi.org/10.1016/j.tig.2018.07.001.
Hayward, J.S., Eckerson, J.D., Collis, M.L., 1975. Effect of behavioral variables on cooling rate of man in cold water. J. Appl. Physiol. 38, 1073–1077. https://doi.org/10.1152/jappl.1975.38.6.1073.
Heinonen, I., Brothers, R.M., Kemppainen, J., Knuuti, J., Kalliokoski, K.K., Crandall, C.G., 2011. Local heating, but not indirect whole body heating, increases human skeletal muscle blood flow. J. Appl. Physiol. 111, 818–824. https://doi.org/10.1152/japplphysiol.00269.2011.
Hennessy, M.B., Deak, T., Schiml, P.A., 2014. Sociality and sickness: Have cytokines evolved to serve social functions beyond times of pathogen exposure? Brain. Behav. Immun. 37, 15–20. https://doi.org/10.1016/j.bbi.2013.10.021.
Hodges, H., Fealko, C., Soares, N., 2020. Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. Transl. Pediatr. 9, S55–S65. https://doi.org/10.21037/tp.2019.09.09.
Horvath, G., Kekesi, G., Petrovszki, Z., Benedek, G., 2015. Abnormal motor activity and thermoregulation in a Schizophrenia rat model for translational science. PLoS One 10, e0143751. https://doi.org/10.1371/journal.pone.0143751.
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., Crow, A., Yoo, A.-C.W., Raja, C., Evans, K., Bernstein, D., Zeineh, M., Goubran, M., Deisseroth, K., 2023. Cardiogenic control of affective behavioural state. Nature 615, 292–299. https://doi.org/10.1038/s41586-023-05748-8.
Hudson, R., Distel, H., 1982. The pattern of behaviour of rabbit pups in the nest. Behaviour 79, 255–271. https://doi.org/10.1163/156853982×00292.
Hung, L.W., Neuner, S., Polepalli, J.S., Beier, K.T., Wright, M., Walsh, J.J., Lewis, E.M., Luo, L., Deisseroth, K., Dölen, G., Malenka, R.C., 2017. Gating of social reward by oxytocin in the ventral tegmental area. Science 357, 1406–1411. https://doi.org/10.1126/science.aan4994.
Hunstiger, M., Johannsen, M.M., Oliver, S.R., 2023. Non-shivering thermogenesis is differentially regulated during the hibernation season in Arctic ground squirrels. Front. Physiol. 14, 1207529 https://doi.org/10.3389/fphys.2023.1207529.
Ike, K.G.O., Lamers, S.J.C., Kaim, S., De Boer, S.F., Buwalda, B., Billeter, J.-C., Kas, M.J. H., 2023. The human neuropsychiatric risk gene Drd2 is necessary for social functioning across evolutionary distant species. Mol. Psychiatry. https://doi.org/10.1038/s41380-023-02345-z.
Ilanges, A., Shiao, R., Shaked, J., Luo, J.-D., Yu, X., Friedman, J.M., 2022. Brainstem ADCYAP1+ neurons control multiple aspects of sickness behaviour. Nature 609, 761–771. https://doi.org/10.1038/s41586-022-05161-7.
James, W., 1884. What is emotion? 1884.. In: Readings in the History of Psychology., Century Psychology Series. Appleton-Century-Crofts, East Norwalk, CT, US, pp. 290–303. https://doi.org/10.1037/11304-033.
James, R.S., 2013. A review of the thermal sensitivity of the mechanics of vertebrate skeletal muscle. J. Comp. Physiol. B 183, 723–733. https://doi.org/10.1007/s00360-013-0748-1.
Janssen, C.W., Lowry, C.A., Mehl, M.R., Allen, J.J.B., Kelly, K.L., Gartner, D.E., Medrano, A., Begay, T.K., Rentscher, K., White, J.J., Fridman, A., Roberts, L.J., Robbins, M.L., Hanusch, K., Cole, S.P., Raison, C.L., 2016. Whole-body hyperthermia for the treatment of major depressive disorder: a randomized clinical trial. JAMA Psychiatry 73, 789. https://doi.org/10.1001/jamapsychiatry.2016.1031.
Jiang, Z., Rompala, G.R., Zhang, S., Cowell, R.M., Nakazawa, K., 2013. Social isolation exacerbates schizophrenia-like phenotypes via oxidative stress in cortical interneurons. Biol. Psychiatry 73, 1024–1034. https://doi.org/10.1016/j.biopsych.2012.12.004.
Jung, S., Lee, M., Kim, D.-Y., Son, C., Ahn, B.H., Heo, G., Park, J., Kim, M., Park, H.-E., Koo, D.-J., Park, J.H., Lee, J.W., Choe, H.K., Kim, S.-Y., 2022. A forebrain neural substrate for behavioral thermoregulation. Neuron 110, 266–279.e9. https://doi.org/10.1016/j.neuron.2021.09.039.
Kappel, S., Hawkins, P., Mendl, M., 2017. To group or not to group? Good practice for housing male laboratory mice. Animals 7, 88. https://doi.org/10.3390/ani7120088.
Kasahara, Y., Sato, K., Takayanagi, Y., Mizukami, H., Ozawa, K., Hidema, S., So, K.-H., Kawada, T., Inoue, N., Ikeda, I., Roh, S.-G., Itoi, K., Nishimori, K., 2013. Oxytocin receptor in the hypothalamus is sufficient to rescue normal thermoregulatory function in male oxytocin receptor knockout mice. Endocrinology 154, 4305–4315. https://doi.org/10.1210/en.2012-2206.
Kataoka, N., Hioki, H., Kaneko, T., Nakamura, K., 2014. Psychological stress activates a dorsomedial hypothalamus-medullary raphe circuit driving brown adipose tissue thermogenesis and hyperthermia. Cell Metab. 20, 346–358. https://doi.org/10.1016/j.cmet.2014.05.018.
Kataoka, N., Shima, Y., Nakajima, K., Nakamura, K., 2020. A central master driver of psychosocial stress responses in the rat. Science 367, 1105–1112. https://doi.org/10.1126/science.aaz4639.
Kavaliers, M., Ossenkopp, K.-P., Tyson, C.-D., Bishnoi, I.R., Choleris, E., 2022. Social factors and the neurobiology of pathogen avoidance. Biol. Lett. 18, 20210371 https://doi.org/10.1098/rsbl.2021.0371.
Keeney, A.J., Hogg, S., Marsden, C.A., 2001. Alterations in core body temperature, locomotor activity, and corticosterone following acute and repeated social defeat of male NMRI mice. Physiol. Behav. 74, 177–184. https://doi.org/10.1016/S0031-9384(01)00541-8.
Keeney, A.J., Hogg, S., 1999. Behavioural consequences of repeated social defeat in the mouse: preliminary evaluation of a potential animal model of depression. Behav. Pharmacol. 10, 753–764. https://doi.org/10.1097/00008877-199912000-00007.
Kikusui, T., Winslow, J.T., Mori, Y., 2006. Social buffering: relief from stress and anxiety. Philos. Trans. R. Soc. B Biol. Sci. 361, 2215–2228. https://doi.org/10.1098/rstb.2006.1941.
Kingma, B., Frijns, A., van Marken Lichtenbelt, W., 2012. The thermoneutral zone: implications for metabolic studies. Front. Biosci. https://doi.org/10.2741/e518.
Kingma, B.R., Frijns, A.J., Schellen, L., Van Marken Lichtenbelt, W.D., 2014. Beyond the classic thermoneutral zone: Including thermal comfort. Temperature 1, 142–149. https://doi.org/10.4161/temp.29702.
Klein, A.S., Dolensek, N., Weiand, C., Gogolla, N., 2021. Fear balance is maintained by bodily feedback to the insular cortex in mice. Science 374, 1010–1015. https://doi.org/10.1126/science.abj8817.
Kleitman, N., 1963. Sleep and wakefulness. Sleep and wakefulness. Univ. Chicago Press, Oxford, England.
Kohl, J., Babayan, B.M., Rubinstein, N.D., Autry, A.E., Marin-Rodriguez, B., Kapoor, V., Miyamishi, K., Zweifel, L.S., Luo, L., Uchida, N., Dulac, C., 2018. Functional circuit architecture underlying parental behaviour. Nature 556, 326–331. https://doi.org/10.1038/s41586-018-0027-0.
Koltyn, K.F., Robins, H.I., Schmitt, C.L., Cohen, J.D., Morgan, W.P., 1992. Changes in mood state following whole-body hyperthermia. Int. J. Hyperth. 8, 305–307. https://doi.org/10.3109/02656739209021785.
Kong, X., Banks, A., Liu, T., Kazak, L., Rao, R.R., Cohen, P., Wang, X., Yu, S., Lo, J.C., Tseng, Y.-H., Cypess, A.M., Xue, R., Kleiner, S., Kang, S., Spiegelman, B.M., Rosen, E. D., 2014. IRF4 is a key thermogenic transcriptional partner of PGC-1α. Cell 158, 69–83. https://doi.org/10.1016/j.cell.2014.04.049.

Krishnan, V., Han, M.-H., Graham, D.L., Berton, O., Renthal, W., Russo, S.J., LaPlant, Q., Graham, A., Lutter, M., Lagace, D.C., Ghose, S., Reister, R., Tannous, P., Green, T.A., Neve, R.L., Chakravarty, S., Kumar, A., Eisch, A.J., Self, D.W., Lee, F.S., Tamminga, C.A., Cooper, D.C., Gershenfeld, H.K., Nestler, E.J., 2007. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell 131, 391–404. https://doi.org/10.1016/j.cell.2007.09.018.

Kroeger, D., Absi, G., Gagliardi, C., Bandaru, S.S., Madara, J.C., Ferrari, L.L., Arrigoni, E., Münzberg, H., Scammell, T.E., Saper, C.B., Vetrivelan, R., 2018. Galanin neurons in the ventrolateral preoptic area promote sleep and heat loss in mice. Nat. Commun. 9, 4129. https://doi.org/10.1038/s41467-018-06590-7.

Kukreti, R., Tripathi, S., Bhatnagar, P., Gupta, S., Chauhan, C., Kubendran, S., Janardhan Reddy, Y.C., Jain, S., Brahmachari, S.K., 2006. Association of DRD2 gene variant with schizophrenia. Neurosci. Lett. 392, 68–71. https://doi.org/10.1016/j.neulet.2005.08.059.

L.Brown, G., 1982. Aggression, suicide, and serotonin: relationship to CSF amine metabolites. Am. J. Psychiatry 139, 741–746.

L.Brown, G., K.Goodwin, F., C.Ballenger, J., F.Goyer, P., F.Major, L., 1979. Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Res 1, 131–139.

Lee, C.R., Chen, A., Tye, K.M., 2021. The neural circuitry of social homeostasis: consequences of acute versus chronic social isolation. Cell 184, 1500–1516. https://doi.org/10.1016/j.cell.2021.02.028.

Lerch-Haner, J.K., Frierson, D., Crawford, L.K., Beck, S.G., Deneris, E.S., 2008. Serotonergic transcriptional programming determines maternal behavior and offspring survival. Nat. Neurosci. 11, 1001–1003. https://doi.org/10.1038/nn.2176.

Lewis, E.M., Stein-O'Brien, G.L., Patino, A.V., Nardou, R., Grossman, C.D., Brown, M., Bangamwabo, B., Ndiaye, N., Giovinazzo, D., Dardani, I., Jiang, C., Goff, L.A., Dölen, G., 2020. Parallel social information processing circuits are differentially impacted in autism. Neuron 108, 659–675.e6. https://doi.org/10.1016/j.neuron.2020.10.002.

Lindenfors, P., S.Tullberg, B., 2011. Evolutionary Aspects of Aggression. in: Advances in Genetics. Elsevier, pp. 7–22. https://doi.org/10.1016/B978-0-12-380858-5.00009-5.

Liu, M., Kim, D.-W., Zeng, H., Anderson, D.J., 2022. Make war not love: the neural substrate underlying a state-dependent switch in female social behavior. Neuron 110, 841–856.e6. https://doi.org/10.1016/j.neuron.2021.12.002.

Lkhagvasuren, B., Nakamura, Y., Oka, T., Sudo, N., Nakamura, K., 2011. Social defeat stress induces hyperthermia through activation of thermoregulatory sympathetic premotor neurons in the medullary raphe region. Eur. J. Neurosci. 34, 1442–1452. https://doi.org/10.1111/j.1460-9568.2011.07863.x.

Long, M.A., Fee, M.S., 2008. Using temperature to analyse temporal dynamics in the songbird motor pathway. Nature 456, 189–194. https://doi.org/10.1038/nature07448.

Lonstein, J.S., Gammie, S.C., 2002. Sensory, hormonal, and neural control of maternal aggression in laboratory rodents. Neurosci. Biobehav. Rev. 26, 869–888. https://doi.org/10.1016/S0149-7634(02)00087-8.

Lopes, P.C., Block, P., König, B., 2016. Infection-induced behavioural changes reduce connectivity and the potential for disease spread in wild mice contact networks. Sci. Rep. 6, 31790 https://doi.org/10.1038/srep31790.

Lowell, B.B., Flier, J.S., 1997. Brown adipose tissue, β3-adrenenergic receptors, and obesity. Annu. Rev. Med. 307–316. https://doi.org/10.1146/annurev.med.48.1.307.

Lowry, C., Flux, M., Raison, C., 2018. Whole-body heating: an emerging therapeutic approach to treatment of major depressive disorder. FOCUS 16, 259–265. https://doi.org/10.1176/appi.focus.20180009.

Lowry, C.A., Hollis, J.H., De Vries, A., Pan, B., Brunet, L.R., Hunt, J.R.F., Paton, J.F.R., Van Kampen, E., Knight, D.M., Evans, A.K., Rook, G.A.W., Lightman, S.L., 2007. Identification of an immune-responsive mesolimbocortical serotonergic system: potential role in regulation of emotional behavior. Neuroscience 146, 756–772. https://doi.org/10.1016/j.neuroscience.2007.01.067.

Ma, Y., Miracca, G., Yu, X., Harding, E.C., Miao, A., Yustos, R., Vyssotski, A.L., Franks, N. P., Wisden, W., 2019. Galanin neurons unite sleep homeostasis and α2-adrenergic sedation. Curr. Biol. 29, 3315–3322.e3. https://doi.org/10.1016/j.cub.2019.07.087.

Machado, N.L.S., Abbott, S.B.G., Resch, J.M., Zhu, L., Arrigoni, E., Lowell, B.B., Fuller, P. M., Fontes, M.A.P., Saper, C.B., 2018. A glutamatergic hypothalamomedullary circuit mediates thermogenesis, but not heat conservation, during stress-induced hyperthermia. Curr. Biol. 28, 2291–2301.e5. https://doi.org/10.1016/j.cub.2018.05.064.

Madden, C.J., Morrison, S.F., 2008. Brown adipose tissue sympathetic nerve activity is potentiated by activation of 5-hydroxytryptamine (5-HT)1A/5-HT7 receptors in the rat spinal cord. Neuropharmacology 54, 487–496. https://doi.org/10.1016/j.neuropharm.2007.10.019.

Marino, F.E., 2002. Methods, advantages, and limitations of body cooling for exercise performance. Br. J. Sports Med. 36, 89–94. https://doi.org/10.1136/bjsm.36.2.89.

Martin, R.A., Fiorentini, M., Connors, F., 1980. Social facilitation of reduced oxygen consumption in Mus musculus and Meriones unguiculatus. Comp. Biochem. Physiol. A Physiol. 65, 519–522. https://doi.org/10.1016/0300-9629(80)90072-9.

Martín-Sánchez, A., McLean, L., Beynon, R.J., Hurst, J.L., Ayala, G., Lanuza, E., Martínez-Garcia, F., 2015. From sexual attraction to maternal aggression: when pheromones change their behavioural significance. Horm. Behav. 68, 65–76. https://doi.org/10.1016/j.yhbeh.2014.08.007.

Mason, A.E., Kasl, P., Soltani, S., Green, A., Hartogensis, W., Dilchert, S., Chowdhary, A., Pandya, L.S., Siwik, C.J., Foster, S.L., Nyer, M., Lowry, C.A., Raison, C.L., Hecht, F. M., Smarr, B.L., 2024. Elevated body temperature is associated with depressive symptoms: results from the TemPredict Study. Sci. Rep. 14, 1884. https://doi.org/10.1038/s41598-024-51567-w.

Maswood, N., Cosmi, S., Alfinito, PeterD., Deecher, DarleneC., 2006. The role of the selective serotonin reuptake inhibitor fluoxetine in temperature regulation in ovariectomized rat models. Neuroendocrinology 84, 330–338.

Mathis, V., Kenny, P.J., 2018. Neuroscience: brain mechanisms of blushing. Curr. Biol. 28, R791–R792. https://doi.org/10.1016/j.cub.2018.06.047.

Matsumura, K., Cao, C., Ozaki, M., Morii, H., Nakadate, K., Watanabe, Y., 1998. Brain endothelial cells express cyclooxygenase-2 during lipopolysaccharide-induced fever: light and electron microscopic immunocytochemical studies. J. Neurosci. 18, 6279–6289. https://doi.org/10.1523/JNEUROSCI.18-16-06279.1998.

Matthews, G.A., Nieh, E.H., Vander Weele, C.M., Halbert, S.A., Pradhan, R.V., Yosafat, A. S., Glober, G.F., Izadmehr, E.M., Thomas, R.E., Lacy, G.D., Wildes, C.P., Ungless, M. A., Tye, K.M., 2016. Dorsal Raphe dopamine neurons represent the experience of social isolation. Cell 164, 617–631. https://doi.org/10.1016/j.cell.2015.12.040.

Matthews, G.A., Tye, K.M., 2019. Neural mechanisms of social homeostasis. Ann. N. Y. Acad. Sci. 1457, 5–25. https://doi.org/10.1111/nyas.14016.

McCutcheon, R., Beck, K., Jauhar, S., Howes, O.D., 2018. Defining the locus of dopaminergic dysfunction in Schizophrenia: a meta-analysis and test of the mesolimbic hypothesis. Schizophr. Bull. 44, 1301–1311. https://doi.org/10.1093/schbul/sbx180.

Meyer, C.W., Ootsuka, Y., Romanovsky, A.A., 2017. Body temperature measurements for metabolic phenotyping in mice. Front. Physiol. 8.

Mitchell, J.C., Flynn, F.W., Evey, L.A., 1981. Heat-induced saliva secretion and thermoregulation in female rats with ventromedial hypothalamic lesions I. Physiol. Behav. 26, 779–782.

Moffitt, J.R., Bambah-Mukku, D., Eichhorn, S.W., Vaughn, E., Shekhar, K., Perez, J.D., Rubinstein, N.D., Hao, J., Regev, A., Dulac, C., Zhuang, X., 2018. Molecular, spatial, and functional single-cell profiling of the hypothalamic preoptic region. Science 362, eaau5324. https://doi.org/10.1126/science.aau5324.

Moreno-De-Luca, D., Martin, C.L., 2021. All for one and one for all: heterogeneity of genetic etiologies in neurodevelopmental psychiatric disorders. Curr. Opin. Genet. Dev. 68, 71–78. https://doi.org/10.1016/j.gde.2021.02.015.

Morrison, S.F., Nakamura, K., 2019. Central mechanisms for Thermoregulation. Annu. Rev. Physiol. 81, 285–308. https://doi.org/10.1146/annurev-physiol-020518-114546.

Moss, J.B., While, G.M., 2021. The thermal environment as a moderator of social evolution. Biol. Rev. 96, 2890–2910. https://doi.org/10.1111/brv.12784.

Muzerelle, A., Soiza-Reilly, M., Hainer, C., Ruet, P.-L., Lesch, K.-P., Bader, M., Alenina, N., Scotto-Lomassese, S., Gaspar, P., 2021. Dorsal raphe serotonin neurotransmission is required for the expression of nursing behavior and for pup survival. Sci. Rep. 11, 6004. https://doi.org/10.1038/s41598-021-84368-6.

Nakamura, K., 2011. Central circuitries for body temperature regulation and fever. Am. J. Physiol. Regul. Integr. Comp. Physiol. 301, R1207–R1228. https://doi.org/10.1152/ajpregu.00109.2011.

Nakamura, K., Matsumura, K., Hubschle, T., Nakamura, Y., Hioki, H., Fujiyama, F., Boldogkoi, Z., Konig, M., Thiel, H., Gerstberger, R., Kobayashi, S., Kaneko, T., 2004. Identification of sympathetic premotor neurons in medullary raphe regions mediating fever and other thermoregulatory functions. J. Neurosci. 24, 5370–5380. https://doi.org/10.1523/JNEUROSCI.1219-04.2004.

Nakamura, K., Morrison, S.F., 2007. Central efferent pathways mediating skin cooling-evoked sympathetic thermogenesis in brown adipose tissue. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R127–R136. https://doi.org/10.1152/ajpregu.00427.2006.

Nakamura, K., Morrison, S.F., 2010. A thermosensory pathway mediating heat-defense responses. Proc. Natl. Acad. Sci. 107, 8848–8853. https://doi.org/10.1073/pnas.0913358107.

Nakamura, K., Morrison, S.F., 2011. Central efferent pathways for cold-defensive and febrile shivering. J. Physiol. 589, 3641–3658. https://doi.org/10.1113/jphysiol.2011.210047.

Nakamura, K., Morrison, S.F., 2022. Central sympathetic network for thermoregulatory responses to psychological stress. Auton. Neurosci. 237, 102918 https://doi.org/10.1016/j.autneu.2021.102918.

Nakamura, K., Nakamura, Y., Kataoka, N., 2022. A hypothalamomedullary network for physiological responses to environmental stresses. Nat. Rev. Neurosci. 23, 35–52. https://doi.org/10.1038/s41583-021-00532-x.

Nakamura, Y., Yahiro, T., Fukushima, A., Kataoka, N., Hioki, H., Nakamura, K., 2022. Prostaglandin EP3 receptor–expressing preoptic neurons bidirectionally control body temperature via tonic GABAergic signaling. Sci. Adv. 8, eadd5463 https://doi.org/10.1126/sciadv.add5463.

Ng, R., Hussain, N.A., Zhang, Q., Chang, C., Li, H., Fu, Y., Cao, L., Han, W., Stunkel, W., Xu, F., 2017. miRNA-32 drives brown fat thermogenesis and trans-activates subcutaneous white fat browning in mice. Cell Rep. 19, 1229–1246. https://doi.org/10.1016/j.celrep.2017.04.035.

Niederkofler, V., Asher, T.E., Okaty, B.W., Rood, B.D., Narayan, A., Hwa, L.S., Beck, S.G., Miczek, K.A., Dymecki, S.M., 2016. Identification of serotonergic neuronal modules that affect aggressive behavior. Cell Rep. 17, 1934–1949. https://doi.org/10.1016/j.celrep.2016.10.063.

Nixdorf-Miller, A., Hunsaker, D.M., Hunsaker Iii, J.C., 2006. Hypothermia and hyperthermia medicolegal investigation of morbidity and mortality from exposure to environmental temperature extremes. Arch. Pathol. Lab. Med. 130, 1297–1304. https://doi.org/10.5858/2006-130-1297-HAHMIO.

Norman, G.J., Cacioppo, J.T., Morris, J.S., Malarkey, W.B., Berntson, G.G., DeVries, A.C., 2011. Oxytocin increases autonomic cardiac control: moderation by loneliness. Biol. Psychol. 86, 174–180. https://doi.org/10.1016/j.biopsycho.2010.11.006.

O'Leary, D.S., Johnson, J.M., Taylor, W.F., 1985. Mode of neural control mediating rat tail vasodilation during heating. J. Appl. Physiol. 59, 1533–1538. https://doi.org/10.1152/jappl.1985.59.5.1533.

Oka, T., 2015. Psychogenic fever: how psychological stress affects body temperature in the clinical population. Temperature 2, 368–378. https://doi.org/10.1080/23328940.2015.1056907.
Okaty, B.W., Commons, K.G., Dymecki, S.M., 2019. Embracing diversity in the 5-HT neuronal system. Nat. Rev. Neurosci. 20, 397–424. https://doi.org/10.1038/s41583-019-0151-3.
Oldfield, B.J., Giles, M.E., Watson, A., Anderson, C., Colvill, L.M., McKinley, M.J., 2002. The neurochemical characterisation of hypothalamic pathways projecting polysynaptically to brown adipose tissue in the rat. Neuroscience 110, 515–526. https://doi.org/10.1016/S0306-4522(01)00555-3.
Olivier, B., 2006. Serotonin and aggression. Ann. N. Y. Acad. Sci. 1036, 382–392. https://doi.org/10.1196/annals.1330.022.
Olivier, B., 2015. Psychogenic fever, functional fever, or psychogenic hyperthermia? Temperature 2, 324–325. https://doi.org/10.1080/23328940.2015.1071701.
Olsson, I.A.S., Westlund, K., 2007. More than numbers matter: the effect of social factors on behaviour and welfare of laboratory rodents and non-human primates. Appl. Anim. Behav. Sci. 103, 229–254. https://doi.org/10.1016/j.applanim.2006.05.022.
Ootsuka, Y., Nalivaiko, E., Blessing, W.W., 2004. Spinal 5-HT2A receptors regulate cutaneous sympathetic vasomotor outflow in rabbits and rats; relevance for cutaneous vasoconstriction elicited by MDMA (3,4-methylenedioxymethamphetamine, “Ecstasy”) and its reversal by clozapine. Brain Res. 1014, 34–44. https://doi.org/10.1016/j.brainres.2004.03.058.
Ootsuka, Y., Tanaka, M., 2015. Control of cutaneous blood flow by central nervous system. Temperature 2, 392–405. https://doi.org/10.1080/23328940.2015.1069437.
Osterhout, J.A., Kapoor, V., Eichhorn, S.W., Vaughn, E., Moore, J.D., Liu, D., Lee, D., DeNardo, L.A., Luo, L., Zhuang, X., Dulac, C., 2022. A preoptic neuronal population controls fever and appetite during sickness. Nature 606, 937–944. https://doi.org/10.1038/s41586-022-04793-z.
Oti, T., Satoh, K., Uta, D., Nagafuchi, J., Tateishi, S., Ueda, R., Takanami, K., Young, L.J., Galione, A., Morris, J.F., Sakamoto, T., Sakamoto, H., 2021. Oxytocin influences male sexual activity via non-synaptic axonal release in the spinal cord. Curr. Biol. CB 31, 103–114.e5. https://doi.org/10.1016/j.cub.2020.09.089.
Owens, A.P., Mathias, C.J., Iodice, V., 2021. Autonomic dysfunction in autism spectrum disorder. Front. Integr. Neurosci. 15, 787037 https://doi.org/10.3389/fnint.2021.787037.
Pagani, J.H., 2015. Raphe serotonin neuron-specific oxytocin receptorknockout reduces aggression without affectinganxiety-like behavior in male mice only. Genes Brain Behav. 14, 167–176.
Pietropaolo, S., Feldon, J., Yee, B.K., 2008. Nonphysical contact between cagemates alleviates the social isolation syndrome in C57BL/6 male mice. Behav. Neurosci. 122, 505–515. https://doi.org/10.1037/0735-7044.122.3.505.
Prychodko, W., 1958. Effect of aggregation of laboratory mice (Mus musculus) on food intake at different temperatures. Ecology 39, 500–503. https://doi.org/10.2307/1931760.
Qian, T., Wang, H., Wang, P., Geng, L., Mei, L., Osakada, T., Wang, L., Tang, Y., Kania, A., Grinevich, V., Stoop, R., Lin, D., Luo, M., Li, Y., 2023. A genetically encoded sensor measures temporal oxytocin release from different neuronal compartments. Nat. Biotechnol. 41, 944–957. https://doi.org/10.1038/s41587-022-01561-2.
Raison, C.L., Hale, M.W., Williams, L.E., Wager, T.D., Lowry, C.A., 2015. Somatic influences on subjective well-being and affective disorders: the convergence of thermosensory and central serotonergic systems. Front. Psychol. 5 https://doi.org/10.3389/fpsyg.2014.01580.
Ray, R.S., Corcoran, A.E., Brust, R.D., Kim, J.C., Richerson, G.B., Nattie, E., Dymecki, S. M., 2011. Impaired respiratory and body temperature control upon acute serotonergic neuron inhibition. Science 333, 637–642. https://doi.org/10.1126/science.1205295.
Reed, M.D., Yim, Y.S., Wimmer, R.D., Kim, H., Ryu, C., Welch, G.M., Andina, M., King, H. O., Waisman, A., Halassa, M.M., Huh, J.R., Choi, G.B., 2020. IL-17a promotes sociability in mouse models of neurodevelopmental disorders. Nature 577, 249–253. https://doi.org/10.1038/s41586-019-1843-6.
Rieger, N.S., Worley, N.B., Ng, A.J., Christianson, J.P., 2022. Insular cortex modulates social avoidance of sick rats. Behav. Brain Res. 416, 113541 https://doi.org/10.1016/j.bbr.2021.113541.
Roesler, A., Kazak, L., 2020. UCP1-independent thermogenesis. Biochem. J. 477, 709–725. https://doi.org/10.1042/BCJ20190463.
Rogers, E., Gresswell, M., Durrant, S., 2023. The relationship between sleep and suicidality in schizophrenia spectrum and other psychotic disorders: a systematic review. Schizophr. Res. 261, 291–303. https://doi.org/10.1016/j.schres.2023.10.010.
Rogers-Carter, M.M., Varela, J.A., Gribbons, K.B., Pierce, A.F., McGoey, M.T., Ritchey, M., Christianson, J.P., 2018. Insular cortex mediates approach and avoidance responses to social affective stimuli. Nat. Neurosci. 21, 404–414. https://doi.org/10.1038/s41593-018-0071-y.
Romanovsky, A.A., 2007. Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R37–R46. https://doi.org/10.1152/ajpregu.00668.2006.
Saito, M., Okamatsu-Ogura, Y., Matsushita, M., Watanabe, K., Yoneshiro, T., Nio-Kobayashi, J., Iwanaga, T., Miyagawa, M., Kameya, T., Nakada, K., Kawai, Y., Tsujisaki, M., 2009. High incidence of metabolically active brown adipose tissue in healthy adult humans. Diabetes 58, 1526–1531. https://doi.org/10.2337/db09-0530.
Sánchez, C., Arnt, J., Hyttel, J., Moltzen, E.K., 1993. The role of serotonergic mechanisms in inhibition of isolation-induced aggression in male mice. Psychopharmacol. (Berl.) 110, 53–59. https://doi.org/10.1007/BF02246950.
Sanford, L.D., Suchecki, D., Meerlo, P., 2014. Stress, arousal, and sleep. In: Meerlo, P., Benca, R.M., Abel, T. (Eds.), Sleep, Neuronal Plasticity and Brain Function, Current Topics in Behavioral Neurosciences. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 379–410. https://doi.org/10.1007/7854_2014_314.
Schiavo, J.K., Valtcheva, S., Bair-Marshall, C.J., Song, S.C., Martin, K.A., Froemke, R.C., 2020. Innate and plastic mechanisms for maternal behaviour in auditory cortex. Nature 587, 426–431. https://doi.org/10.1038/s41586-020-2807-6.
Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–427. https://doi.org/10.1038/nature13595.
Seebacher, F., Krause, J., 2017. Physiological mechanisms underlying animal social behaviour. Philos. Trans. R. Soc. B Biol. Sci. 372, 20160231. https://doi.org/10.1098/rstb.2016.0231.
Seeley, W.W., 2019. The salience network: a neural system for perceiving and responding to homeostatic demands. J. Neurosci. 39, 9878–9882. https://doi.org/10.1523/JNEUROSCI.1138-17.2019.
Sela, Y., Hoekstra, M.M., Franken, P., 2021. Sub-minute prediction of brain temperature based on sleep–wake state in the mouse. eLife 10, e62073. https://doi.org/10.7554/eLife.62073.
Signoret-Genest, J., Schukraft, N., L. Reis, S., Segebarth, D., Deisseroth, K., Tovote, P., 2023. Integrated cardio-behavioral responses to threat define defensive states. Nat. Neurosci. 26, 447–457. https://doi.org/10.1038/s41593-022-01252-w.
Škop, V., Guo, J., Liu, N., Xiao, C., Hall, K.D., Gavrilova, O., Reitman, M.L., 2020. Mouse thermoregulation: introducing the concept of the thermoneutral point. Cell Rep. 31, 107501 https://doi.org/10.1016/j.celrep.2020.03.065.
Škop, V., Guo, J., Liu, N., Xiao, C., Hall, K.D., Gavrilova, O., Reitman, M.L., 2023. The metabolic cost of physical activity in mice using a physiology-based model of energy expenditure. Mol. Metab. 71, 101699 https://doi.org/10.1016/j.molmet.2023.101699.
Škop, V., Xiao, C., Liu, N., Gavrilova, O., Reitman, M.L., 2021. The effects of housing density on mouse thermal physiology depend on sex and ambient temperature. Mol. Metab. 53, 101332 https://doi.org/10.1016/j.molmet.2021.101332.
Sokoloff, G., Blumberg, M.S., 2001. Competition and cooperation among huddling infant rats. Dev. Psychobiol. 39, 65–75. https://doi.org/10.1002/dev.1030.
Son, S., Manjila, S.B., Newmaster, K.T., Wu, Y., Vanselow, D.J., Ciarletta, M., Anthony, T. E., Cheng, K.C., Kim, Y., 2022. Whole-brain wiring diagram of oxytocin system in adult mice. J. Neurosci. 42, 5021–5033. https://doi.org/10.1523/JNEUROSCI.0307-22.2022.
Stanier, M.W., 1975. Effect of body weight, ambient temperature and huddling on oxygen consumption and body temperature of young mice. Comp. Biochem. Physiol. A Physiol. 51, 79–82. https://doi.org/10.1016/0300-9629(75)90416-8.
Sutton, A.K., Pei, H., Burnett, K.H., Myers, M.G., Rhodes, C.J., Olson, D.P., 2014. Control of food intake and energy expenditure by Nos1 neurons of the paraventricular hypothalamus. J. Neurosci. 34, 15306–15318. https://doi.org/10.1523/JNEUROSCI.0226-14.2014.
Swardfager, W., Rosenblat, J.D., Benlamri, M., McIntyre, R.S., 2016. Mapping inflammation onto mood: Inflammatory mediators of anhedonia. Neurosci. Biobehav. Rev. 64, 148–166. https://doi.org/10.1016/j.neubiorev.2016.02.017.
Tan, C.L., Knight, Z.A., 2018. Regulation of body temperature by the nervous system. Neuron 98, 31–48. https://doi.org/10.1016/j.neuron.2018.02.022.
Tanaka, M., McKinley, M.J., McAllen, R.M., 2011. Preoptic–Raphé connections for thermoregulatory vasomotor control. J. Neurosci. 31, 5078–5088. https://doi.org/10.1523/JNEUROSCI.6433-10.2011.
Tang, Y., Benusiglio, D., Lefevre, A., Hilfiger, L., Althammer, F., Bludau, A., Hagiwara, D., Baudon, A., Darbon, P., Schimmer, J., Kirchner, M.K., Roy, R.K., Wang, S., Eliava, M., Wagner, S., Oberhuber, M., Conzelmann, K.K., Schwarz, M., Stern, J.E., Leng, G., Neumann, I.D., Charlet, A., Grinevich, V., 2020. Social touch promotes interfemale communication via activation of parvocellular oxytocin neurons. Nat. Neurosci. 23, 1125–1137. https://doi.org/10.1038/s41593-020-0674-y.
Terrien, J., Perret, M., Aujard, F., 2011. Behavioral thermoregulation in mammals: a review. Front. Biosci. 16, 1428. https://doi.org/10.2741/3797.
Thorstenson, C.A., Pazda, A.D., Lichtenfeld, S., 2020. Facial blushing influences perceived embarrassment and related social functional evaluations. Cogn. Emot. 34, 413–426. https://doi.org/10.1080/02699931.2019.1634004.
Tiwari, P., Panik, R., Bhattacharya, A., Ahirwar, D., Chandy, A., 2012. Evidences of possible side effects of neuroleptic drugs: a systematic review. Asian Pac. J. Reprod. 1, 330–336. https://doi.org/10.1016/S2305-0500(13)60105-0.
Trowbridge, S., Narboux-Nême, N., Gaspar, P., 2011. Genetic models of serotonin (5-HT) depletion: what do they tell us aboutthe developmental role of 5-HT? Anat. Rec. 1615–1623.
Tsuneoka, Y., Funato, H., 2021. Cellular composition of the preoptic area regulating sleep, parental, and sexual behavior. Front. Neurosci. 15, 649159 https://doi.org/10.3389/fnins.2021.649159.
Urisarri, A., González-García, I., Estévez-Salguero, Á., Pata, M.P., Milbank, E., López, N., Mandiá, N., Grijota-Martinez, C., Salgado, C.A., Nogueiras, R., Diéguez, C., Villarroya, F., Fernández-Real, J.-M., Couce, M.L., López, M., 2021. BMP8 and activated brown adipose tissue in human newborns. Nat. Commun. 12, 5274. https://doi.org/10.1038/s41467-021-25456-z.
Van Veen, J.E., Kammel, L.G., Bunda, P.C., Shum, M., Reid, M.S., Massa, M.G., Arneson, D.V., Park, J.W., Zhang, Z., Joseph, A.M., Hrncir, H., Liesa, M., Arnold, A. P., Yang, X., Correa, S.M., 2020. Hypothalamic oestrogen receptor alpha establishes a sexually dimorphic regulatory node of energy expenditure. Nat. Metab. 2, 351–363. https://doi.org/10.1038/s42255-020-0189-6.

Vestergaard, M., Carta, M., Güney, G., Poulet, J.F.A., 2023. The cellular coding of temperature in the mammalian cortex. Nature 614, 725–731. https://doi.org/10.1038/s41586-023-05705-5.

Voronova, I.P., 2021. 5-HT receptors and temperature homeostasis. Biomolecules 11, 1914. https://doi.org/10.3390/biom11121914.

Wang, Z., Ning, T., Song, A., Rutter, J., Wang, Q.A., Jiang, L., 2020. Chronic cold exposure enhances glucose oxidation in brown adipose tissue. EMBO Rep. 21, e50085 https://doi.org/10.15252/embr.202050085.

Wang, H., Wang, B., Normoyle, K.P., Jackson, K., Spitler, K., Sharrock, M.F., Miller, C.M., Best, C., Llano, D., Du, R., 2014. Brain temperature and its fundamental properties: a review for clinical neuroscientists. Front. Neurosci. 8 https://doi.org/10.3389/fnins.2014.00307.

Wanner, S.P., Guimarães, J.B., Rodrigues, L.O.C., Marubayashi, U., Coimbra, C.C., Lima, N.R.V., 2007. Muscarinic cholinoceptors in the ventromedial hypothalamic nucleus facilitate tail heat loss during physical exercise. Brain Res. Bull. 73, 28–33. https://doi.org/10.1016/j.brainresbull.2007.03.004.

Webster, R., 2001. Schizophrenia - symptoms and general aspects. In: Webster, R.A. (Ed.), Neurotransmitters, Drugs and Brain Function. Wiley, pp. 351–373. https://doi.org/10.1002/0470846577.ch17.

Wei, D., Talwar, V., Lin, D., 2021. Neural circuits of social behaviors: innate yet flexible. Neuron 109, 1600–1620. https://doi.org/10.1016/j.neuron.2021.02.012.

Williams, A.V., Duque-Wilckens, N., Ramos-Maciel, S., Campi, K.L., Bhela, S.K., Xu, C.K., Jackson, K., Chini, B., Pesavento, P.A., Trainor, B.C., 2020. Social approach and social vigilance are differentially regulated by oxytocin receptors in the nucleus accumbens. Neuropsychopharmacology 45, 1423–1430. https://doi.org/10.1038/s41386-020-0657-4.

Wright, K.P., Hull, J.T., Czeisler, C.A., 2002. Relationship between alertness, performance, and body temperature in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 283, R1370–R1377. https://doi.org/10.1152/ajpregu.00205.2002.

Wu, Z., Autry, A.E., Bergan, J.F., Watabe-Uchida, M., Dulac, C.G., 2014. Galanin neurons in the medial preoptic area govern parental behaviour. Nature 509, 325–330. https://doi.org/10.1038/nature13307.

Yahiro, T., Kataoka, N., Nakamura, K., 2023. Two ascending thermosensory pathways from the lateral parabrachial nucleus that mediate behavioral and autonomous thermoregulation. J. Neurosci. 43, 5221–5240. https://doi.org/10.1523/JNEUROSCI.0643-23.2023.

Yi, K.J., So, K.H., Hata, Y., Suzuki, Y., Kato, D., Watanabe, K., Aso, H., Kasahara, Y., Nishimori, K., Chen, C., Katoh, K., Roh, S.G., 2015. The regulation of oxytocin receptor gene expression during adipogenesis. J. Neuroendocrinol. 27, 335–342. https://doi.org/10.1111/jne.12268.

Yin, L., Hashikawa, K., Hashikawa, Y., Osakada, T., Lischinsky, J.E., Diaz, V., Lin, D., 2022. VMHvllCckar cells dynamically control female sexual behaviors over the reproductive cycle. Neuron 110, 3000–3017.e8. https://doi.org/10.1016/j.neuron.2022.06.026.

Yu, X., Zhao, G., Wang, D., Wang, S., Li, R., Li, A., Wang, H., Nollet, M., Chun, Y.Y., Zhao, T., Yustos, R., Li, H., Zhao, J., Li, J., Cai, M., Vyssotski, A.L., Li, Y., Dong, H., Franks, N.P., Wisden, W., 2022. A specific circuit in the midbrain detects stress and induces restorative sleep. Science 377, 63–72. https://doi.org/10.1126/science.abn0853.

Zonnenberg, C., Bueno-de-Mesquita, J.M., Ramlal, D., Blom, J.D., 2017. Hypothermia due to antipsychotic medication: a systematic review. Front. Psychiatry 8, 165. https://doi.org/10.3389/fpsyt.2017.00165.