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The neural circuits of thermal perception

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Thermal information about skin surface temperature is a key sense for the perception of object identity and valence. The identification of ion channels involved in the transduction of thermal changes has provided a genetic access point to the thermal system. However, from sensory specific 'labeled-lines' to multimodal interactive pathways, the functional organization and identity of the neural circuits mediating innocuous thermal perception have been debated for over 100 years. Here we highlight points in the system that require further attention and review recent advances using *in vivo* electrophysiology, cellular resolution calcium imaging, optogenetics and thermal perceptual tasks in behaving mice that have begun to uncover the anatomical principles and neural processing mechanisms underlying innocuous thermal perception.

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Introduction

From the warmth of an open fire to the cold touch of a chilled beer bottle, thermal sensation is tightly woven into our everyday sensory experience. Subconscious monitoring of temperature is essential for core body temperature regulation and survival in an ever-changing thermal environment. Thermal information, however, can also evoke rapid motor and emotional responses and is tightly integrated with tactile information to generate a unified, coherent percept of an object during haptic exploration. Thermal stimuli can lead to the formation of highly acute percepts, with the threshold for detecting temperature changes by the human hand being $<0.5\,^{\circ}$C [1,2]. Similarly, thermal stimuli can also trigger perceptual paradoxes such as Thunberg's 'thermal grill' illusion where painful, burning sensations can be evoked by touching alternating bars of innocuous cold and warm temperatures [3]; or Weber's phenomenon where an object appears heavier when it is cold than warm [4]. Taken together, these observations reveal that the thermal system has neural processing, wiring and perceptual repertoires reminiscent of better studied sensory pathways.

Despite its strong links to survival, emotion and behavior, the neural pathways and cellular mechanisms of thermal processing remain relatively poorly understood. In 1882, Blix used electrical current delivered via a pin, or water via a small cone, to study innocuous thermal sensations in humans [5]. Because the tiny stimulation spots evoked discrete cold or touch percepts, and more recent afferent ablation studies alter percepts of specific modalities, it has been suggested that the circuits carrying thermal information are anatomically distinct from touch, pain, and proprioception — a 'labeled line' system [5–9]. However, the perception of cold and warm co-varies in humans [10] and multi-modal (mostly touch and temperature) responses have been observed at the afferent [11,12,13,14•], thalamic [15–17], and cortical [14•,18] levels of the thermal system. These observations of functional and perceptual integration of somatosensory modalities has prompted models of sensory coding that combine specialized receptors pathways with temporal coding schemes [12,13,19,20].

Here we summarize the current knowledge about the neural circuits underlying thermal perception (see also [21•]) and examine recent functional studies in the mouse. We highlight the mouse thermal system as amenable for integrating genetic, systems and behavioral analysis in the search for the neural mechanisms of sensory perception and principles of sensory wiring.

Thermal psychophysics

While psychophysical studies have revealed fundamental principles of thermal perception in humans [10,21•], this is not true for mice. In part, this reflects the different questions asked in rodent studies, such as, how do mice avoid thermal stimuli or regulate body temperature? Classic thermal behaviors have used measurements of paw withdrawal latency to strong thermal stimuli, or assessments of dwell times in chamber systems where floor plates are set to different temperatures [22–26] (Figure 1a,b). These behavioral assessments are useful for monitoring reflexive movements and innate thermoregulatory behaviors like cold avoidance, but do not

Figure 1

Thermal behavioral tasks for rodents. **(a)** A 2-plate thermal avoidance task. Floor plates have different temperatures and experimenters monitor the time spent on either plate. **(b)** Similar task as in (a) but animals walk around within a ring-shaped disk (white circle on infrared image) with a gradient of floor temperatures. **(c)** A thermal discrimination task where freely moving mice are trained to discriminate between two temperatures of water droplets delivered to the central spout, mice report the temperature by moving to one of two reporting nose-poke ports. **(d)** Cartoon schematic showing different stages of thermal perception task in head-fixed paw-tethered mice based on task in [14•]. Mice are trained to report a thermal stimulus delivered to the glabrous skin of the right forepaw by licking a reward port. Following correct licking, mice are rewarded with water. Figure panels adapted with permission, from (a) [22], (b) [26], (c) [31••].

necessarily reflect the perception of a sensory stimulus. Moreover, the limited spatial and temporal control of the thermal stimulus in floor plate experiments is problematic. For example, floor plate experiments where rodents can gather thermal information using different body parts, have led to different conclusions about the cortical representation of thermal input, with some lesion studies suggesting that the primary somatosensory cortex is not required for thermal sensation while others have suggested that it is [27–30].

To address these problems, faster, goal-directed thermal perception behaviors have been recently developed for mice (Figure 1c,d). For example, Yarmolinksy *et al.* [31••] designed a warmth discrimination task where freely moving mice were trained to sample and report the temperature of drinking water using a three-port chamber consisting of a central sample port and a left or right reporting port. Mice could reach 90% discrimination accuracy within 2–3 weeks. To have stable access to the brain and improved stimulus control, Milenkovic *et al.* [14•] developed a head-fixed, paw-tethered task where mice are trained to report a thermal stimulus delivered to the glabrous skin of the right forepaw by licking a water reward with short latency. Mice learnt the behavior within a few days and can detect a <0.5 °C cooling stimulus (Paricio-Montesinos *et al.*, unpublished observations), making their thermal perception abilities equivalent to that of humans. These approaches will make it possible to measure other fundamental aspects of thermal perception in mice (e.g. warming thresholds, the impact of baseline temperature, ramp speed, stimulus size, and somatotopic location) as well as the interaction between thermal and touch percepts. Moreover, head-fixation allows easier coupling of neuronal recordings and manipulations with behavior to investigate the neural mechanisms of thermal perception.

From skin to spinal cord

In recent years, the identification of the transient receptor potential (TRP) family of thermally sensitive ion channels in primary sensory afferent neurons [32–34], has provided a genetic access point to the thermal system. The thermal activation thresholds of TRP channels span the environmental temperature range and it is becoming increasingly evident they are co-expressed in adult primary sensory neurons [35–37]. TRPM8 [22–24] and TRPA1 [38,39], for example, are thought to act in concert